Reduction of pro-inflammatory cytokine levels and cellular adhesion in CABG procedures with separated pulmonary and systemic extracorporeal circulation without an oxygenator

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Abstract

Objective: We have recently shown that a considerable amount of pro-inflammatory cytokines is released during pulmonary passage after aortic declamping in patients undergoing coronary artery bypass grafting. The present study was performed to investigate whether bilateral extracorporeal circulation with the lungs as oxygenators can reduce the inflammatory responses of the lungs. Methods: Eighteen consecutive patients undergoing coronary artery bypass grafting were randomly assigned to routine extracorporeal circulation with cannulation of right atrium and aorta (routine circulation, ten patients) or to a bilateral extracorporeal circulation with additional cannulation of left atrium and pulmonary artery (bilateral circulation, eight patients). Blood was simultaneously drawn from right atrium and pulmonary vein at 1, 10 and 20 min reperfusion. The levels of interleukin (IL)-6 and IL-8 and the adhesion molecules CD41 and CD62 on platelets and CD11b and CD41 on leukocytes were determined. Because of considerable interindividual scatter, the pulmonary venous levels are normalized to percent of the respective right atrial value at each time point. Results: At 1 min reperfusion pulmonary venous levels of IL-6 and IL-8 in routine circulation were 144±15% and 143±28% of the respective right atrial values. The respective values in bilateral circulation were 23±4% and 26±7% (P = 0.02 and P = 0.05 vs. respective right atrium). Similar increments were found after 10 and 20 min. Platelet-monocyte coaggregates were retained during pulmonary passage at 1 min reperfusion in routine circulation (221±6%), but washed out in bilateral circulation (15±8%, P = 0.007). At 20 min reperfusion, activated polymorphonuclear neutrophils (PMN) were retained in routine circulation (16±9%) but washed out in bilateral circulation (19±29%, P = 0.05; all data given as mean ± SEM). Conclusions: Bilateral extracorporeal circulation without an artificial oxygenator significantly reduces the inflammatory responses during pulmonary passage after aortic declamping. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Extracorporeal circulation; Drew technique; Coronary artery bypass grafting; Pulmonary inflammatory response; Cytokine; Adhesion molecule

1. Introduction

Routine cardiac surgery conducted with cardiopulmonary bypass (CPB) is performed by draining blood from the right atrium and excluding the lungs from the circulation. During aortic clamping, only the nutritive blood supply to the lungs via the bronchial arteries continues. In this setting the development of a systemic inflammatory response (SIRS) has been well established [1,2]. Moreover, the heart and the lungs were shown to add to the inflammatory response by releasing cytokines and favoring cellular adhesion during postischemic reperfusion [3,4].

Extracorporeal circulation can also be performed using the patients lungs as physiologic oxygenators during the operation. This procedure is named after Charles Drew [5–7]. Surgical procedure is different in that right and left atrium, pulmonary artery and aorta have to be cannulated. Thereafter, the pulmonary and the systemic circulation are perfused separately. Even during cardiac ischemia, perfusion of the lungs is maintained. Recent data of our group show that postoperative lung function is significantly
improved in these patients, which leads to shorter extubation times. Consequently, the length of stay on the intensive care unit is also reduced [8]. At the same time there is a considerable reduction of the systemic inflammatory response, suggesting the use of an oxygenator as one of the main reasons for this phenomenon.

Recently, we have shown that significant inflammatory changes occur during reperfusion of the lungs in patients undergoing coronary artery bypass grafting (CABG) with conventional CPB [3]. The aim of the present study was to examine these changes in CABG patients undergoing CABG with bilateral extracorporeal circulation.

2. Subjects and methods

Eighteen patients undergoing coronary artery bypass grafting (CABG) were randomized to either conventional cardiopulmonary bypass or bilateral extracorporeal circulation. In all patients blood was simultaneously drawn from the right atrium and the right upper pulmonary vein at 1, 10 and 20 min reperfusion after release of the aortic cross-clamp. For blood sampling from the right atrium, the central part of a Swan-Ganz catheter was used. Blood from the pulmonary vein was directly drawn with a syringe and a 26-gauge cannula. The study was approved by the local Ethics Committee, and informed consent was obtained from all patients for the performance of the study.

2.1. Surgery

All patients underwent CABG with CPB using roller pumps (Stöckert, München, Germany) and disposable membrane oxygenators (Dideco, Mirandola, Italy). Anesthesia was conducted as a total intravenous technique as previously described [9]. Aprotinin (Trasylol, Bayer, Leverkusen, Germany) was given according to the Hammersmith protocol (total dose 6 million KIU). CPB was instituted at a flow rate of 2.4 l/min per m² BSA after systemic heparinization. Perfusion pressure during CPB was maintained between 50 and 70 mmHg in both groups. The body temperature was cooled to 28–30°C (moderate hypothermia) and 1000 ml of 4°C cold Bretschneider solution (Custodiol, Köhler Chemie, Alsbach-Hähnlein, Germany) was applied as antegrade cardioplegia after clamping of the aorta. Before termination of CPB, an infusion of dopamine (3–5 µg/kg per min) was used as first line drug in both groups. After termination of CPB its infusion rate was adapted according to the patient’s circulatory state. A cardiac index ≥2.3 l/min per m² and a mean arterial pressure ≥60 mmHg were the targets. Protamine was given to neutralize anticoagulation according to the patient’s ACT.

2.2. Drew perfusion technique

After systemic heparinization the aorta was cannulated, then a two-stage venous cannula was inserted into the right atrium and the inferior caval vein (Two stage, Stöckert, Munich, Germany). The main pulmonary artery was cannulated approximately 2 cm distal the pulmonary valve with a wire-reinforced cannula (Stöckert). Right heart bypass was then started and a 28–32-gauge wire-wound cannula (Stöckert) was inserted into the left atrium via a teflon-reinforced purse-string suture at the junction of the right superior pulmonary vein or between the aorta and the superior caval vein. Left-hear bypass was then started and the patient cooled to 28–30°C rectal temperature under the conditions of bilateral extracorporeal circulation. Controlled ventilation of the lungs was maintained throughout the procedure. Alveolar ventilation of the lungs during bilateral extracorporeal circulation was reduced as temperature decreased. Continuous measurement of blood gases and acid–base balance made control of ventilation and oxygenation easy. The flow of the right-heart bypass was kept at 0.2–0.3 l/min higher than for the left-sided circulation. By opening of a shunt, balancing of the levels in the two reservoirs was facilitated. After completion of distal anastomoses, rewarming of the patient, and as soon as the heart was beating sufficiently and performing pressure–volume work, the right-sided cannulas were removed. Thereafter left-heart bypass was terminated and the respective cannulas removed.

2.3. Flow cytometry

Flow cytometry was performed as previously described [9]. In brief, for analysis of leukocytes, 100-µl aliquots of the blood samples were immediately mixed with 1 ml FACS lysis solution (Becton Dickinson, Heidelberg, Germany). Leukocytes were pelleted and then double-stained with FITC-labeled anti-CD41 antibodies (Serotec, Kidlington, UK) and PE labeled anti-CD11b antibodies (Exalpha, Boston, MA). The measurement of the platelet marker CD41 on leukocytes served to determine the percentages of neutrophils and monocytes carrying platelets.

For analysis of platelets, 100 µl of blood and 1 ml Cellfix (Becton Dickinson) were employed. After centrifugation the pellet was incubated with antibodies against CD41 (FITC-labeled, Serotec) and CD62 (PE-conjugated, Harlan Seralab, Crawley Down, UK).

Flow cytometry was performed with a FACScan and Lysis II software (Becton Dickinson). The mean fluorescence intensity was taken as a measure of antibody binding. Reproducibility of flow cytometry was ensured by regular measurement of calibrated standards. The non-specific background was quantified by measurement of the fluorescence intensity of samples labeled with non-binding, isotype-matched antibodies, and subsequently subtracted. Results were calculated as relative fluorescence units.

2.4. Cytokines

For analysis of cytokines, blood specimens were
collected into ammonium-heparin-tubes (Sarstedt, Nümbrecht, Germany). Plasma samples were stored frozen at \(-20°C\) until assayed within batches. Interleukin (IL)-6 and IL-8 were measured using a solid phase, two-site chemiluminescent enzyme immunometric assay (Immulite system, Diagnostic Products Corp., Los Angeles, CA).

2.5. Statistics

All results are expressed as mean ± SEM. Student’s \(t\)-test for paired samples was used to evaluate the differences between the two groups. A difference on a two-tailed test was considered as statistically significant for \(P < 0.05\). No within-group comparison was made regarding results at different time points.

3. Results

Basal values of the cytokines IL-6 and IL-8, the adhesion parameters CD11b on monocytes and polymorphonuclear neutrophils (PMN), CD41 on platelets, monocytes and PMN and CD62 on platelets are presented in Table 1. All values are given in absolute numbers for right atrial and pulmonary venous blood. The latter are also expressed in percent of the respective right atrial value. IL-6 and activated PMN tended to be sequestered in the lungs before CPB. In contrast, microaggregates of platelets and leukocytes emerged form the pulmonary vessel bed.

Pre- and intraoperative data of the 18 study patients are shown in Table 2. No significant differences were found between the groups.

Absolute levels of cytokines and adhesion molecules at all reperfusion time points are listed in Table 3. Owing to considerable interindividual scatter of absolute values, mean value differences between RA and PV obscure individual changes of parameters during pulmonary passage. Therefore, all results were recalculated on a percentage basis, with the pulmonary venous levels at 1, 10 and 20 min reperfusion referring to their respective right atrial values. The percent results for IL-6 and IL-8 are shown in Fig. 1. There was mitigated pulmonary release of cytokines in the group with bilateral circulation at all time points measured.

Modest differences between the groups were found in adhesion molecule levels. In the first minute of reperfusion fewer platelet–monocyte microaggregates were retained during pulmonary passage in Bilateral Circulation (Fig. 2). At 20 min reperfusion, fewer CD11b-positive monocytes and CD11b-positive PMN were retained during lung passage in Bilateral Circulation (Fig. 2).

4. Discussion

The conventional technique of cardiopulmonary bypass using cannulas in right atrium and ascending aorta and an artificial oxygenator has been shown to be associated with a considerable increase of the levels of pro-inflammatory cytokines IL-6 and IL-8 during pulmonary passage after declamping of the aorta [3]. With the Drew technique of bilateral extracorporeal circulation using the patients lungs as oxygenators [7], cytokine levels in systemic blood are lower than in patients operated with a regular CPB circuit [8].

In the present study, using the Drew circulation technique more or less equal cytokine levels in right atrium and pulmonary vein were observed after declamping of the aorta. In addition, the retention of activated leukocytes and leukocyte–platelet coaggregates was attenuated. These changes speak for a reduced pulmonary inflammatory response under the drew perfusion technique.

The cellular origin of cytokines during pulmonary passage is unclear. With 8 and 20% leukocytes trapped within the pulmonary circulation before and after ischemia, respectively, these blood cells may well be a source of the observed cytokine release [10]. IL-6 and IL-8 have been shown to be produced by a variety of leukocyte subsets [11]. Whether lung tissue itself can prove responsible for the observed cytokine production is unclear. IL-8 is known to be localized, preformed, in the Weibel–Palade bodies of the vascular endothelial cells, from where it can be released into the circulation.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Right atrium</th>
<th>Pulmonary vein</th>
<th>PV/RA%</th>
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</thead>
<tbody>
<tr>
<td>IL-6 (pg/ml)</td>
<td>14.6 ± 4.6</td>
<td>12.4 ± 3.4</td>
<td>89 ± 4 ((P = 0.01))</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>27.4 ± 12.8</td>
<td>26.1 ± 12.4</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>CD11b on monocytes</td>
<td>14.5 ± 1.9</td>
<td>13.8 ± 4.3</td>
<td>96 ± 26</td>
</tr>
<tr>
<td>CD11b on PMN</td>
<td>16.6 ± 2.2</td>
<td>12.0 ± 0.9 ((P = 0.04))</td>
<td>81 ± 10 ((P = 0.03))</td>
</tr>
<tr>
<td>CD41 on platelets</td>
<td>153.2 ± 20.1</td>
<td>151.7 ± 14.6</td>
<td>104 ± 6</td>
</tr>
<tr>
<td>CD62 on platelets</td>
<td>17.1 ± 3.8</td>
<td>17.7 ± 3.5</td>
<td>110 ± 11</td>
</tr>
<tr>
<td>CD41 on monocytes</td>
<td>32.3 ± 3.6</td>
<td>39.8 ± 5.2</td>
<td>124 ± 8 ((P = 0.006))</td>
</tr>
<tr>
<td>CD41 on PMN</td>
<td>13.9 ± 2.3</td>
<td>21.6 ± 3.6 ((P = 0.04))</td>
<td>176 ± 25 ((P = 0.003))</td>
</tr>
</tbody>
</table>

* When % values were given, each pulmonary venous (PV) level was normalized to percentage of the respective right atrial (RA) value. Values are given as mean ± SEM. All results concerning adhesion molecules are expressed as relative fluorescence units. Significance levels in parentheses between pulmonary venous and respective right atrial levels.
Table 2
Pre- and intraoperative patient dataa

<table>
<thead>
<tr>
<th></th>
<th>Routine Circulation</th>
<th>Bilateral Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>65 ± 4 years</td>
<td>65 ± 4 years</td>
</tr>
<tr>
<td>Patient sex</td>
<td>Three women, seven men</td>
<td>One woman, seven men</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>58 ± 3%</td>
<td>65 ± 4%</td>
</tr>
<tr>
<td>Duration of ischemia</td>
<td>69 ± 5 min</td>
<td>61 ± 8 min</td>
</tr>
<tr>
<td>Duration of reperfusion</td>
<td>35 ± 3 min</td>
<td>30 ± 3 min</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>One of ten</td>
<td>Two of eight</td>
</tr>
<tr>
<td>COLD</td>
<td>One of ten</td>
<td>One of eight</td>
</tr>
</tbody>
</table>

a Values are mean ± SEM; n = 10 patients (Routine Circulation), n = 8 patients (Bilateral Circulation).

upon stimulation [12]. Thus, less contact between activated leukocytes and the pulmonary vascular endothelium, as indicated by less retention of these cells in the lungs of patients perfused with the Drew technique, may be responsible for less cytokine release by the endothelium. The cytokines themselves play a pivotal role by increasing the expression of cell surface receptors [13]. In the present study, absolute cell counts in right atrium and pulmonary vein were not determined. Whether reduced cytokine levels are accompanied by less leukocyte retention has to be the subject of future investigation.

One important difference between the two perfusion techniques is that contact activation of blood elements by the artificial surface of a machine oxygenator is prevented in the case of the Drew technique. The tubing system with its artificial surface persists, its length even being doubled compared to the conventional CPB technique because of bilateral circulation with four instead of two cannulas.

Another main difference between conventional CPB and the Drew technique is the continuous perfusion of the lungs during cardiac ischemia in the latter. With the Drew technique, the lungs do not undergo reperfusion as does the heart. In contrast, in routine CPB there is almost no antegrade flow over the pulmonary artery into the lungs and the amount of blood entering the lungs over bronchial artery flow is negligible. Thus, with the routine technique, after declamping of the aorta and termination of CPB, the reperfusion of the lungs may lead to the complex of leukocyte–endothelial interaction, sequestration of leukocytes, release of oxygen reactive compounds, subsequent tissue damage and organ dysfunction, known as reperfusion damage [14].

Earlier studies have shown that diminished pulmonary

Table 3
Absolute values of cytokines and adhesion molecules in Routine Circulation and Bilateral Circulation determined in right atrium (RA) and pulmonary vein (PV) at 1, 10 and 20 min reperfusiona

<table>
<thead>
<tr>
<th></th>
<th>RA 1</th>
<th>PV 1</th>
<th>RA 10</th>
<th>PV 10</th>
<th>RA 20</th>
<th>PV 20</th>
</tr>
</thead>
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<tr>
<td><strong>Routine Circulation</strong></td>
<td></td>
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</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>39.9 ± 12.6</td>
<td>55.4 ± 11.6</td>
<td>68.5 ± 19.6</td>
<td>126.8 ± 29.6</td>
<td>94.9 ± 27.8</td>
<td>174.6 ± 41.5</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>8.9 ± 1.5</td>
<td>11.5 ± 1.9</td>
<td>11.6 ± 1.8</td>
<td>15.6 ± 3.2</td>
<td>13.4 ± 2.1</td>
<td>17.7 ± 3.1</td>
</tr>
<tr>
<td>CD11b monocytes</td>
<td>21.9 ± 5.3</td>
<td>19.4 ± 5.7</td>
<td>18.1 ± 5.1</td>
<td>14.0 ± 5.1</td>
<td>15.0 ± 4.2</td>
<td>14.8 ± 4.4</td>
</tr>
<tr>
<td>CD11b PMN</td>
<td>13.8 ± 4.6</td>
<td>18.4 ± 6.2</td>
<td>16.4 ± 5.4</td>
<td>14.0 ± 4.5</td>
<td>13.6 ± 4.6</td>
<td>11.9 ± 4.3</td>
</tr>
<tr>
<td>CD41 on platelets</td>
<td>159 ± 13</td>
<td>159 ± 13</td>
<td>161 ± 12</td>
<td>154 ± 15</td>
<td>157 ± 15</td>
<td>159 ± 16</td>
</tr>
<tr>
<td>CD62 on platelets</td>
<td>26.3 ± 7.9</td>
<td>25.1 ± 6.5</td>
<td>24.0 ± 5.4</td>
<td>24.5 ± 6.4</td>
<td>26.7 ± 8.5</td>
<td>26.4 ± 8.2</td>
</tr>
<tr>
<td>CD41 monocytes</td>
<td>55.4 ± 4.3</td>
<td>44.2 ± 4.5</td>
<td>49.9 ± 4.3</td>
<td>48.6 ± 3.9</td>
<td>47.2 ± 4.3</td>
<td>48.5 ± 4.6</td>
</tr>
<tr>
<td>CD41 PMN</td>
<td>22.2 ± 2.5</td>
<td>22.9 ± 2.9</td>
<td>19.3 ± 2.2</td>
<td>19.0 ± 2.0</td>
<td>22.8 ± 3.5</td>
<td>23.2 ± 5.4</td>
</tr>
<tr>
<td><strong>Bilateral Circulation</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>58.9 ± 20.3</td>
<td>63.3 ± 22.3</td>
<td>83.8 ± 27.1</td>
<td>95.7 ± 29.6</td>
<td>109.9 ± 32.8</td>
<td>130.3 ± 37.9</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>12.2 ± 3.0</td>
<td>11.3 ± 2.9</td>
<td>14.1 ± 3.7</td>
<td>14.0 ± 3.4</td>
<td>16.6 ± 4.4</td>
<td>16.7 ± 3.9</td>
</tr>
<tr>
<td>CD11b monocytes</td>
<td>25.4 ± 8.9</td>
<td>21.6 ± 4.7</td>
<td>18.3 ± 3.0</td>
<td>16.4 ± 2.6</td>
<td>16.2 ± 2.0</td>
<td>20.2 ± 3.2</td>
</tr>
<tr>
<td>CD11b PMN</td>
<td>14.0 ± 1.6</td>
<td>14.0 ± 1.8</td>
<td>15.2 ± 2.4</td>
<td>14.0 ± 2.3</td>
<td>14.1 ± 2.1</td>
<td>15.6 ± 2.1</td>
</tr>
<tr>
<td>CD41 on platelets</td>
<td>112 ± 16a</td>
<td>107 ± 17c</td>
<td>115 ± 17b</td>
<td>115 ± 17</td>
<td>119 ± 16</td>
<td>115 ± 18d</td>
</tr>
<tr>
<td>CD62 on platelets</td>
<td>17.7 ± 2.2</td>
<td>17.2 ± 2.4</td>
<td>18.6 ± 2.4</td>
<td>18.3 ± 2.5</td>
<td>18.6 ± 2.4</td>
<td>18.9 ± 2.7</td>
</tr>
<tr>
<td>CD41 monocytes</td>
<td>43.6 ± 6.6</td>
<td>44.2 ± 6.7</td>
<td>41.6 ± 8.0</td>
<td>42.1 ± 6.1</td>
<td>40.0 ± 6.5</td>
<td>42.1 ± 6.3</td>
</tr>
<tr>
<td>CD41 PMN</td>
<td>20.7 ± 3.2</td>
<td>21.2 ± 3.2</td>
<td>18.0 ± 2.9</td>
<td>19.5 ± 3.3</td>
<td>19.8 ± 2.4</td>
<td>19.3 ± 3.2</td>
</tr>
</tbody>
</table>

a Values are given as mean ± SEM. All results concerning adhesion molecules are expressed as relative fluorescence units.

b P = 0.03 vs. respective level in Routine Circulation.

c P = 0.02 vs. respective level in Routine Circulation.

d P = 0.05 vs. respective level in Routine Circulation.
blood flow during total CPB results in postoperative impairment of vascular endothelial function [15]. At the same time, as an indicator of endothelial dysfunction, an inability to release nitric oxide is observed [16]. When nitric oxide is supplemented exogenously with the beginning of reperfusion, a considerable reduction of the systemic inflammatory response is achieved [9]. Taken together, in routine CPB the two main stimuli for an inflammatory reaction are the use of an oxygenator and the reperfusion of the previously excluded lungs, which are the only organs to receive the entire cardiac output.

In the late 1950s, cardiac surgeons were concerned about the high mortality in experimental series and in the early clinical experience. The problem seemed to be related to the oxygenators with their direct blood–gas interface [5]. The use of an oxygenator implies the application of high-dose heparin. However, even under this regimen the generation of thrombin by activation of the coagulation cascade can not be completely inhibited [17]. Using the Drew technique, the degree of contact activation is supposed to be considerably reduced [8]. During routine CPB thrombin levels are increased, which is considered to be due to contact activation [17]. Thrombin is involved in the activation of leukocytes and platelets and acts on the endothelium to release a variety of vasoactive and inflammatory mediators [18]. In the present study, thrombin was not determined. Further studies have to show whether lower cytokine levels are accompanied by less thrombin production in patients operated with the Drew technique.

Reperfusion induces a number of pathophysiological changes, although it is necessary to re-establish organ function [14]. In the lungs, neutrophils have been shown to be sequestered [10]; at the same time, increased levels of pro-inflammatory mediators are observed [3]. The sequestration of neutrophils leads to the release of proteolytic enzymes and toxic oxygen radicals [17]. The consequence is a swelling of endothelial cells, fluid and plasma extravasation [19]. In the case of the lungs, alveolar pneumocytes disrupt, alveoli fill with inflammatory debris and red blood cells, finally leading to severe pulmonary dysfunction [20]. The clinical picture that follows can be barely noticeable symptoms leading to lethal respiratory failure [8]. In general, about 1.7% of CPB patients develop adult respiratory distress syndrome (ARDS). But when acute severe lung injury occurs, mortality is high [17]. Recent studies have shown an activation of both humoral and cellular components of the inflammatory system in response to CPB [21]. Interestingly, not only the peak of the systemic inflamma-

![Fig. 1. Pulmonary venous levels of IL-6 and IL-8 expressed in percentage of right atrial values at 1, 10 and 20 min reperfusion in Routine Circulation (■) and Bilateral Circulation (●). Mean ± SEM; between-group significance levels are placed above error bars.](image-url)
tory response takes place 2–4 h after termination of CPB [22], but also the slope of the increase observed after termination of CPB is much steeper than that during CPB [22]. Thus, reperfusion of the previously ischemic heart and lungs seems to promote this phenomenon. In fact, after release of the aortic cross-clamp the production of inflammatory mediators and cellular activation has been shown during reperfusion of the heart [4]. However, because only about 5% of the cardiac output perfuses the heart, the cardiac inflammatory reaction would not be expected to lead to a considerable increase of systemic levels of inflammatory mediators. In contrast, the entire cardiac output passes the lungs as soon as CPB is terminated. With ongoing pulmonary cytokine release even after termination of CPB, the lungs would thus be a major promoter of the systemic inflammatory response. Accordingly, with the use of the Drew technique, the attenuation of the systemic inflammatory response at the time of the expected peak levels has been shown to be comparable with the results achieved by using anti-inflammatory substances such as high-dose steroids [8].

The impact of our results on routine CABG procedures has to be further evaluated. We are currently investigating whether the Drew technique is a viable option in high-risk patients with compromised pulmonary function in whom continuous perfusion and ventilation of the lungs during surgery may reduce postoperative morbidity and mortality. It will also be important to compare the benefits of the Drew technique with minimally invasive techniques. In addition to maintaining lung perfusion, minimally invasive CABG is performed without an extracorporeal circuit, without, however, offering a blood- and motionless surgical field as does the Drew technique.

In conclusion, there is a considerable increase of cytokine levels in blood emerging from the pulmonary vascular bed during the early phase of pulmonary reperfusion after declamping of the aorta in CABG patients. In contrast, no such increase is found in patients operated with the Drew technique of bilateral extracorporeal circuits. In addition, retention of activated leukocytes and platelet–monocyte coaggregates is less in patients operated with the Drew technique. Two factors are deemed responsible for the observed effects. First, no artificial oxygenator with the intrinsic problem of contact activation is needed using the Drew technique. The patient’s lungs function as oxygenators. Second, during cardiac ischemia, there is no reduction...
in pulmonary flow or oxygen delivery to the lungs. Accord-
ingly, the pathophysiological changes of pulmonary reper-
fusion are prevented.

Acknowledgements

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References


Appendix A. Conference discussion

L. von Segesser (Lausanne, Switzerland): Just to make up our minds, you didn’t use an oxygenator in this system?

Dr Massoudy: No.

Dr von Segesser: And handling of patients with chronic obstructive pulmonary disease was no problem, the lungs coming over the heart and so on?

Dr Massoudy: You mean a surgical problem in the sense of the lungs intruded the surgical field?

Dr von Segesser: Yes.

Dr Massoudy: No, it wasn’t. But I must say, we only had one patient with chronic obstructive lung disease in that group.

Dr von Segesser: In this one it was no problem?

Dr Massoudy: No. And in the others it wasn’t also.

Dr J. Svennevig (Oslo, Norway): What do you think is the most important site of cytokine production during cardiopulmonary bypass?

Dr Massoudy: Well, the activation that occurs during passage of the lung is astonishing during reperfusion, so I think besides the oxygenator as the artificial blood gas surface which is used in the conventional technique, we have the problem of organ reperfusion. And this study is part of the investigation of the lung response, and obviously the lung response seems to be much more important in that sense as opposed to the heart, which we performed studies on before. And more important, the entire cardiac output has to pass the lungs, whereas only 5% of the cardiac output perfused the heart. So I think the lungs are very important in that sense.

Dr von Segesser: Is it lung ischemia or lack of metabolic function of the lung that brings up the problems?

Dr Massoudy: Well, it is hard to quantify the amount of bronchial artery flow. So I think it is mainly lung ischemia.

Dr V. Subramanian (New York, NY, USA): This is a very ingenious model you have presented, which may be extended to beating heart surgery because it will obviously provide a tremendous decompression of the right and the left heart to do complete revascularization, and I am not sure what the leukocyte response would be on that. Are you planning to extend the old model you have presented, which may be extended to beating heart surgery?
first phase of this study. Perhaps you ought to try to do this in a beating heart. It would be an ideal, interesting model.

**Dr A.M. El Gamel (London, UK):** The results that you have shown us today are quite interesting, but I am quite perplexed about the clinical implications of what you have done today, because the lung problems that we see postoperatively, if you are talking about ARDS, comprise a very small percentage. Most of the patients who go on bypass have release of cytokines. Why don’t all of them have problems with their lungs? And that is the question that we need to answer. Although the cytokines are released, it doesn’t mean that all these patients would be harmed by the release of cytokines. There are other mechanisms that protect the patients from the inflammatory cascade. And only a small proportion of the patients probably cannot cope with the inflammation, so how are you going to apply a procedure to every patient you operate on to catch the 1% that is going contract ARDS postoperatively, and have you got any thoughts on that?

**Dr Massoudy:** As I said, looking at the previous study, not only preliminary inflammatory response but lung function was also improved. And what I didn’t show because it wasn’t actually standardized, was that intubation time was shorter and stay in the intensive care unit was shorter. So these are factors that influence overall organization of the cardiothoracic department, I think, and actually can accelerate the patient’s recovery.

**Dr El Gamel:** So how many patients normally in your practice have you been able to extubate early and how many you think with using this technique you will be able to reach? How big a percentage of improvement is in this technique routinely where it will have an impact on your work?

**Dr Massoudy:** Well, I think the technique is applicable to every patient, but standardized studies and randomized studies will have to show how much the improvement actually is.

**Dr L. Parenzan (Bergamo, Italy):** This paper took me back to the year when I read for the first time in the Lancet this Drew technique. You know, it was a very important paper because it was treating Down’s syndrome, complete correction of Down’s syndrome, the AV canal, in very small children. So this was pushing us to tell us of early repair of congenital heart disease. Now, I have been interested very much in trying to do cardiac surgery in the eastern part of Africa, actually in Nairobi, and I did find many problems, and the main problem is money; money in order to buy valves and oxygenators. Would you think it would be possible right now, in 1999, to use the Drew technique without an oxygenator in underdeveloped countries?

**Dr Massoudy:** Well, it is a technique without an oxygenator, so you could use it anywhere in the world without an oxygenator, and actually there are some papers which were published in the 1980s using a similar technique without an oxygenator, and at that time cost and money was actually a motive to investigate and put the method into practice.