Respiratory dysfunction after cardiac surgery: effects of avoiding cardiopulmonary bypass and the use of bilateral internal mammary arteries

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Abstract

Background: The quantitative contribution of cardiopulmonary bypass (CPB) to respiratory dysfunction after cardiac surgery is not documented and the effect of the use of bilateral internal mammary artery (IMA) grafts is not clear. Methods: One hundred and seventy-five patients undergoing CABG with (CPB, n = 150) and without (NOCPB, n = 25) CPB were studied. PMN elastase (as a marker of the systemic inflammatory response) and serial arterial oxygen (paO₂) and carbon dioxide (paCO₂) tension, alveolar arterial oxygen (AaO₂) gradient and percent saturation were measured. The CPB group was subdivided into three groups by the number of IMA grafts used: 0IMA (n = 12), 1IMA (n = 82) and 2IMA (n = 51). Results: The NOCPB group was younger, had significantly better preoperative blood gases, received fewer grafts and had lower PMN elastase levels than the CPB group. In both groups maximum respiratory dysfunction occurred at 48 h (paO₂, percentage saturation and Aa gradient all P < 0.001 versus baseline) with partial recovery by 5 days. The percentage decline and subsequent recovery in all blood gas parameters was near identical in the CPB and NOCPB groups. Amongst the three IMA groups the percentage changes in all blood gas parameters were similar, as was the duration of postoperative ventilation and time to discharge. There was no correlation between blood gas parameters at 48 h with age, CPB time, blood loss, duration of ventilation or peak PMN elastase level. Conclusions: Changes in postoperative gas exchange are similar in patients undergoing CABG with and without CPB even although PMN elastase levels indicate that CPB produces a more marked inflammatory response. The use of 2IMA compared with 1IMA does not increase respiratory dysfunction. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Respiratory; Pulmonary; Cardiopulmonary bypass; Internal mammary artery

1. Introduction

Respiratory dysfunction is one of the most frequent complications of coronary artery bypass grafting (CABG) [1]. Its pathophysiology is complex and reflects the combined effects of general anaesthesia, surgical injury, median sternotomy and cardiopulmonary bypass (CPB) to produce hypoxia, atelectasis, pleural effusion and dysfunction of the diaphragm.

We previously reported that cardiac surgery using CPB produces greater respiratory dysfunction than general surgical operations, consistent with the hypothesis that lung injury after CPB is due, at least in part, to a generalized systemic inflammatory response syndrome [2,3]. Theoretically and intuitively, therefore, the avoidance of CPB in CABG patients should reduce postoperative respiratory dysfunction.

Furthermore, while there is general agreement that the use of a single IMA graft causes increased pleuropulmonary morbidity in comparison to the use of only vein grafts [5–9] there are few data comparing changes in respiratory function, as opposed to chest wall mechanics [10–13], in patients receiving single or bilateral IMA grafts.

Consequently, two specific questions were posed in this study:

(i) Does avoidance of CPB reduce postoperative respiratory dysfunction?
(ii) Does the use of bilateral IMA grafts increase postoperative respiratory dysfunction?

To answer these serial arterial oxygen (paO₂) and carbon dioxide (paCO₂) tensions, alveolar arterial oxygen (AaO₂) gradients and saturation percentage (% saturation) were measured in 150 patients undergoing CABG with CPB and 25 patients undergoing CABG without CPB (NOCPB). Additionally PMN elastase, a major constituent of polymorphonuclear leukocyte granules and stimulated by any factors which activate white blood cells including CPB.
[14,15] was used to quantify the severity of the systemic inflammatory response syndrome.

### 2. Methods

#### 2.1. Patients

The patients and the study from which they are drawn have been described in detail previously [16]. Briefly, the 150 CPB patients in the current study constituted the study population of a randomized control trial of an anti-inflammatory agent (which showed no statistically significant difference for respiratory performance between active and placebo groups) between February 1996 and March 1997. The inclusion criteria for that study included patients undergoing first time CAGB for angiographically demonstrated coronary stenoses. Exclusion criteria included emergency surgery, significantly impaired ventricular function (ejection fraction < 30%) or a previous cerebrovascular accident.

The 25 patients undergoing CAGB without CPB (NOCPB) were from a group of 26 such patients operated consecutively between March 1996 and February 1997. One patient who underwent emergency surgery was excluded. The NOCPB patients were defined solely by the absence of circumflex coronary artery disease on preoperative coronary angiography and otherwise met all criteria to be entered into the anti-inflammatory trial.

#### 2.2. Anaesthesia

The CPB and NOCPB patients received the same anaesthetic regimen. Premedication was achieved with morphine (10–15 mg) and scopolamine (0.3–0.4 mg). Anaesthesia was induced with fentanyl (1 mg), pancuronium (8 mg), and etomidate (4–10 mg). Anaesthesia was maintained with a combination of oxygen, nitrous oxide, and halothane before CPB, and during CPB with propofol (6 mg/kg per h). Benzodiazepines were not used.

#### 2.3. Surgery

All operations were performed through a median sternotomy incision. Harvest of the IMA, whether single or bilateral was accompanied by pleurotomy and chest drainage of each pleural cavity entered and the mediastinum with separate drains.

CAGB without CPB was performed in patients requiring grafts to any coronary vessels excluding the circumflex marginal or its branches. These patients received half dose heparin and the heart was displaced medially with a swab placed in the left side of the pericardium. This usually reduced the mean arterial pressure to 50–60 mmHg but if necessary a short acting β-blocker was added to reduce blood pressure to this level. Stay sutures placed proximal and distal to the intended site of anastomosis secured the coronary artery. Proximal anastomoses, where relevant, were constructed with a side-biting clamp occluding a palpably normal portion of ascending aorta.

#### 2.4. Cardiopulmonary bypass (CPB)

CPB was achieved using a pump flow rate of 2.4 l/m² per min at normothermia with temperature allowed to drift to 34°C. Topical cooling was not used, and there was no direct or indirect left ventricular venting. A Cobe CML membrane oxygenator (Cobe Cardiovascular Inc., Arvada) and a roller pump producing non-pulsatile flow were used without an arterial line filter. Alpha stat control of acid-base management was used and the mean arterial pressure maintained between 50 and 60 mmHg with pharmacological manipulation if necessary. Distal anastomoses were constructed during brief periods (approximately 10 min) of aortic clamping and induced fibrillation. On completion of the distal anastomosis the aortic clamp was released and the proximal anastomosis was constructed after isolation of a portion of the ascending aorta in a side-biting clamp. If the heart did not defibrillate spontaneously, this was achieved with 10–20 J.

#### 2.5. Perioperative ventilation

During anaesthesia the lungs were ventilated with 100% O₂. During CPB the lungs remained collapsed. In the postoperative period ventilation was managed according to blood gases resulting from a standardized protocol of supplementary intermittent mandatory ventilation (SIMV) consisting of:

- Ten breaths per min;
- tidal volume of 10 ml/kg of body weight;
- FiO₂ (inspired oxygen) of 60%;
- pressure support of 20 cmH₂O;
- positive end expiratory pressure (PEEP) of 5 cmH₂O;
- inspiratory/expiratory ratio of 1:2.

#### 2.6. Postoperative management

All patients were managed by the same standardized cardiovascular, respiratory and renal protocols aimed at early extubation. Timing of extubation was managed by nursing staff in alert, haemodynamically stable patients capable of maintaining self ventilation. Chest tubes were left in situ until the first postoperative day and when drainage was less than 100 ml in the previous 5 h.

#### 2.7. Blood gas sampling and analysis

Blood gases were taken pre-dose and at 1, 6, 24 and 48 h and 5 days. For the preoperative, 48-h and 5-day samples the patient breathed room air for 10 min to allow for equilibration and then samples of arterial blood were taken for oxygen partial pressure (paO₂) and carbon dioxide partial
pressure (paCO\(_2\)). The Aa gradient was calculated from these values [1]. If the patient was ventilated and highly dependent on FiO\(_2\), the samples were taken without equilibrating to room air. Arterial oxygen saturation was obtained from blood gas determinations.

2.8. Statistical analysis

Statistical analysis was undertaken using the SPSS (version 9.0; SPSS Inc., Chicago, IL) computer program. The Kolmogorov–Smirnov test was used to check for normality of data in the two groups before further analysis. Data for most variables is presented as means (SD) and medians and IQ (25th–75th percentile) ranges. Confidence intervals for normally distributed data between the groups was compared with \(t\)-tests for independent samples. Confidence intervals for data that was not normally distributed were calculated after logarithmic transformation and examination by \(t\)-tests for independent samples between the groups. Comparisons of normally distributed tests within the CPB group were performed with analysis of variance (ANOVA) and post hoc analysis with \(t\)-tests for independent samples. Within the CPB group data that was not normally distributed was examined with the Kruskal–Wallis test with post hoc Mann–Whitney tests and Bonferroni correction. Depending on normality of data distribution, Pearson or Spearman rank correlation coefficients were determined to investigate correlations between paO\(_2\), Aa gradient and % saturation at 48 h with age, CPB time, blood loss, duration of ventilation or peak PMN elastase level. A Bonferroni correction was used to allow for multiple comparisons amongst the groups so that a \(P\)-value of less than 0.005 was considered significant.

3. Results

The 150 CPB patients were drawn from an anti-inflammatory study which showed no significant difference in respiratory performance between the active and placebo groups. Of 150 CPB patients, three (2%) died within 5 days of surgery.

3.1. CPB vs. NOCPB group

Patient demographics of the 150 CPB and 25 NOCPB patients are summarized in Table 1. PMN elastase levels were significantly greater in the CPB group at all time points (Table 2). The CPB group was older by a mean of 4 years (\(P < 0.05\)) and received more grafts (2.8(0.6) vs. 1.5 (0.5): \(P < 0.000\)) than the NOCPB group. Absolute and percent changes from baseline in paO\(_2\), Aa gradient, % saturation and paCO\(_2\) for the CPB and NOCPB groups are shown in Table 3. The NOCPB group had a marginally higher preoperative paO\(_2\) (\(P \approx 0.09\)) and lower Aa gradient (\(P < 0.001\)). In both groups postoperative percentage changes in all respiratory parameters were near identical with paO\(_2\) and % saturation reaching a nadir at 48 h (both \(P < 0.001\)) accompanied by the maximum increase in the Aa gradient (\(P < 0.001\)). All parameters demonstrated partial recovery by 5 days although still remaining significantly (\(P < 0.001\)) impaired in comparison to baseline values. paCO\(_2\) fell to nadir at 5 days (\(P < 0.001\)). The postoperative ventilation time was longer in the CPB group by a mean of 1.6 h (95% confidence interval (CI): -0.4–3.5 h).

<table>
<thead>
<tr>
<th>Variable</th>
<th>NOCPB</th>
<th>CPB</th>
<th>(P)-value</th>
<th>Mean (95% CI) difference CPB vs. NOCPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 (10)</td>
<td>62 (9)</td>
<td>NS</td>
<td>4 (-8 to -0.3)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>0</td>
<td>65 (20)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>1.5 (0.5)</td>
<td>2.8 (0.6)</td>
<td>&lt;0.001</td>
<td>1.3 (0.7 to 1.6)</td>
</tr>
<tr>
<td>Ventilation (h)</td>
<td>2.8 (2.2)</td>
<td>4.4 (4.3)</td>
<td>NS</td>
<td>1.6 (3.5 to -0.4)</td>
</tr>
<tr>
<td>Discharge (days)</td>
<td>6.7 (2.4)</td>
<td>6.6 (3.3)</td>
<td>NS</td>
<td>0.6 (1.6 to -1.6)</td>
</tr>
</tbody>
</table>

\(^a\) First line, mean (SD), second line, median and IQ (25th–75th percentile) range.
\(^b\) Data not normally distributed and CI calculated after log transformation.

Table 2

Serial release of PMN elastase, expressed as median and IQ range in the CPB and NOCPB group

<table>
<thead>
<tr>
<th>PMN elastase (µg/l)</th>
<th>NOCPB (n = 21)</th>
<th>CPB (n = 150)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop.</td>
<td>24 (17–31)</td>
<td>44 (36–54)</td>
<td>0.000</td>
</tr>
<tr>
<td>1 h</td>
<td>33 (25–44)</td>
<td>110 (76–163)</td>
<td>0.000</td>
</tr>
<tr>
<td>6 h</td>
<td>34 (29–49)</td>
<td>99 (80–1221)</td>
<td>0.000</td>
</tr>
<tr>
<td>24 h</td>
<td>37 (32–60)</td>
<td>105 (86–123)</td>
<td>0.000</td>
</tr>
<tr>
<td>48 h</td>
<td>43 (35–60)</td>
<td>129 (104–153)</td>
<td>0.000</td>
</tr>
<tr>
<td>5 days</td>
<td>36 (24–46)</td>
<td>81 (62–103)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
although this failed to reach statistical significance. The duration of post operative stay was similar in both groups.

### 3.2. Effects of no, single or bilateral IMA grafts (Tables 4 and 5)

The CPB group was subdivided into three groups by the number of IMA grafts used (0IMA = no IMA grafts; 1IMA = single IMA graft; 2IMA = bilateral IMA grafts). No formal criteria were employed to determine which type of graft each patient received. The groups were similar in terms of age, and preoperative PaO\(_2\), PaCO\(_2\), Aa gradient and % saturation. Although the single and bilateral IMA groups received significantly more grafts and had significantly longer CPB times than the group receiving only vein grafts (Table 4), the only difference in absolute or percentage changes in any respiratory parameter amongst the three groups was percentage saturation at 48 h (Table 5). This was clinically insignificant at less than 1% amongst the three groups and while reaching a conventional level of significance (P = 0.03), disappeared after Bonferroni correction for multiple comparisons (P < 0.005).

### 3.3. Correlations (Table 6)

There was no significant correlation between PaO\(_2\), Aa gradient and % saturation at 48 h with age, CPB time, blood loss, duration of ventilation or peak PMN elastase level.

### 4. Discussion

The major potential limitation of this study lies in the design weakness of non-randomization. A randomized trial of an anti-inflammatory agent in CPB patients had already begun when the feasibility of CABG without CPB was advocated. The NOCPB patients were, however, exclusively defined by the absence of disease in the circumflex territory and otherwise met all the criteria to be entered into the anti-inflammatory trial. However, as less than 2% of our patients were considered suitable for CABG without CPB,
at that time, it was impractical during the time frame of the study to randomize these patients to CPB or NOCPB.

The major reason for studying the NOCPB patients was the expectation that avoidance of CPB would reduce lung injury. In a previous study we demonstrated that respiratory dysfunction was greater in patients undergoing cardiac surgery than general surgery. Our assumption that the difference was largely due to CPB was consistent with the hypothesis that the general inflammatory response associated with CPB allows macromolecules to enter the pulmonary interstitium and the alveoli contributing to respiratory dysfunction [2,3].

The current study confirms our previous report that maximum respiratory dysfunction is observed on the second day after cardiac surgery [1]. It extends the findings of that study in demonstrating near identical changes in respiratory function in patients undergoing CABG without CPB. Although absolute blood gas parameters were significantly better both preoperatively and at 5 days in the NOCPB group, deterioration and subsequent recovery in each parameter, expressed as a percentage change from baseline, was similar in both groups.

This counter-intuitive observation is even more surprising given that CPB, as evidenced by PMN concentrations, results in a more severe systemic inflammatory response syndrome and that the NOCPB group were younger, had better preoperative respiratory status and received fewer grafts. These results suggest that contemporary CPB for durations of up to 90 min is quantitatively of little aetiological importance in postoperative respiratory dysfunction compared with that reported over the last two decades [2,3]. In support of this view is the lack of correlation between any parameter of respiratory dysfunction and duration of CPB or peak PMN elastase (Table 6). This hypothesis is also consistent with our recent report that contemporary CPB plays little role in subclinical cerebral dysfunction, as defined by neuropsychological testing, after cardiac surgery and that, quantitatively, median sternotomy and/or general anaesthesia may be more relevant [16].

In comparison to our previous study the deterioration in \(\text{paO}_2\) and Aa gradient in this study was less severe and with more marked recovery by the fifth postoperative day although the current patients were older and with more impaired preoperative blood gases [1]. In our previous study 25% of patients still had a \(\text{paO}_2\) less than 8.0 kPa (60 mmHg) breathing room air on the fifth day compared with 18% in this study. The most likely explanation for this difference is improvement in anaesthetic management techniques such as early extubation and continuing refinement in extracorporeal perfusion technology (e.g. in our previous study a bubble oxygenator was employed compared a to a membrane oxygenator in the current study).

### Table 5
Changes in blood gas parameters (mean (SD) [%change from baseline]) in the three IMA groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No IMA</th>
<th>One IMA</th>
<th>Two IMA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>87</td>
<td>51</td>
<td>–</td>
</tr>
<tr>
<td>(\text{paO}_2) (pre)</td>
<td>10.8 (0.5) 100%</td>
<td>10.6 (1.4) 100%</td>
<td>10.2 (1.0) 100%</td>
<td>NS</td>
</tr>
<tr>
<td>(\text{paO}_2) (48 h)</td>
<td>7.6 (1.1) 72%</td>
<td>7.5 (1.3) 71%</td>
<td>7.7 (1.5) 75%</td>
<td>NS</td>
</tr>
<tr>
<td>(\text{paO}_2) (5 days)</td>
<td>9.4 (1.2) 87%</td>
<td>8.9 (1.1) 84%</td>
<td>8.9 (1.1) 87%</td>
<td>NS</td>
</tr>
<tr>
<td>(\text{paCO}_2) (pre)</td>
<td>5.2 (0.3) 100%</td>
<td>5.0 (0.4) 100%</td>
<td>5.1 (0.4) 100%</td>
<td>NS</td>
</tr>
<tr>
<td>(\text{paCO}_2) (48 h)</td>
<td>4.4 (0.6) 85%</td>
<td>4.6 (0.6) 92%</td>
<td>4.6 (0.5) 90%</td>
<td>NS</td>
</tr>
<tr>
<td>(\text{paCO}_2) (5 days)</td>
<td>4.2 (0.5) 81%</td>
<td>4.3 (0.5) 86%</td>
<td>4.2 (0.4) 82%</td>
<td>NS</td>
</tr>
<tr>
<td>Aa gradient (pre)</td>
<td>4.0 (0.6) 100%</td>
<td>4.3 (1.3) 100%</td>
<td>4.7 (1.0) 100%</td>
<td>NS</td>
</tr>
<tr>
<td>Aa gradient (48 h)</td>
<td>7.9 (1.5) 198%</td>
<td>9.9 (8.8) 230%</td>
<td>11.0 (12.2) 234%</td>
<td>NS</td>
</tr>
<tr>
<td>Aa gradient (5 days)</td>
<td>6.3 (1.5) 156%</td>
<td>7.3 (4.4) 170%</td>
<td>6.8 (1.2) 145%</td>
<td>NS</td>
</tr>
<tr>
<td>% Saturation (pre)</td>
<td>96.0 (0.5) 100%</td>
<td>95.8 (1.7) 100%</td>
<td>95.2 (1.5) 100%</td>
<td>NS</td>
</tr>
<tr>
<td>% Saturation (48 h)</td>
<td>90.6 (3.7) 94%</td>
<td>89.6 (4.0) 94%</td>
<td>89.5 (4.8) 94%</td>
<td>NS</td>
</tr>
<tr>
<td>% Saturation (5 days)</td>
<td>94.9 (1.6) 99%</td>
<td>94.0 (2.1) 98%</td>
<td>94.1 (2.0) 99%</td>
<td>NS</td>
</tr>
</tbody>
</table>

a All units measured in kPa except % saturation. NS, not significant.

b Data not normally distributed.

### Table 6
Pearson or Spearman rank correlation coefficients (\(r\)-value) and significance

<table>
<thead>
<tr>
<th></th>
<th>(\text{paO}_2) (48 h) (r)-value</th>
<th>(P)-value</th>
<th>Aa gradient (48 h) (r)-value</th>
<th>(P)-value</th>
<th>% Saturation (48 h) (r)-value</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.067</td>
<td>NS</td>
<td>0.136</td>
<td>NS</td>
<td>0.073</td>
<td>NS</td>
</tr>
<tr>
<td>CPB time</td>
<td>-0.13</td>
<td>NS</td>
<td>0.001</td>
<td>NS</td>
<td>-0.014</td>
<td>NS</td>
</tr>
<tr>
<td>Blood loss</td>
<td>-0.065</td>
<td>NS</td>
<td>0.082</td>
<td>NS</td>
<td>-0.091</td>
<td>NS</td>
</tr>
<tr>
<td>Ventilation (h)(^a)</td>
<td>-0.033</td>
<td>NS</td>
<td>0.025</td>
<td>NS</td>
<td>-0.057</td>
<td>NS</td>
</tr>
<tr>
<td>PMN elastase (peak)(^a)</td>
<td>0.078</td>
<td>NS</td>
<td>0.135</td>
<td>NS</td>
<td>0.083</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) Spearman rank correlation.
The optimal management of the lungs during surgery and in the perioperative period remains to be defined. It is our practice to disconnect the lungs during CPB. Boldt and colleagues reported that static inflation with air and moderate positive end expiratory pressure (+5 cmH2O) reduced the accumulation of extravascular lung water up to five hours after the termination of CPB [17]. The potential clinical relevance of this finding, however, is uncertain as they did not provide data on the effects of this policy on gas exchange indices at 48 h when maximum respiratory dysfunction is apparent [17].

Although the NOCPB ventilation times were a mean of 96 min shorter than the CPB group, this should be interpreted cautiously as there was an expectation by the nursing staff in charge of extubation that the NOCPB patients should be extubated more quickly. This did not result in earlier discharge (although all patients were requested to stay until at least the fifth postoperative day to complete the study).

Most studies assessing the effects of bilateral IMA grafts on respiratory function have concentrated on chest wall mechanics with few data regarding effects on gas exchange. Using a variety of functional and clinical end points, but excluding data on arterial blood gases, increased [10,11] and no difference [12,13] in pleuropulmonary morbidity between the use of a single and bilateral IMA grafts has been reported. In one small study comparing 60 single and ten bilateral IMA grafts Singh and colleagues found no difference in arterial blood gases [4]. The current study clearly demonstrates no additional adverse respiratory effect by the use of bilateral IMA grafts in patients with at least moderate ventricular function and relatively short CPB times. Although the bilateral IMA group had worse pre-operative respiratory function than the single IMA group there was no significant difference in any blood gas parameter between these groups in the postoperative period.

The mean increase in ventilation time in the bilateral as opposed to single IMA group was 1 h, although this did not reach statistical significance. Ventilation times in our unit are shorter than those generally reported in literature for similar operations [10] and mean ventilation times were less than 5 h for patients receiving one or two IMA grafts.

Singh and colleagues previously reported that mild respiratory alkalosis after CABG was due to a compensatory hyperventilation in response to decreased oxygen levels [4]. This does not, however, explain the continuing decrease in paCO₂ in our patients between the second and fifth postoperative days when paO₂ had partially recovered. It may reflect a relatively faster and shallower form of respiration in response to decreasing analgesic therapy although respiratory rate was not measured.

Interestingly, there was no correlation between any parameter of maximum lung injury at 48 h with age, CPB time, blood loss, duration of postoperative ventilation or peak PMN elastase level.

In summary, this study suggests that the avoidance of CPB has little beneficial effect on respiratory dysfunction after cardiac surgery and that the use of bilateral IMA grafts does not increase functional respiratory injury.

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