Immune Dysfunction After Cardiac Surgery with Cardiopulmonary Bypass: Beneficial Effects of Maintaining Mechanical Ventilation

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Conflicts of interest: none

Words count: 2480

Key words: Cardiopulmonary bypass, cardiac surgery, mechanical ventilation, immune dysfunction, myeloid derived suppressor cells

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Abstract

Introduction: Cardiac surgery with cardiopulmonary bypass (CPB) induces postoperative immunosuppression and impaired pulmonary function. Maintaining mechanical ventilation (MV) during CPB improves pulmonary function and diminishes postoperative systemic inflammation. However, there is no data about the influence of maintaining MV during CPB on postoperative immune dysfunction.

Material and methods: 50 patients were prospectively divided into two groups: without MV during bypass (n=25) and dead space MV with PEEP (n = 25). PaO_2/FiO_2 ratio, CXCL10, CCL2, TNF-α, IL-10, HLA-DR, monocytic myeloid-derived suppressor cells (Mo-MDSC, $CD14^+HLA-DR^{lo/-}$ monocytes) and blood cell count were collected before and after surgery.

Results: CPB induced a marked immunosuppression with a significant increase of plasmatic levels of TNF-α and IL-10, and a significant decrease in HLA-DR monocytic expression. The postoperative proportion of Mo-MDSC was subsequently significantly increased. Maintaining MV during CPB significantly improved PaO_2/FiO_2 ratio and decreased postoperative plasmatic levels of TNF-α and IL-10 compared to patients without MV during CPB. Furthermore, non-ventilated patients had a lower lymphocyte count after surgery compared to patients with MV during CPB.

Conclusion: Our study suggests that maintaining MV during CPB for cardiac surgery decreases postoperative immune dysfunction and could be an interesting strategy to diminish the occurrence of postoperative nosocomial infection without hampering the surgical procedure. However, these findings have to be confirmed in a clinical trial using the incidence of nosocomial infection as an endpoint.

Introduction

Cardiopulmonary bypass (CBP) during cardiac surgery induces a systemic inflammatory response associated with an immune dysregulation and a significant pulmonary dysfunction [1-5]. These two phenomena have been well characterized. Firstly, the inflammatory response, usually attributed to surgical trauma, contact of blood with artificial surfaces and ischemia-reperfusion injury, is responsible for a postoperative immunodepression. Mekontso et al. have shown that bactericidal activity of polymorphonuclear neutrophils against *Staphylococcus aureus* was decreased after cardiac surgery [3]. In a prospective study, Chalk et al. have also reported a dysfunction of pulmonary macrophages after CPB. In particular, they have described an early impairment of lung cellular immune response, which could promote the development of postoperative pneumonia [6]. Along these lines, a down-regulation of human leucocyte antigen-DR antigen (HLA-DR) expression on monocytes and an increase of plasma interleukine (IL)-10 associated with the occurrence of nosocomial infections have been reported [4,6,7]. Secondly, CPB induces a pulmonary dysfunction which ranges from a temporary and clinically insignificant reduction in arterial oxygenation to a life-threatening injury manifested as acute respiratory distress syndrome. This phenomenon is of multifactorial sources but one of the main mechanisms is the occurrence of atelectasis during surgery [8-15]. Atelectasis have been associated with lung injury and release of cytokines (TNF-α) by shear forces on alveoli and small airways [12-15]. However, it is not clear whether this injury is due to a recruitment/de-recruitment phenomenon (ie atelectrauma) or whether it might by itself lead to the release of cytokines [15-17]. Nevertheless, addition of a positive end-expiratory pressure (PEEP) during CPB for cardiac surgery diminished the occurrence of atelectasis and the postoperative inflammatory response without hampering the surgical progress [10-12].

Since maintaining mechanical ventilation (MV) with PEEP during CPB diminishes postoperative inflammation, a relationship between pulmonary dysfunction and postoperative immunosuppression should be investigated. We thus conducted a prospective study to

investigate the effects of maintaining lung ventilation during CPB in patients undergoing cardiac surgery on postoperative immune dysfunction using IL-10 and HLA-DR as major endpoints. We also investigated the CD14$^+$HLA-DR$^{lo/-}$ monocytes, which have been described as immunosuppressive monocytic myeloid derived suppressor cells (Mo-MDSC) in humans [18-20], before and after CPB.

Materials and methods

Patient population

All patients were > 18 years old and were scheduled for cardiac surgery using cardio-pulmonary bypass (valve replacement and/or coronary artery bypass grafting).

Exclusion criteria were as follows: systemic steroid therapy, chronic lung diseases (including chronic obstructive or restrictive pulmonary diseases), left ventricular dysfunction (left ventricular ejection fraction <50%) and the need for vasopressor or inotropic agents before surgery.

Anaesthesia, CPB, and surgical procedure

General anaesthesia was induced with propofol, sufentanil 0.3μg/kg and was followed by cisatracurium 0.15 mg/kg for muscular relaxation. Anaesthesia, muscle relaxation and analgesia were respectively maintained with inhalated sevoflurane during off-pump surgery or propofol infusion during CPB, boluses of atracurium and sufentanil. Baseline ventilation: the patients received volume-controlled ventilation with a tidal volume of 8 mL/kg of predicted body weight (PBW) and a ventilatory frequency of 10–15 b.p.m. ($PETCO_2$ between 34 and 38 mmHg). Inspired oxygen fraction (FiO_2) was 0.50, inhalation: exhalation ratio was 1:2, and the level of positive end-expiratory pressure (PEEP) was 5 cmH2O.

During CPB, two settings were used depending on the surgeon in charge: (1) absence of mechanical ventilation (and no positive end-expiratory pressure) by disconnecting the tracheal tube from the ventilator (MV- group), (2) dead space ventilation using tidal volume of 2.5 mL/kg (predicted body weight, PBW) with 5cmH$_2$O PEEP (MV+ group). After CPB, ventilatory parameters were turned back to to baseline settings and no recruitment manoeuvres were performed before oxygenation determination. PaO_2 /FiO_2 was obtained before surgery (after induction of anaesthesia) and 3 h after the end of CPB in the surgical intensive care unit (under baseline mechanical ventilation settings). We took advantage of the different ventilatory settings that are commonly used by the surgeon and the anaesthetist

in charge: consequently, the patients were not randomised in the different ventilatory settings for the purpose of this study. The study was approved by our Local Ethics Committee. Patients were informed of the observational nature of the study and gave their consent. The design of the study is summarized in Figure 1*A*.

Study procedures.

Blood samples treated with heparin were collected for all patients immediately after induction of anesthesia (T1) and within an hour following the end of intervention (T2). The delay between blood sampling and the beginning of laboratory procedures was <1h. Plasma samples were stored at -80°C until use.

Flow cytometry. The level of HLA-DR expression on monocytes was measured on whole blood using fluorescein isothiocyanate-conjugated anti-human leukocyte antigen DR (HLA-DR-FITC, Beckman Coulter) with isotype- and fluorophore-matched control to confirm binding specificity, and phyco-erythrin-cyanin-7 anti-CD14 antibody (CD14-PC7; Beckman Coulter). Samples were run on a flow cytometer (Navios, Beckman Coulter) and data were analysed using Kaluza software (Beckman Coulter). Monocytes were characterized on the basis of their CD14 expression (See Figure 1*B* for gating strategy).

ELISA

TNF-α, IL-10, C-X-C motif chemokine 10 (CXCL10) and chemokine ligand 2 (CCL2) were quantified by DuoSet ELISA (R&D Systems, Abingdon, UK) in peripheral blood plasma according to the manufacturer instructions.

Data collection

The following data were collected: Age, Body Mass Index (BMI), central venous pressure (CVP) and mean pulmonary arterial pressure (mPAP) before and after CPB, PaO_2/FiO_2 ratio before and after CPB, type of heart surgery (valvular replacement, coronary artery bypass grafting (CABG) or mixed), surgery duration, ICU and hospital length of stay. The occurrence of postoperative infections (nosocomial infections) within 14 days was also recorded and defined as previously described [21]. Lastly, blood cell count with differential (including lymphocyte, neutrophil (PMN), and monocyte counts) was collected before and after surgery.

Statistical analysis

Quantitative variables were expressed as median and interquartile range (IQR). Differences observed between groups were analyzed using the nonparametric Mann-Whitney U test. In each group, differences between pre- (T1) and post-CBP times (T2) were analyzed using the Wilcoxon matched-pairs signed rank test. Correlations between two continuous variables were investigated using the nonparametric Spearman rank correlation test. All statistical analyses were performed using GraphPad Prism Version 5 (GraphPad Prism Software Inc) at a significance level of $p < 0.05$.

Results

Patients characteristics

50 patients completed the study. The baseline characteristics are given in Table 1. No difference was found between the two groups except for body mass index (BMI).

Effects of maintaining MV during CPB on pulmonary function

The effects of mechanical ventilation on outcome as well as clinical parameters are summarized in Table 2. Of note, maintaining MV during CPB did not influence procedure duration.

Maintaining MV during CPB significantly improved postoperative PaO_2 /FiO_2 ratio (+6% in ventilated patients vs. -15% in non-ventilated patients, p= 0.005, Figure 2*A*). No difference was found between the two groups regarding hemodynamic parameters (CVP and mPAP) before and after CPB (Table 1). Lastly, MV duration, length of stay in ICU and hospital stay were not different between the two groups.

Plasmatic levels of CXCL10 and CCL2 were significantly increased after cardiac surgery (Figure 2*B*). No difference was found between patients with and without MV during CPB (Figure 2*C*).

CPB during cardiac surgery decreased HLA-DR expression, increased CD14⁺HLA-DR^{low/neg} monocytes count and induced IL-10 and TNF-α production.

A significant decrease in HLA-DR expression occurred after CPB (MFI 7.3 [IQR, 5.4 – 9.3] before vs 2.8 [2.3 – 3.4] after; p<0.001, Figure 3*A*). CPB was subsequently associated with a significant increase in CD14⁺HLA-DR^{low/neg} monocytes (10.3% of CD14⁺ monocytes [IQR, 3.9 – 17.4] before vs. 29.5% [IQR, 20.9 – 40.9] after; p<0.0001). TNF-α and IL-10 levels were higher after surgery (respectively, 45.24 pg/mL [IQR, 43.14 – 48.47] before vs. 48.47 pg/mL [43.14 – 56.14] after; p=0.0183, and 66.77 pg/mL [IQR, 62.78 – 72.95] before vs. 114.7 pg/mL [IQR, 86.55 – 153.9] after; p<0.0001, Figure 3*B*). White blood cell counts were also

modified after surgery, compared to WBC before CPB: we found a significant increase in PMN count (4.42 /mm^3 [IQR, 3.31 – 5.22] before vs. 8.58 /mm^3 (IQR, 6.47 – 12.69] after; p<0.0001) and a significant decrease in lymphocyte count (1.69 /mm^3 [1.34 – 2.205] before vs. 1.3 /mm^3 [IQR, 0.9 – 1.625] after; p<0.0001), while monocyte count remained unchanged (0.63 /mm^3 (IQR, 0.53 – 0.795) before vs. 0.63 /mm^3 IQR, 0.39 – 0.9] after; ns, Figure 3*C*). Lastly, there was a significant inverse correlation between postoperative levels of IL-10 and lymphocytes count (Figure 3*D*).

Effects of maintaining MV during CPB on immune parameters

Patients ventilated during CPB showed lower levels of TNF-α and IL-10 compared to non-ventilated patients (44.2 pg/mL [IQR, 42.1 – 48.5] and 98.7 pg/mL [IQR, 86.5 – 129.0] vs. 53.5 pg/mL [IQR, 48.4 – 64.4] and 129.1 pg/mL [IQR, 89.0 – 198.7], p<0.05 and p<0.05 respectively, Figure 4*A*). Furthermore, non-ventilated patients had a lower lymphocyte count after surgery compared to patients ventilated during CPB (1.05 /mm^3 [IQR, 0.88 – 1.465] vs. 1.48 /mm^3 [IQR, 1.128 – 1.74] respectively, p=0.04, Figure 4*B*). Lymphocyte count remained significantly lower 48 hours after surgery (0.73 /mm^3 [IQR, 0.59 – 1.05] vs. 1.36 /mm^3 [IQR, 0.96 – 1.47], p<0.05, Figure 4*C*).

No significant difference was found in HLA-DR down-regulation between the two groups (MFI (T2-T1) -4.3 [IQR, -6.7 - -2.4] in non-ventilated patients vs. -3.8 [IQR, -5.0 - -2.8] in ventilated patients; ns, Figure 4*D*). Consequently, CD14$^+$HLA-DR$^{low/neg}$ monocytes count was not different between the two groups (32.23% of CD14$^+$ monocytes [IQR, 24.23 – 40.40] in non-ventilated patients vs. 24.87% [IQR, 15.81 – 41.73] in ventilated patients; p=0.2, Figure 4*E*).

Discussion

Our results suggested that maintaining MV during cardiac surgery with CPB could be of interest to decrease postoperative immunosuppression. We found that patients ventilated during CPB had lower postoperative levels of immunosuppressive IL-10 and proinflammatory TNF-α, and a higher postoperative lymphocytes count. However, the proportion of CD14+HLA-DR^{lo/-} monocytes was not statistically different between both groups. These beneficial effects on postoperative immunosuppression could be related to an enhancement in pulmonary function since maintaining MV during CPB abolished the postoperative decrease of PaO_2 /FiO_2 ratio.

Firstly, cardiac surgery with CPB induced postoperative immunosuppression. This effect has been well characterized and previous studies have demonstrated that HLA-DR expression was significantly decreased, and IL-10 was increased after cardiac surgery [4,5,18]. The loss of HLA-DR expression on monocyte, which indicates their functional deactivation, had previously been described after cardiac surgery and sepsis [5], and the persistence of this alteration is associated with severity, nosocomial infection, and death [7,22]. IL-10 is an immunosuppressive cytokine which could be involved in HLA-DR down regulation [23] and an increase in TNF-α has been shown to be counterbalanced by early expression of anti-inflammatory IL-10 [24]. Thus, strategies that could decrease postoperative IL-10 levels could be of interest to decrease postoperative infectious complications. In agreement, we found that total lymphocyte count was significantly decreased after cardiac surgery in non-ventilated patients compared to patients ventilated during CPB. Lymphopenia has been associated with immune dysfunction during septic shock and it has been shown that low absolute lymphocyte counts were predictive of postoperative sepsis [25-26]. In a recent retrospective study, Drewry et al. have demonstrated that persistent lymphopenia after sepsis predicted mortality, and could be a valuable biomarker of immunosuppression since lymphopenia predicted an increased risk of secondary infection [27]. Lastly, we found an increased number of CD14+HLA-DR^{lo/-} monocytes after cardiac surgery. This phenotype is

consistent with a monocytic-MDSC phenotype. To our knowledge, no study has previously reported this finding. MDSC comprise a heterogeneous population of immature myeloid cells at different stages of differentiation [19,20]. Although many subtypes of MDSC have been described in mice and humans, they can be classified into two major subsets: a monocytic MDSC population (CD14$^+$HLA-DR$^{lo/-}$) and a granulocytic MDSC population ([CD3, CD19, CD56, CD14]$^-$CD15$^+$HLA-DR$^-$). Those cells have been shown to be increased in critically ill patients and associated with a poor prognosis [28]. This finding raises the question of targeting those cells to reduce immunosuppression after cardiac surgery. However, as the proportion of CD14$^+$-HLA-DR$^{lo/-}$ monocytes was not different between both groups, mechanical ventilation doesn't seem to have any impact on HLA-DR expression.

Since we found significantly lower TNF-α and IL-10 plasma levels, as well as an increased lymphocyte count in ventilated patients compared to non-ventilated patients during CPB, we assume that maintaining MV during CPB may decrease both pro- and compensatory anti-inflammatory responses by preventing lung injury and/or atelectasis.

Indeed, we found that maintaining MV during CPB improved postoperative index of oxygenation. This result was expected and several studies have already demonstrated the beneficial effects of MV with PEEP during cardiac surgery with CPB [10-12]. As previously reported, postoperative plasmatic levels of CXCL10 and CCL2 were significantly increased [29]. CXCL10 is involved in acute lung injury and ARDS and induces neutrophils migration into the lung [30]. In particular, a recent study has shown that CXCL10 and its receptor CXCR3 were critical factors for the exacerbation of the pathology of ARDS [31]. CCL2 has been shown to be involved in neutrophils recruitment during ARDS. In a mouse model of ARDS, neutralization of this chemokine significantly decreased severity of lung injury [32]. Our ventilation strategy did not have a significant influence on post-CPB increased permeability edema since postoperative levels of CCL2 and CXCL10 were similar in ventilated and non-ventilated patients with a similar count of PMN. Thus, we believe that maintaining ventilation during CPB decreases rather the occurrence of post-CPB atelectasis which has been regarded as a main cause of post-CPB lung injury [13-14]. Furthermore, we

found that maintaining MV during CPB significantly decreased postoperative levels of TNF-α. TNF-α is released by a large number of pulmonary cells including alveolar macrophages and epithelial cells including pulmonary cells (alveolar macrophages and pulmonary epithelial cells…) and has been considered as a marker of lung injury [15,33,]. Occurrence of atelectasis when MV is discontinued during CPB [13,14,34] could generate alveolar injury and inflammation in the surrounding lung tissue [16] which could be worsened by MV after CPB (ie atelectrauma). Alternatively, hypoxia associated with atelectasis may be injurious and has been associated with an increased wet-to-dry ratio in an animal study [15,17,].

Limitations

This study has several limitations. First, it is an observational study and the lack of randomization may have induced some bias. We found a difference between two groups with a significantly higher BMI in the ventilated group, and a nearly statistically significant difference in baseline PaO_2 /FiO_2 ratio. Despite BMI having been described as a risk factor for early onset of severe pulmonary dysfunction after surgery [35], we still found that PaO_2 /FiO_2 ratio was improved in ventilated patients. Secondly, in contrast to murine MDSC, human MDSC are not so clearly defined because of the lack of specific markers. Although $CD14^+HLA-DR^{low/neg}$ phenotype is consistent with a Mo-MDSC phenotype, *in vitro* studies would be required to confirm the suppressive properties of those cells after CPB [20].

Figure legends

Figure 1: Design of the study and gating strategy for HLA-DR monocytic expression measurement.
(A) Design of the study.
(B) Following an initial FS/SS discrimination of the monocytic subset, $CD14^+$ monocytes were gated, and HLA-DR mean fluorescence intensity (MFI) was measured before (T1) and after CBP (T2). Green areas represent mean channel fluorescence for FITC anti-HLA-DR. Unfilled histograms are isotype control results from the same sample. As monocytic MDSC (Mo-MDSC) in humans were previously described as $CD14^+HLA-DR^{lo/-}$ monocytes, we also quantified the proportion of this subset among $CD14^+$ monocytes.
CBP, Cardio-pulmonary bypass; CCL2, Chemokine ligand-2; CXCL-10, CXC motif chemokine-10; IL-10, Interleukin-10; FS, Forward scatter; ICU, Intensive care unit; mHLA-DR, Monocytic expression of human leukocyte antigen-DR; MV, Mechanical ventilation; PaO_2/FiO_2, Ratio of arterial oxygen tension over inspired oxygen fraction; PEEP, Positive end-expiratory pressure; RR, respiratory rate; SS, Side scatter; TNF-α, Tumor necrosis factor alpha.

Figure 2: Effects of maintaining mechanical ventilation during CPB on pulmonary function
(A) Variation of PaO_2/FiO_2 ratio between pre- (T1) and post-CBP time (T2) in patients with (MV+) and without (MV-) mechanical ventilation during CPB.
(B) Plasma levels of CCL2 and CXCL10 before (T1) and after (T2) CPB.
(C) Plasma levels of CCL2 and CXCL10 according to maintenance (MV+) or not (MV-) of mechanical ventilation during CBP.
Boxes represent median, 25th and 75th percentiles. Whiskers represent 5th and 95th percentiles. Bars on dot plots represent medians. P values were obtained using Mann-Whitney *U* test for comparisons between MV+ and MV- groups, and Wilcoxon match-pairs signed rank test for comparisons between T1 and T2 periods within each group.
CCL2, Chemokine ligand 2; CXCL-10, CXC motif chemokine 10; MV, Mechanical ventilation; PaO_2/FiO_2, Ratio of arterial oxygen tension over inspired oxygen fraction; T1, before cardiopulmonary bypass; T2, After cardiopulmonary bypass.

Figure 3: Immunological effect of CPB during cardiac surgery
(A) HLA-DR expression on $CD14^+$ monocytes determined by flow cytometry, and proportion of $CD14^+HLA-DR^{lo}$ monocytes among $CD14^+$ monocytes, before (T1) and after (T2) CPB.
(B) Plasma levels of TNF-α and IL-10 before (T1) and after (T2) CBP.
(C) Number of circulating neutrophils (PMN), lymphocytes and monocytes before (T1) and after (T2) CBP.
(D) Correlation between circulating lymphocyte count and plasma level of IL-10 after CPB (T2).
P values were obtained using Wilcoxon match-pairs signed rank test for comparisons between T1 and T2 periods. Correlations were investigated using the nonparametric Spearman rank correlation test.
IL-10, Interleukin-10; mHLA-DR, Monocytic expression of human leukocyte antigen-DR; MFI, Mean fluorescence intensity; MV, Mechanical ventilation; PaO_2/FiO_2, Ratio of arterial oxygen tension over inspired oxygen fraction; T1, before cardiopulmonary bypass; T2, After cardiopulmonary bypass; TNF-α, Tumor necrosis factor alpha.

Figure 4: Immunological effect of maintaining mechanical ventilation (MV) during CPB
(A) Plasma levels of TNF-α and IL-10, (B) Number of circulating neutrophils (PMN), lymphocytes and monocytes, (C) Number of circulating lymphocytes at day 2, (D) expression

of HLA-DR on CD14^{+} monocytes and (E) percentage of CD14^{+}HLA-DR$^{lo/-}$ monocytes according to maintenance (MV+) or not (MV-) of mechanical ventilation during CPB.

Bars on dot plots represent medians. P values were obtained using Mann-Whitney U test for comparisons between MV+ and MV- groups, and Wilcoxon match-pairs signed rank test for comparisons between T1 and T2 periods within each group.

IL-10, Interleukin-10; mHLA-DR, Monocytic expression of human leukocyte antigen-DR; MFI, Mean fluorescence intensity; MV, Mechanical ventilation; PMN, Neutrophils; T1, before cardiopulmonary bypass; T2, after cardiopulmonary bypass; TNF-α, Tumor necrosis factor alpha.

	MV- N=25	MV+ N=25	p
Age (years)	75[65-79]	73[69-80]	0.79
Surgery			
- Valvular replacement	17	8	
- CABG	5	9	
- Mixed (valvular and CABG)	3	8	
BMI (kg/m^2)	26[23-28]	30[27-33]	0.007
Euroscore II	2.2[1.4-2.9]	2.3[1.4-3.3]	0.6
CVP before CPB (mmHg)	7[6-10]	10[7-12]	0.15
mPAP before CPB (mmHg)	23[20-24]	19[11-25]	0.28
P/F ratio before CPB	326[225-381]	240[173-320]	0.07

Table1. Baseline characteristics of patients before CBP

	MV- N=25	MV+ N=25	p
CVP after CPB (mmHg)	8[6-11]	11[8-12]	0.16
mPAP after CPB (mmHg)	19[18-27]	21[16-24]	0.74
P/F ratio after CPB	276[199-360]	242[211-310]	0.34
CPBP duration (min)	61[52-76]	54[48-68]	0.32
Surgery duration (min)	170[148-210]	150[139-182]	0.3
ICU stay (days)	3[3-6]	3[3-5]	0.59
Hospital stay (days)	10[4-16]	10[4-13]	0.52
Postoperative Infections	5 (20%)	2 (8%)	0.5

Table 2. Effects of mechanical ventilation on outcome and clinical parameters.

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