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Intraoperative ventilation strategy during cardiopulmonary bypass attenuates the release of matrix metalloproteinases and improves oxygenation

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ABSTRACT

Background: Patients undergoing open heart surgery with cardiopulmonary bypass (CPB) often develop a systemic immune reaction, characterized by an increase of proinflammatory and anti-inflammatory mediators. We previously demonstrated that continued mechanical ventilation during CPB reduces this response. We hypothesized that this strategy may also impact on matrix metalloproteinase (MMP) release.

Material and methods: Thirty consecutive patients undergoing coronary artery bypass grafting with CPB were randomized into a ventilated (VG) ($n = 15$) and a standard non-ventilated group (NVG) ($n = 15$). Blood was collected at the beginning, at the end of surgery, and on the five consecutive days. MMPs, tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), and lipocalin 2 (LCN2) were measured by enzyme-linked immunosorbent assay. Parameters of transpulmonary oxygen transport were assessed at different time points.

Results: MMP-8, MMP-9, and LCN2 were significantly lower at the end of surgery in VG compared with those in NVG patients (MMP-8 [ng/mL]: 7.1 [3.5] *versus* 12.5 [7.7], $P = 0.02$; MMP-9 [ng/mL]: 108 [42] *versus* 171 [98], $P = 0.029$; LCN2 [ng/mL]: 109 [42] *versus* 171 [98], $P = 0.03$). TIMP-1 concentrations were lower on postoperative day one, (TIMP-1 [ng/mL]: 174 [55] *versus* 273 [104], $P = 0.003$), whereas MMP-3 levels were lower on postoperative days four and five (MMP-3 [ng/mL]: 44 [17] *versus* 67 [35], $P = 0.026$). The arterial partial pressure of oxygen/fraction of inspired oxygen ratio was significantly higher in VG patients

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throughout the postoperative observation period, which did not affect the length of postoperative ventilatory support.

Conclusions: Continued mechanical ventilation during CPB reduces serum levels of MMPs, their inhibitor TIMP-1 and LCN2, which preserves MMP-9 activity. The present study suggests that continued mechanical ventilation improves postoperative oxygenation and could potentially prevent aggravation of lung injury after CPB.

1. Introduction

Coronary artery bypass graft (CABG) surgery using cardiopulmonary bypass (CPB), that is the on-pump procedure, represents a routine surgical technique with low overall mortality [1]. However, the triggered immune response characterized by intraoperative and postoperative elevation of both proinflammatory and anti-inflammatory mediators [2–7] could potentially lead to multiple organ dysfunction and favor adverse outcome. Approximately 10%–25% of patients after CPB develop mild respiratory dysfunction [8], and up to 2%–5% of patients after on-pump procedures are at risk to develop severe lung dysfunction most likely as a consequence of the systemic immune response [1,9].

Therefore, different strategies have been investigated to prevent systemic immune activation during cardiac surgery. Previous studies have demonstrated that continued mechanical ventilation during CPB reduces systemic levels of proinflammatory and anti-inflammatory mediators [5,10,11]. Furthermore, it has been shown that mechanical ventilation during CPB has beneficial effects on clinical outcome variables such as extravascular lung water or time to extubation [12]. Nevertheless, maintaining mechanical ventilation during CPB has not yet become daily practice in most cardiac surgical centers.

The systemic immune reaction, which accompanies CPB, is of multifactorial origin. Previously, contact activation, endotoxemia, and ischemia–reperfusion (I/R) injury of the lung, heart, or liver have been discussed in the pathogenesis of CPB-associated immune activation [13]. Pulmonary I/R injury after CPB involves infiltration of polymorphonuclear cells into pulmonary tissue and release of cytokines and other mediators (e.g., proteases, matrix metalloproteinases [MMPs] and so forth.) [13].

MMPs belong to a family of zinc- and calcium-dependent endopeptidases and play a key role in the degradation of proteins of the extracellular matrix and in tissue remodeling. The expression and release of different MMPs are triggered, that is, by endotoxin-induced cytokines (tumor necrosis factor-alpha, interleukin [IL]-6, IL-8, and IL-10) and reactive oxygen species [14]. MMPs support leukocyte extravasation and can thereby amplify local immune responses [15].

In the field of cardiac surgery, neutrophil-derived MMP-8 and MMP-9 and fibroblast-derived MMP-3 deserve closer attention. Serum levels of these MMPs are elevated in patients undergoing open heart surgery [16]. Interestingly, patients undergoing off-pump CABG surgery showed lower MMP-9 concentrations compared with on-pump surgery patients indicating that use of CPB substantially contributes to MMP-9 release [6].

The activity of MMPs is counterbalanced by tissue inhibitors of metalloproteinases (TIMPs). Accordingly, Ng *et al.* [5] found higher levels of TIMP-1 in ventilated (VG) compared with non-ventilated (NVG) patients undergoing on-pump CABG.

Lipocalin 2 (LCN2) or neutrophil gelatinase-associated lipocalin, a small protein highly expressed in response to infections [17], tissue injury, or I/R injury builds complexes with MMP-9 thereby stabilizing MMP-9 activity [18]. Notably, LCN2 can be induced in the lungs, which we could demonstrate is associated with anti-inflammatory effects on macrophages in an IL-10 STAT3-dependent manner [17].

Previous studies have shown that IL-10 was generated early during CPB [2,3], whereas it was significantly higher in NVG patients [10]. Given that IL-10 can induce LCN2 [17], the latter might also be differentially expressed in ventilated and non-ventilated lungs after CPB.

Several studies have previously investigated the effect of continued mechanical ventilation during CPB on oxygenation parameters and the levels of certain inflammatory mediators. However, up to date there are no data available on the interplay between MMPs, TIMP1, and LCN2 in the context of CPB and ventilation. Therefore, the aim of the present study was to evaluate if continued mechanical ventilation during CPB affects the MMP-TIMP-1-LCN2 axis. Changes in postoperative transpulmonary oxygen transport served as the secondary end point.

2. Material and methods

2.1. *Patients and clinical features*

The study was approved by the Institutional Ethics Committee at the University of Debrecen (No. 2894-2008 DEOEC RKEB/IKEB-nél: 3849–2013, 021096-2014-OTIG), and was performed in accordance with the Helsinki Declaration of 1975 and the guidelines for Good Scientific Practice of the Medical University of Vienna. It was registered at ClinicalTrials.gov (identifier: NCT01627756).

Serum samples from patients studied here have also been used for other investigations [10,11]. Every patient enrolled in the study gave informed consent. Inclusion criteria were as follows: isolated CABG surgery on CPB without valvular pathology, two- or three-vessel coronary artery disease, elective or urgent surgery, and age 45–80 y. Exclusion criteria were as follows: emergent CABG, unstable angina, ST-segment elevation or non-ST-segement elevation myocardial infarction within the last 3 months, any acute infection or infection within the last 3 mo, fever, hematologic disorders, autoimmune disease, immunodeficiency, immunosuppressive