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Does On-Pump Normothermic Beating-Heart Valve Surgery with Low Tidal Volume Ventilation Protect the Lungs?

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ABSTRACT

Background: Postoperative pulmonary dysfunction following cardiopulmonary bypass (CPB) usually develops secondary to the inflammatory process with contact activation, hypothermia, operative trauma, general anesthesia, atelectasis, pain, and pulmonary ischemia/reperfusion due to cross-clamping. The aim of the present study was to evaluate the effects of an on-pump, normothermic, and beating-heart technique and of low-volume ventilation on lung injury.

Methods: We compared the results for 20 patients who underwent operations with an on-pump, normothermic, and beating-heart technique of mitral valve surgery with low-volume ventilation (group 1) with the results for 23 patients who underwent their operations with an on-pump, hypothermic cardiac-arrest technique (group 2). In both groups, blood samples were collected from the right superior pulmonary vein, and inflammation and oxidative stress markers (malondialdehyde, lactic acid, platelet-activating factor, and myeloperoxidase) were studied.

Results: Malondialdehyde, myeloperoxidase, and lactate values were significantly lower in group 1 than in group 2 just before the termination of CPB ($P < .05$). We observed no differences between the 2 groups with regard to values for platelet-activating factor.

Conclusions: Inflammation and oxidative stress markers were lower in the group of patients who underwent beating-heart valve surgery with low-volume ventilation. These results reflect less of an ischemic insult and lower inflammation compared with the results for the patients who underwent conventional operations.

INTRODUCTION

Respiratory dysfunction following cardiopulmonary bypass (CPB) usually develops secondary to the inflammatory process, with contact activation of the complement system, hypothermia, operative trauma, collapse and altered mechanical properties of the lung during CPB, pleural disruption, and endotoxemia [Johnson 1994; Ege 2004; Zupancich 2005]. Ischemia/reperfusion injury of the lung is another factor [Liu 2000; Kagawa 2010]. As the cross-clamp is applied to the aorta with the pulmonary arteries, blood is diverted from the pulmonary arteries, causing pulmonary ischemia. After the release of the cross-clamp, blood is reperfused in the pulmonary arteries. Many toxic agents (oxygen free radicals, leukotrienes, elastase, and so forth) are released by the activated and sequestrated neutrophils in the lung [Liu 2000]. A significant consequence of reperfusion injury is dysfunction of the pulmonary vascular endothelium, with secondary vasoconstriction and increased vascular permeability leading to pulmonary hypertension, pulmonary edema, and hypoxia. Various reports in the literature have established the role of CPB in the setting of lung injury [Taggart 2000; Cleveland 2001]. These results were obtained by comparing patients who underwent off-pump cardiac surgery with those who underwent traditional open heart surgery. Excluding the pulmonary artery during aortic cross-clamping and perfusion of the lungs have been reported to be useful measures for protecting the lungs [Richter 2000; Suzuki 2001; Ege 2004]. Alternative methods for protecting the lungs have been investigated in various experimental studies [Liu 2000; Zheng 2004; Kagawa 2010].

We have been performing beating-heart valve surgery without cross-clamping of the aorta in mitral valve procedures for 4 years [Katircioglu 2008], and we hypothesized that although we do not perfuse the lungs separately with this procedure, the elimination of hypothermia and reperfusion injury and ventilation with small tidal volumes might have some protective effect on the lungs. Therefore, we looked at lactic acid (lactate), myeloperoxidase (MPO), platelet-activating factor (PAF), and malondialdehyde (MDA) as markers of inflammation, ischemia/reperfusion, and hypoperfusion. We studied 2 groups of patients, those who underwent mitral valve replacement with normothermic CPB via a beating-heart technique (group 1) and patients who underwent mitral valve replacement with CPB, hypothermia, and cardioplegic arrest (group 2).

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Patient Characteristics and Perioperative Data*

Parameters	Group 1 (n = 20)	Group 2 (n = 23)	*P*
Male/female sex, n	12/8	10/12	NS
Age, y	50.9 ± 3.5	48.0 ± 2.2	NS
Cross-clamp time, min	—	67.5 ± 4.4	NS
Pump time, min	62.4 ± 5.0	95.4 ± 5.8	<.05
Operative time, min	106.6 ± 8.8	238.0 ± 9.8	<.05
Intubation time, h	15.4 ± 2.6	22.7 ± 12.1	NS
ICU stay, d	1.6 ± 0.6	1.7 ± 0.3	NS
Drainage, cm^3	619.6 ± 69.6	660.5 ± 77.8	NS
Blood transfusion, units	3.3 ± 0.3	4.2 ± 0.7	NS

*Data are presented as the mean ± SEM where indicated. Group 1 comprises patients who underwent on-pump beating-heart surgery with ventilation; group 2 comprises patients who underwent their on-pump surgeries with cardioplegic arrest. NS indicates not statistically significant; ICU, intensive care unit.

MATERIALS AND METHODS

Forty-three patients who underwent elective heart valve surgery were included in the study. The study group (group 1) consisted of 20 patients with mitral valve disease who underwent mitral valve replacement via a beating-heart technique. The technique has been described in more detail elsewhere. In brief, the heart was not arrested, and CPB was instituted with an aortic cannula and 2 venous cannulas (Jostra HL 20 pump [Maquet Critical Care, Solna, Sweden]; D 708 Simplex III oxygenator [Dideco, Rome, Italy]) [Katircioglu 2008]. A cross-clamp was not applied, and the patient was placed in a deep Trendelenburg position. The mitral valve was replaced while the heart was perfused and beating. Normothermia (rectal temperature, 35°C-37°C) was maintained with a warming blanket. The lungs were ventilated with a 200-mL tidal volume at a rate of 16 cycles/min, a fraction of inspired oxygen of 40%, and an end-expiratory pressure of 0 cm H2O. The control group (group 2) consisted of 23 patients who underwent mitral valve replacement with CPB, hypothermia (rectal temperature, 28°C-31°C), and cardioplegic arrest without ventilation during CPB. Patients with tricuspid valve disease who required tricuspid valve exploration or repair were not included in the study. The patients' demographic and perioperative data are shown in the Table. The study was carried out in accordance with the principles outlined in the Declaration of Helsinki. The Education-Research Ethics Coordination Committee of the Hospital approved the study protocol. All patients were informed about the surgical procedure, and all signed the informed-consent form.

In all patients, blood samples were collected from the right superior pulmonary vein before the institution of CPB and just before its termination. MDA, lactic acid (lactate), PAF, and MPO values were measured.

Statistical Analysis

All results are expressed as the mean ± SEM. The Wilcoxon test with the Bonferroni correction and the Mann-Whitney *U* test for unpaired samples were used to evaluate the differences between pre-CPB and end-CPB time points. A difference in a 2-tailed test was considered statistically significant for *P* values <.05.

RESULTS

The lengths of the operations and CPB times were significantly longer in the control group (group 2) than in the study group (group 1) ($P < .05$). This difference was most probably due to the cooling and rewarming times during CPB in the control group. The 2 groups were similar with respect to other preoperative, operative, and postoperative variables (Table).

Lactate values were significantly elevated at the termination of CPB in both groups (Figure 1). The increase in lactate in group 2 was significantly higher.

MPO values were significantly elevated at the termination of CPB in group 2; no difference was observed for group 1

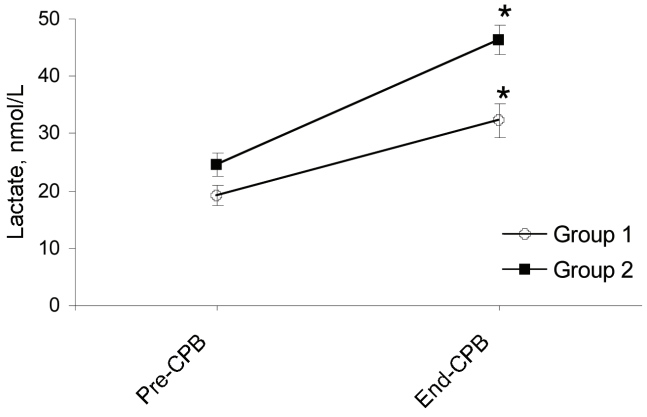

Figure 1. Changes in the lactate level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. End-CPB values were significantly different from pre-CPB values in both groups (*$P < .01$). Data are expressed as the mean ± SEM.

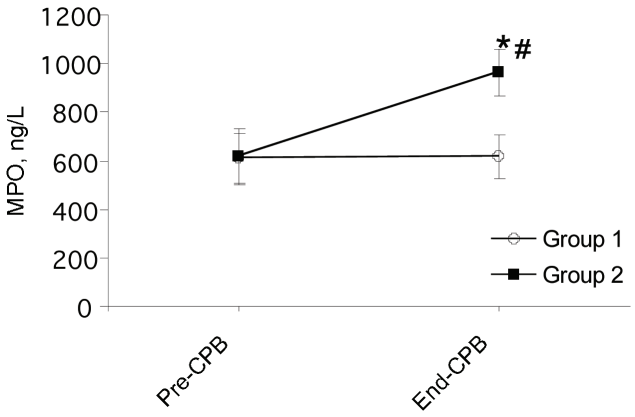

Figure 2. Changes in the myeloperoxidase (MPO) level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. The mean end-CPB value for group 2 was significantly different from the mean pre-CPB value (*P < .01) and from the mean group 1 end-CPB value (#P < .05). Data are expressed as the mean ± SEM.

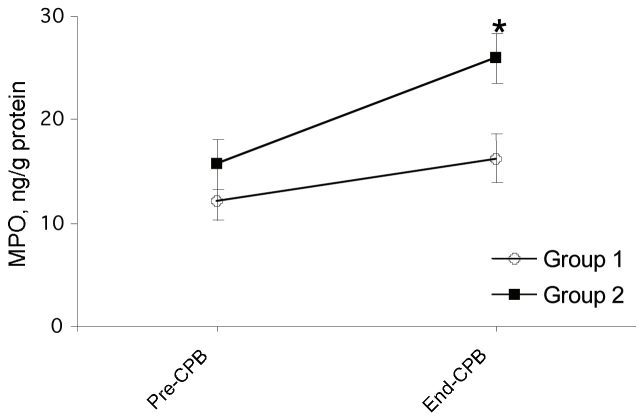

Figure 3. Changes in the myeloperoxidase (MPO) protein level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. The mean end-CPB value for group 2 was significantly different from the pre-CPB value (*P < .001). Data are expressed as the mean ± SEM.

(Figure 2). The MPO protein level in group 2 was significantly elevated at the termination of CPB (Figure 3).

The PAF level did not change in either group (Figure 4). The PAF protein level was significantly elevated at the termination of CPB in both groups (Figure 5).

The MDA level was significantly elevated at the termination of CPB in group 2 (Figure 6). The MDA protein level was significantly elevated at the termination of CPB in both groups (Figure 7). End-CPB MDA and MDA protein levels in group 2 were significantly higher than those in group 1.

DISCUSSION

PAF is a powerful mediator of inflammation and mediates tissue injury induced by tumor necrosis factor α. Its role in inducing the systemic inflammatory response in patients undergoing CPB has been well demonstrated [Ansley 1997; Schlame 1998]. Degradation of PAF was found to be depressed in cardiac surgery patients postoperatively, especially in those with a poor postoperative condition (ie, with a worse acute physiological score) [Schlame 1998]. Increased levels of PAF have been demonstrated to have some clinical correlates, such as the need for inotrope support and ventilator dependence, especially in high-risk patients compared with lower-risk patients in one study [Ansley 1997]. Experimental studies have also demonstrated a better global myocardial function following ischemia/reperfusion injury when the patient was pretreated with a PAF antagonist (TCV-309) [Qayumi 1998] and have also demonstrated better pulmonary functions and pulmonary hemodynamics in a porcine model that received a competitive inhibitor of PAF (SDZ HUL-412) and underwent

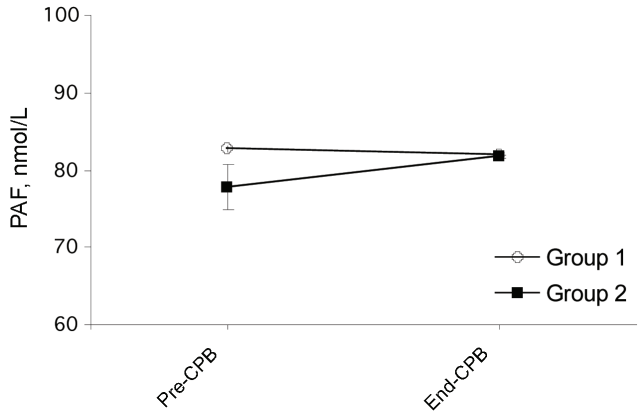

Figure 4. Changes in the platelet-activating factor (PAF) level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. Differences between the 2 groups were not statistically significant (P > .05). Data are expressed as the mean ± SEM.

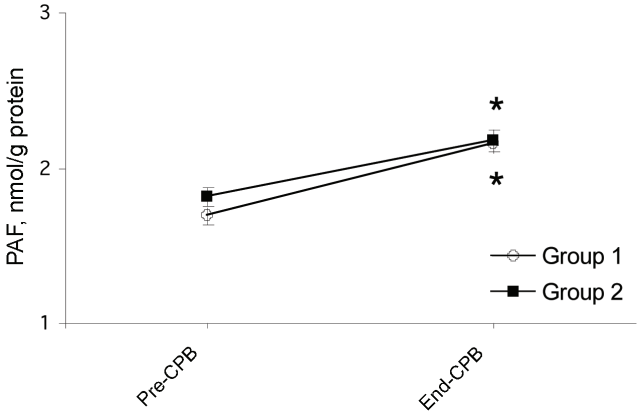

Figure 5. Changes in the platelet-activating factor (PAF) protein level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. For both groups, the mean end-CPB values were significantly different from mean pre-CPB values (*P < .001). Data are expressed as the mean ± SEM.

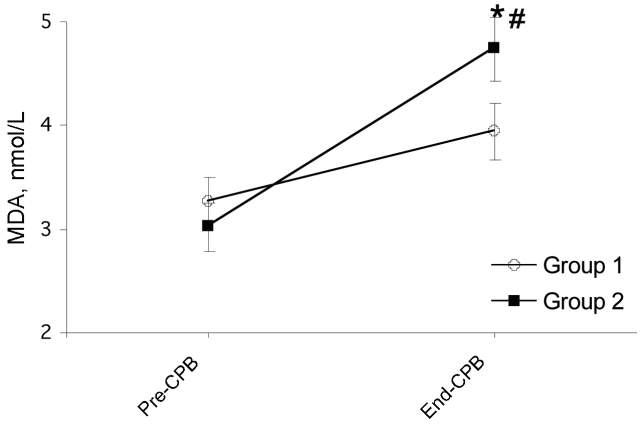

Figure 6. Changes in the malondialdehyde (MDA) level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. The mean end-CPB value for group 2 was significantly different from the pre-CPB value (*P < .01) and was significantly different from the mean end-CPB value for group 1 (#P < .05). Data are expressed as the mean ± SEM.

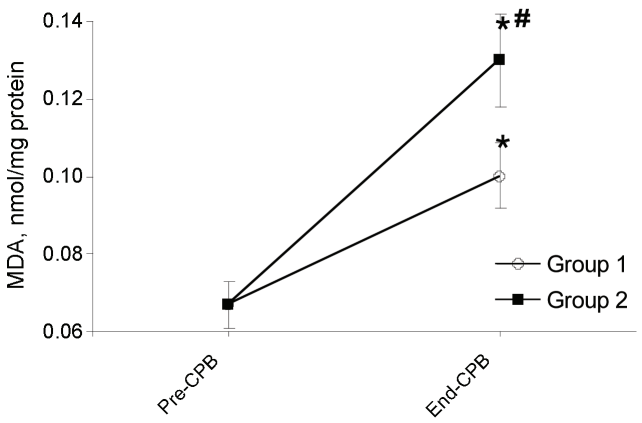

Figure 7. Changes in the malondialdehyde (MDA) protein level in blood from the right superior pulmonary vein before the institution of cardiopulmonary bypass (CPB) and just before its termination. For both groups, mean end-CPB values were significantly different from mean pre-CPB values (*P < .001). The mean end-CPB value for group 2 was significantly different from the end-CPB value for group 1 (#P < .001). Data are expressed as the mean ± SEM.

CPB [Zehr 1995]. On the other hand, some studies have not found reduced perioperative myocardial injury with the use of PAF antagonists [Taggart 2000]. An elevation in PAF levels at the end of CPB was encountered in both groups of the present study; however, the 2 groups were not significantly different with respect to PAF level (P > .05). This result is apparent in the clinical results as well. As the patients in the 2 groups underwent CPB, both groups had elevated PAF levels, but the elimination of reperfusion and hypothermia did not produce a difference in PAF levels between the 2 groups in this study.

MPO is an enzyme and produces oxygen free radicals that are released from activated neutrophils [Ng 2002]. Along with other enzymes (matrix metalloproteinase, polymorphonuclear neutrophil elastase, and so forth), MPO breaks down the pulmonary ultrastructure, leading to increased pulmonary endothelial/alveolar permeability. The MPO activity in myocardial tissue samples after aortic declamping in patients undergoing heart valve surgery and MPO levels after CPB were elevated, reflecting the activation of the inflammatory reaction after ischemia/reperfusion injury [Gessler 2002; Luo 2007]. One study also found bronchoalveolar lavage fluids to be rich in MPO after CPB [Alat 2001]. The mean MPO level was higher in group 2 than in group 1 in the present study.

MDA is an indicator of lipid peroxidation, which is caused by reperfusion injury after an ischemic insult. Increases in the MDA level in the coronary sinus blood in the early reperfusion period reflect oxidative stress in the myocardial tissue [van Boven 2008]. Liu and colleagues also showed that the use of a hypothermic anti-inflammatory solution for pulmonary artery perfusion may help to prevent lung injury, as measured by a better post-CPB pulmonary histology and lung function, as well as by a lower plasma MDA level [Liu 2000]. In the present study, MDA levels increased after CPB in both groups, and this increase was significant in group 2. Oxidative stress was also prominent in group 1, but it occurred to a lesser extent in this group.

The lactate concentration usually reflects the adequacy of perfusion levels, and lactate concentrations were elevated in systemic arteries and the coronary sinus during CPB. The lactate level was accentuated by CPB, and a longer duration of mechanical ventilation and inotropic support was associated with a more prominent increase in lactate levels [Bendjelid 2004; Shinde 2005; Gasparovic 2007]. There are few descriptions in the literature regarding lactate levels in the pulmonary veins during or after CPB. Lactate levels in the pulmonary veins were significantly elevated at the end of CPB in both groups of the present study, but the lactate concentration was significantly higher in the control group.

The lungs are not perfused specifically during CPB with the heart beating. As Friedman et al pointed out, however, it is better than no perfusion and no ventilation at all. In their application with a sheep model that was very similar to our technique, they compared total CPB to partial CPB [Friedman 1995] and suggested that ventilation with pulmonary artery perfusion during CPB may have a beneficial role in preserving lung function by limiting platelet and neutrophil sequestration and attenuating the thromboxane B_2 response after CPB [Friedman 1995].

Imura and colleagues demonstrated that low-frequency mechanical ventilation during CPB in a pig model reduced tissue metabolic and histopathologic damage to the lungs and was associated with improved postoperative gas exchange [Imura 2009]. A recent report described findings in which ventilation during CPB in coronary artery bypass grafting was associated with lower extravascular lung water and a short intubation time [John 2008]. Lamarche and colleagues reported that mechanical ventilation in an animal model prevented pulmonary endothelial dysfunction due to reperfusion after CPB [Lamarche 2004].

CONCLUSIONS

Regarding the clinical parameters, there were no differences between the groups, but our small number of patients precludes a robust conclusion. We can say, however, that the parameters of inflammation and oxidative stress were better for the patients who underwent beating-heart valve surgery, and that improvement reflected a lower ischemic insult and less inflammation than in the patients who underwent conventional operations. The elimination of hypothermia and reperfusion injury of the myocardium and the application of ventilation during CPB may have contributed to this result.

LIMITATION

The patient groups were not randomized or blinded to the surgical techniques used because the surgeons determined the methodology according to their preferred technique.

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