Association of Hyperlactatemia and IL-6 Hypercytokinemia after Cardiopulmonary Bypass

- A Preliminary Report -

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Background: In cardiac surgery with cardiopulmonary bypass (CPB), hyperlactatemia (HL) is common and is associated with postoperative morbidity and mortality. At present, the cause of HL during CPB is proposed to be tissue hypoxia. Tissue perfusion and oxygen delivery can be impaired to varying degrees during CPB. Although surgery involving CPB apparatus is associated with increased pro-inflammatory mediators, such as TNF-α and IL-6, tissue hypoxia that occurs during CPB may be an additionally potent stimulus to inflammation. We hypothesized that hypoxic patients during CPB that experience elevated serum lactate levels, may be related to higher serum cytokine level after CPB than normoxic patients during CPB with normal serum lactate levels.

Methods: Levels of TNF-α and IL-6 were measured by ELISA in a) Time 1; before initiation of CPB, b) Time 2; 30 min after aortic de-clamping, c) Time 3; 24 hrs after aortic de-clamping. Levels of lactate was measured at a) Time A; before initiation of CPB, b) Time B; 30 min after aortic de-clamping. Postoperative ICU stay, intubation time and oxygen index were evaluated as postoperative morbidity scale.

Results: There were no statistical differences between HL (n = 43, lactate ≥3 mMol/L at time B) and normal lactate group (NL) (n = 63, lactate <3 mMol/L at time B) in demographic data, preoperative left ventricular ejection fraction, CPB time, and aortic cross-clamp time. Level of IL-6 in HL at time 3 was higher than that of NL. The ICU stay and intubation time were longer in HL. The oxygen index on 1st postoperative day was lower in HL.

Conclusions: Our results suggest that hyperlactatemia after weaning from CPB may be related to IL-6 hypercytokinemia, and therefore related to postoperative morbidity.

Key Words: cardiopulmonary bypass, cytokine, interleukin-6, lactate, morbidity, tumor necrosis factor-α.

INTRODUCTION

Hyperlactatemia (HL) associated with metabolic acidosis is common in critically ill patients with systemic hypoperfusion and tissue hypoxia. In addition, HL is a well-recognized marker of circulatory failure, and it’s severity has been associated with mortality in different clinical conditions. In cardiac surgery with cardiopulmonary bypass (CPB), HL is detectable at a considerable (10% to 20%) rate and is associated with postoperative morbidity and mortality. At present, the nature of HL during CPB is not well known, some authors proposed a tissue hypoxia (type A HL) as a cause of post-CPB HL. Type A HL results from an imbalance between tissue oxygen supply and demand. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic condition. Therefore, blood lactate level in type A HL is related to the oxygen debt and the magnitude of tissue hypoperfusion.

During CPB, cardiac output and arterial pressure can be easily maintained at normal values. However, several observations suggest that tissue perfusion and oxygen delivery can be impaired to varying degree during CPB. Conventional monitoring of arterial blood gas during CPB may detect tissue hypoxia. However, the serum lactate concentration during CPB might be more sensitive to detect an imbalance between oxy-
There are many similarities between the host response to inflammation and the vascular response to hypoxia or ischemia. Vascular tissue subject to oxygen deprivation reacts in similar fashion to the response to sepsis. When endothelial cells are stimulated with lipopolysaccharide, a cascade of events occurs which amplifies the proinflammatory vascular milieu. Complement is activated locally, and tumor necrosis factor - alpha (TNF-α) or IL-6 are released from endothelial cells or activated macrophages. These substances can further activate endothelium, exacerabtating inflammation and injury. Many pathologic conditions relevant to clinical medicine are not primarily driven by the hypoxic or ischemic primary event, but rather by inflammatory cascade triggered as a secondary response. Examples include myocardial infarction or stroke, CPB and organ transplantation.

Therefore, we hypothesized that the hypoxic patients during CPB which is evidenced by elevated serum lactate level might be related to higher postoperative serum cytokine level than normoxic patient during CPB evidenced by normal serum lactate level.

**MATERIALS AND METHODS**

After Institutional Review Board approval and written informed consent, patients aged over 18 years scheduled for elective cardiac surgery using CPB at our institute for one year were included in the study. Exclusion criteria were diabetes, patients with ischemic heart disease, left ventricular dysfunction (ejection fraction below 40%) and right ventricular dysfunction. Patients with preoperative signs of infection (leukocyte count >12,000/ml, body temperature >38°C, CRP >5) and hyperlactatemia (>3 mmol/L) were excluded also. In the author’s institute, over 90% of coronary artery bypass surgery is performed without CPB. Accordingly, patient undergoing coronary artery bypass surgery or aortic surgery with deep hypothermic circulatory arrest was excluded.

Anesthesia was induced and maintained with midazolam, rocuronium, and sufentanil. Before initiation of CPB, tidal volume was adjusted to achieve normoventilation with oxygen in air (FiO2 0.5) and was controlled by means of blood gas analysis to maintain normal arterial carbon dioxide tension.

The operation was performed with standard nonpulsatile CPB technique (2.4 l/min/m²) with moderate hypothermia (nasopharyngeal temperature 32 – 34°C) with the administration of heparin (300 IU/kg). Since the report of Mangano et al.,11 our institute has not used APROTININ in cardiac surgery. Therefore, the activated clotting time was maintained at above 400s. The circuit was primed with Ringer’s lactated solution, albumin, and mannitol. Cardioprotection was achieved with cold blood cardioplegia. After separation from CPB (rectal temperature 36.5 – 37°C) anticoagulation activity was reversed with protamine sulfate, given a ratio of 1 mg: 100 IU of heparin.

Blood samples were collected at a) Time 1; before initiation of CPB, b) Time 2; 30 min after aortic de-clamping, c) Time 3; 24 hrs after de-clamping. All blood samples were anticoagulated with ethylene diaminetetraacetic acid, immediately cooled to 4°C, centrifuged within 10 minutes and stored at −80°C until assay. Levels of TNF-α and IL-6 were assayed by means of commercially available enzyme-linked immunosorbant assay (ELISA). Levels of lactate were measured at a) Time A; before initiation of CPB, b) Time B; 30 min after aortic de-clamping using arterial blood gas analyzer (GEM® Premier™ 3000, Instrumentation Laboratory, Lexington, MA).

Postoperative ICU stay, intubation time, serum creatinine level for 2 days and oxygen index at ICU were evaluated as postoperative morbidity scale. The tracheal extubation criteria were full consciousness, hemodynamic stability, adequate muscle strength and adequate respiration (required positive end-expiratory pressure, < or = to 5 cmH2O; breathing rate, <30/min) as well as adequate gas exchange value (PaO2, > or = to 80 mmHg/FiO2 = 0.4; PaCO2, 35 – 50 mmHg). Oxygen index was calculated (arterial PO2/inspired fraction of oxygen) based on the arterial blood gas analysis performed on arrival at ICU and on 1st day of ICU at 8 A.M. Serum creatinie level was examined preoperatively, on 1st day of ICU at 8 A.M., and on 2nd day of ICU at 8 A.M. Postoperatively, blood loss from the mediastinal chest tubes was reported at 6, 12, and 24 hours from the time the patient arrived in the ICU. The 24 hour blood loss was documented.

**Statistical Analysis** For estimation of sample size, preliminary survey was performed. The standard deviation of the underlying population (n = 20) was 20 pg/ml. We calculated that 40 patients in each group were needed for the detection of 65% effect size at a power of 0.8, an α = 0.05.

To compare the categorical data, chi-square test was used. Continuous variables were expressed as mean ± SD compared by means of a parametric (Student t-test) or were expressed as median (25th and 75th percentiles) compared by means of a nonparametric (Wilcoxon signed-rank sum) test, on the basis of the distribution of variables. Before the multiple regression analysis, the peak plasma IL-6 and TNF-α values underwent