学 位 論 文 の 要 旨

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学 位 論 文 名　Hypothermic Effects on Gas Exchange Performance of Membrane Oxygenator and Blood Coagulation During Cardiopulmonary Bypass in Pigs

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論 文 内 容 の 要 旨

INTRODUCTION

It remains uncertain whether hypothermia could reduce blood component activation by contact with the cardiopulmonary bypass (CPB) circuit. On the other hand, many studies have shown that hypothermia could reduce inflammation caused by ischemic/traumatic injuries. Evidence has been convincing that there is crosstalk between inflammation and blood coagulation. Hypothermia was also shown to decrease complement, coagulation, neutrophil and platelet activities during/after surgery with CPB or therapeutic hypothermia. However, there have been several evidences that moderate hypothermic (24℃, 25℃) CPB could not impact on cytokine levels compared to mild (32℃, 34℃) one in pediatric cardiac surgery. Furthermore, the CPB-induced inflammation has been shown to be stronger in children compared with adults because of simply small body size relative to CPB circuit size. The objective of this study was to ascertain whether deep (23℃) hypothermic CPB reduces blood component activation including blood coagulation compared with normothermic CPB in juvenile pigs; with both procedures the circuits were fully polymer-coated. The deep hypothermic CPB has be widely used in complex congenital surgeries such as Norwood procedure or aortic arch reconstruction in order to safely extend hypothermic circulatory arrest time. We previously reported that a polymer-coated CPB circuit attenuated up-regulation of proteins in both proteases/protease inhibitors and platelet degranulation. The aim of this study was to verify whether deep hypothermic CPB could reduce upregulation of blood proteins activated by contact with a polymer-coated CPB circuit in juvenile pigs.

MATERIALS AND METHODS

Biocompatibility of a polymer-coated cardiopulmonary bypass circuit was comparatively assessed by plasma proteomics between juvenile pigs undergoing hypothermic (23°C) cardiopulmonary bypass and those undergoing normothermic (37°C) cardiopulmonary bypass (n = 6, respectively). Plasma samples were taken three times: 5 minutes after initiation of cardiopulmonary bypass (T5, before cooling), just before declamping and rewarming (Tc), and just before termination of cardiopulmonary bypass (Trw, 120 minutes). Proteomic analysis was quantitively performed by isobaric tags for relative and absolute quantification labeling. Thrombin-antithrombin complexes (TAT III) were measured by enzyme immunoassay, and vitamin K-dependent protein C (PROC), β-thromboglobulin (TG), and P-selectin were measured by enzyme-linked immunosorbent assay. Blood gas analyses evaluated oxygenator performance.

RESULTS AND DISCUSSION

Hypothermic cardiopulmonary bypass had a significantly higher PaO2 at Tc and lower PaCO2 at Trw than normothermic cardiopulmonary bypass. Hypothermic CPB improved oxygenation by oxygenators during blood cooling at Tc. Two hundred twenty-four proteins were identified with statistical criteria of both protein confidence (>95%) and false discovery rate (<5%). Six of these proteins significantly decreased at Tc than at T5 in hypothermic cardiopulmonary bypass ($p = 0.02$-0.04), with three related to platelet degranulation. Our study also demonstrated that hypothermic CPB suppressed upregulation of proteins belonging to coagulation/fibrinolysis and TATIII. Proteomic and ELISA analyses demonstrated that levels of protein C were slightly increased during cooling (at Tc) in hypothermic CPB, while proteomic analysis showed a significant decreased level of protein C at Trw in normothermic CPB. TAT III had a slightly larger increase with normothermic cardiopulmonary bypass at Trw than with Hypothermic cardiopulmonary bypass. Levels of two platelet activation markers, β-thromboglobulin and P-selectin levels were significantly lower at Trw with hypothermic cardiopulmonary bypass than with normothermic cardiopulmonary bypass ($p = 0.04$), indicating that hypothermia could attenuate platelet degranulation induced by exposure to the CPB circuit.

In hypothermic CPB, the hemoglobin level decreased at Tc and then increased at Trw; however, such changes did not occur in normothermic CPB. Core cooling by CPB, decreases venous return because of an increased vascular capacity. Therefore, in order to maintain the pump reservoir level, a larger volume of infusion is mandatory in hypothermic CPB compared with normothermic CPB.

In order to obtain more wide range of findings, additional studies using adult animals at different temperatures, i.e., moderate hypothermia (25-30℃) or mild hypothermia (31-34℃) are required.

All experiments with animals in this study were approved by the Animal Care and Use Committee of Shimane University.

CONCLUSION

The present study of juvenile pig CPB experiments revealed that hypothermic (23℃) CPB attenuated both blood coagulation and platelet degranulation activated by contact with the CPB circuit compared with those in normothermic CPB. Furthermore, hypothermic CPB was accompanied by a higher performance of the oxygenator compared with normothermic CPB.