Remifentanil Prevents Increases of Blood Glucose and Lactate Levels during Cardiopulmonary Bypass in Pediatric Cardiac Surgery

Abstract

Introduction: Cardiopulmonary bypass (CPB) can cause stress response that increases levels of cytokine and catecholamine in plasma, resulting in hyperglycemia. In adults, it has been demonstrated that remifentanil infusion during CPB could prevent increases of cytokine, catecholamine, and blood glucose levels, but such effects of remifentanil in children have not been elucidated. Aim: In this study, we investigated the preventive effects of remifentanil on blood glucose and lactate levels during CPB in children. Materials and Methods: This retrospective study included children who underwent ventricular septal defect or atrial septal defect closure. Data for patients who did not receive, during CPB period, remifentanil infusion (non-Remi group) and patients who received remifentanil infusion at 0.5 µg/kg/min (Remi group) during CPB were used for analysis. Primary outcomes were lactate and blood glucose levels just before and after CPB. Data are presented as medians and interquartile ranges. Data were analyzed by the Mann–Whitney U-test and Chi-square test. A P < 0.05 was considered statistically significant. Results: During CPB, 13 and 11 patients were allocated into Remi and non-Remi groups, respectively. Pre-CPB lactate and blood glucose levels were not significantly different between the two groups, but post-CPB lactate and blood glucose levels in the Remi group were significantly lower than that in the non-Remi group. Conclusion: 0.5 µg/kg/min remifentanil infusion during CPB suppresses the increases of blood glucose and lactate levels in children.

Keywords: Cardiopulmonary bypass, children, hyperglycemia, hyperlactatemia, remifentanil

Introduction

Cardiopulmonary bypass (CPB) is essential for cardiac surgery, for example, congenital heart disease repair, at CPB period. However, CPB can cause inflammatory responses that increase cytokine and catecholamine levels in plasma, resulting in hyperglycemia and hyperlactatemia. Moreover, perioperative hyperglycemia and hyperlactatemia exacerbate postoperative outcomes. In adults, it has been demonstrated that remifentanil infusion during CPB could prevent increases of cytokine, catecholamine, and blood glucose levels, but such effects of remifentanil in children have not been elucidated. In this study, we investigated the preventive effects of remifentanil on the increases of blood glucose and lactate levels during CPB in children.

Materials and Methods

We retrospectively reviewed anesthetic records of patients with 0–7 years old, from the right internal jugular vein. Two peripheral venous and an arterial cannula were inserted, and 0.6–0.8 mg/kg rocuronium was administered, and children were tracheally intubated. After intubation, central venous catheter was inserted from the right internal jugular vein. Noninvasive blood pressure, invasive blood pressure, central venous pressure, and blood oxygen saturation were monitored. Physiological records, such as arterial blood gas and blood glucose levels, were checked every 5 min. CPB was performed with a pump oxygenator device from the right atrium to the right ventricle through an arterial cannula and a venous cannula from the right atrium to the superior and inferior vena cavae. Cardiac output was measured by thermodilution. A standard microsensor catheter inserted into the superior vena cavae was used to monitor transpulmonary thermodilution with a microthermocouple device. A standard arterial catheter was placed in the femoral artery to monitor arterial blood gases and blood glucose levels. Data were analyzed by the Mann–Whitney U-test and Chi-square test. A P < 0.05 was considered statistically significant. Results: During CPB, 13 and 11 patients were allocated into Remi and non-Remi groups, respectively. Pre-CPB lactate and blood glucose levels were not significantly different between the two groups, but post-CPB lactate and blood glucose levels in the Remi group were significantly lower than that in the non-Remi group. Conclusion: 0.5 µg/kg/min remifentanil infusion during CPB suppresses the increases of blood glucose and lactate levels in children.

Keywords: Cardiopulmonary bypass, children, hyperglycemia, hyperlactatemia, remifentanil

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heart rate, electrocardiography, core body temperature, \( \text{SpO}_2 \), end-tidal \( \text{CO}_2 \), and cerebral tissue oxygen index were continuously recorded. During pre-CPB period, anesthesia was maintained with 1.5% sevoflurane, fentanyl, and 0.25–0.5 \( \mu \text{g/kg/min} \) remifentanil. Just after start of CPB, sevoflurane inhalation was stopped, and 10 mg/kg/h propofol, 0.7 \( \mu \text{g/kg/h} \) dexmedetomidine, and remifentanil infusion were started. During CPB, anesthesiologist decided whether to administer 0.5 \( \mu \text{g/kg/min} \) remifentanil or not at all. Concurrently, with the end of CPB, propofol infusion was stopped, and sevoflurane inhalation was started again. After the operation procedure, all children were transferred to the Intensive Care Unit with tracheary intubation and 0.7 \( \mu \text{g/kg/h} \) dexmedetomidine infusion. Blood gas analysis was performed at just before and after CPB period.

Intraoperative data were obtained from anesthetic and CPB records. Patients were divided into two groups; Remi group included patients who received 0.5 \( \mu \text{g/kg/min} \) remifentanil infusion, and non-Remi groups included patients who did not receive remifentanil infusion during CPB. Primary outcomes were blood glucose and lactate just before and after CPB. Secondary outcomes include base deficit before and after CPB, dose of \( \text{NaHCO}_3 \) and chlorpromazine, perfusion pressure and cerebral tissue oxygen index during CPB, urine output, and dose of furosemide during a postoperative 24-h period.

**Ethics**

Hokkaido Medical Center for Child Health and Rehabilitation Institutional Review Board approved this study (Date of approval: July 2015, 28, Approval code: 142). This study was in accordance with the ethical standards of our institution and with the Helsinki Declaration of 1975.

**Statistics**

Statistical analysis was performed with Mann–Whitney U-test for primary outcomes. Secondary outcomes were analyzed with Chi-square test and Mann–Whitney U-test. A \( P < 0.05 \) was considered statistically significant. Data were presented as absolute number or median (interquartile range).

**Results**

Twenty-three patients were included this retrospective study. Thirteen and 11 patients were included in Remi and non-Remi groups, respectively. There was no significant difference in characteristics between two groups, including CPB time, aortic clamp time, and flow rate of CPB [Table 1]. Fentanyl dose was slightly lower in Remi group, but this was not significantly. Pre-CPB blood glucose was not significantly different (Remi group; 93 [88–100], non-Remi group; 101 [85–101] mg/dL, \( P = 0.395 \)) [Figure 1a], but post-CPB blood glucose was significantly lower in Remi group (Remi group; 111 [105–138], non-Remi group; 174 [162–194] mg/dL, \( P < 0.05 \)) [Figure 1b]. Similarly, pre-CPB lactate was not significantly different (Remi group; 6.0 [5.7–7.0], non-Remi group; 6.5 [5.0–8.0] mg/dL, \( P = 0.552 \)) [Figure 2a], but post-CPB lactate was significantly lower in Remi group (Remi group; 8.0 [7.0–9.2], non-Remi group; 10.0 [8.0–12.0] mg/dL, \( P = 0.018 \)) [Figure 2b].

| Table 1: Characteristics of the patients |
|------------------------------------------|
|                                           |
| Number                                   |
| Remi                                     |
| n = 13                                   |
| Non-remi                                 |
| n = 10                                   |
| VSD / ASD                                |
| 10 / 3                                   |
| 9 / 1                                    |
| p value                                  |
| 0.412                                    |
| Age (month)                              |
| 14 (2 – 66)                              |
| 3 (2-19)                                 |
| p = 0.316                                |
| Height (cm)                              |
| 75 (58 – 110)                            |
| 60 (55 – 80)                             |
| p = 0.191                                |
| Weight (kg)                              |
| 9 (4.5 – 16.5)                           |
| 5.6 (4.5 – 10)                           |
| p = 0.401                                |
| Qp/Qs                                    |
| 1.8 (1.3 – 1.9)                          |
| 2.0 (1.3 – 2.3)                          |
| p = 0.462                                |
| CPB time (min)                           |
| 72 (52 – 93)                             |
| 80 (71 – 83)                             |
| p = 0.963                                |
| Aorta Clump time (min)                   |
| 39 (26 – 56)                             |
| 44 (42 – 45)                             |
| p = 0.615                                |
| Minimum temperature during CPB (°C)      |
| 36.4 (36.0 – 36.7)                       |
| 36.0 (35.7 – 36.4)                       |
| p = 0.170                                |
| Fentanyl dose (µg·kg⁻¹)                  |
| Pre CPB                                  |
| 11 (10 – 16)                             |
| 17 (14 – 24)                             |
| p = 0.118                                |
| Total                                    |
| 15 (14 – 22)                             |
| 21 (16 – 28)                             |
| p = 0.152                                |
| CPB flow rate (mL·kg⁻¹·min⁻¹)            |
| 138 (112 – 157)                          |
| 146 (130 – 159)                          |
| p = 0.340                                |

Data were presented as median (IQR) and absolute number. IQR: Interquartile range.
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12.0 [10.7–13.5] mg/dL, \( P < 0.01 \) [Figure 2b]. Secondary outcomes were presented in Table 2. Perfusion pressure during CPB in Remi group was significantly lower in non-Remi group. On the other hand, cerebral tissue oxygen index was not significantly different. Doses of NaHCO\(_3\) and chlorpromazine during CPB were not significantly different but tend to be higher in non-Remi group. Postoperative serum creatinine, urine output, and dose of furosemide, relating to renal function, were not significantly different between two groups.

**Discussion**

Our study has three major findings. First, this study indicates remifentanil has the preventive effect on increases of blood glucose and lactate levels during CPB in children. In adult, this effect of remifentanil has been reported.[9] It is well known that CPB induces a systemic inflammatory response and stimulates cytokine signaling.[1,2] Von Dossow *et al.* reported that remifentanil infusion for coronary artery bypass graft surgery decreased the interferon (INF)-γ/interleukin (IL)-6 ratio and suppressor of cytokine signaling-3 gene expression,[1] which is known as a feedback inhibitor of cytokine receptor signaling and negative regulator of CD4+ T-cell differentiation.[10,11] Moreover, remifentanil infusion suppresses post-CPB stress hormone levels such as norepinephrine, antiuretic hormone compared with intermittent fentanyl administration.[8] These stress hormones have potent vasoconstrictive effects, inducing the disturbance of peripheral tissue perfusion. At low-perfusion tissue, oxygen delivery was exacerbated and anaerobic metabolism was facilitated, resulting in hyperglycemia and

**Figure 1:** The results of blood glucose levels at pre- and post-cardiopulmonary bypass period. (a) Precardiopulmonary bypass glucose, (b) postcardiopulmonary bypass glucose. \(* P < 0.05\) CPB: Cardiopulmonary bypass

**Figure 2:** The results of lactate levels at pre- and post-cardiopulmonary bypass period. (a) Precardiopulmonary bypass lactate, (b) postcardiopulmonary bypass lactate. \(** P < 0.01\) CPB: Cardiopulmonary bypass

**Table 2:** The result of secondary outcomes

|                         | Remi     | Non-remi | \( p \) value |
|-------------------------|----------|----------|--------------|
| Perfusion pressure (mmHg) | 42 (32 – 44) | 49 (45 – 50) | 0.024        |
| Cerebral tissue oxygen index (%) | 56 (55 – 62) | 58 (55 – 61) | 0.962        |
| Base deficit (mmol/L) | 2.9 (0.4 – 3.3) | 2.1 (0.3 – 3.2) | 0.749        |
| Pre CPB | 2.5 (1.8 – 2.5) | 3.1 (1.7 – 4.8) | 0.289        |
| Post CPB | 2.14 (143 – 326) | 364 (240 – 470) | 0.105        |
| NaHCO\(_3\) (mg/kg) | 0 (0 – 0.03) | 0.13 (0 – 0.25) | 0.368        |
| Chlorpromazine (mg/kg) | 0.25 (0.21 – 0.35) | 0.22 (0.21 – 0.25) | 0.382        |
| Serum creatinine (mg/dL) | 0.23 (0.22 – 0.31) | 0.26 (0.22 – 0.26) | 0.914        |
| Urine output during postoperative | 76 (69 – 96) | 89 (63 – 94) | 0.766        |
| 24 hour (mL/kg/day) | 0.9 (0.5 – 1.7) | 1.4 (0.8 – 1.9) | 0.419        |

Data were presented as median (IQR). IQR: Interquartile range
hyperlactatemia. It is thought to be that remifentanil could suppress inflammatory response, stress hormone release and improve tissue perfusion, and consequently prevent blood glucose and lactate elevations.

Second, remifentanil infusion might be useful as an antihypertensive agent during CPB period in children. In pediatrics, hypertension often occurs during CPB as a result of systemic vasoconstriction. To prevent hyperperfusion pressure, chlorpromazine and nitroprusside are useful as vasodilative drugs.[12,13] In this study, perfusion pressure was significantly lower in Remi group. In addition, chlorpromazine dose during CPB had a tendency to be lower in Remi group. This effect is thought to be the result of the anti-inflammatory effect of remifentanil as described above mention. Therefore, remifentanil infusion during CPB in children is also expected to fulfill a role as an antihypertensive agent.

Third, no adverse effect was observed in Remi group. In pediatric cardiac surgery, renal dysfunction is important complication, and the incidence is reported 42%.[14] In our results, secondary outcomes relating to postoperative renal function, such as urine output, serum creatinine, and dose of furosemide, were not different between the two groups. There is some possibility that remifentanil can use safely during CPB in pediatric cardiac surgery.

In addition, remifentanil infusion during CPB might improve postoperative outcomes. Intraoperative hyperglycemia and hyperlactatemia are known as the factors that exacerbate postoperative outcomes.[5‑7] To prevent hyperglycemia, intensive insulin therapy is desirable,[15] but it might be harmful, because of a risk of hypoglycemia in pediatrics.[16‑18] From this point, stress-free perioperative management, stabilizing blood glucose, and lactate levels are thought to be apposite. Remifentanil may incarnate this management and improve postoperative outcomes for children.

In the current study, pre-CPB and total fentanyl dose were higher in non-Remi group. These differences were not significant but might influence some outcomes. In pediatrics, CPB induction causes the huge increases of circulatory and drug distribution volume, resulting in the change of pharmacokinetics and pharmacodynamics, compared with adults. Koren et al. reported that plasma fentanyl concentration does not change between before and during CPB periods.[19] According to this study, it is thought that the plasma fentanyl concentrations were different between Remi and non-Remi group in this study. However, Stanley et al. reported that approximately 100 mcg/kg fentanyl administration could not suppress the elevations of stress hormones during CPB.[20] Consequently, it is seems that the differences of fentanyl dose (6 mcg/kg) were too slight to affect our blood glucose and lactate results.

We use blood glucose and lactate levels as the results of stress responses caused by CPB, but inadequate sedation also affects these values. In our institution, 10 mg/kg/h propofol infusion was applied as a sedative during CPB period. In pediatrics, because the dimension of their forehead is limited, bispectral index was not monitored routinely. There is possibility that insufficient sedation and anesthesia-induced stress response resulting in blood glucose and lactate increases in the current study. Dawson et al. investigated the effects of CPB on total and unbound plasma concentrations of propofol.[21] According to their results, after CPB start, total plasma propofol concentration decreased transiently, but unbounded portion of propofol increased. As a result, unbounded plasma propofol concentration, which had drug efficacy, small increased and the depth of anesthesia became deeper. Our 10 mg/kg/h propofol infusion rate for anesthetic maintenance is advocated by McFarlan et al. in 1999 and widely used for many years clinically.[22] Moreover, in pediatric cardiac surgery, 4–8 mg/kg propofol infusion is recommended.[23] In summary, 10 mg/kg/h propofol infusion was sufficient for anesthetic maintenance during CPB in children and did not influence increase levels of blood glucose and lactate in non-Remi group in this study.

This current study has four limitations. First, it is unclear that our 0.5 µg/kg/min remifentanil infusion rate is optimal to prevent CPB stress. In adult, various infusion rates were applied during CPB to elucidate the effect of stress response suppression.[1,3,24] Sato et al. reported that 1 µg/kg/min remifentanil infusion was effect for suppression of stress responses.[9] Considering the difference of pharmacokinetics and pharmacodynamics between adult and children, higher infusion rate might be necessary to perform the maximum antistress effect of remifentanil during CPB. Second, this study is retrospective trial and based on small sample size and does not include quantitative evaluation of stress hormones or inflammatory cytokines. In our institution, the surgeons changed the CPB priming fluid, from 5% glucose to bicarbonate Ringer solution at March 2014; therefore, we cannot collect only 23 patients. These hormone and cytokine values are not measured routinely, and usage of remifentanil infusion during CPB is imperative by surgeon’s request. For measurement of these items, huge amount of blood sample is mandatory, and it induces severe anemia for children. From these reasons, we could not add more number of cases and construct prospective comparative study including stress response measurement. Third, our anesthetic management includes the routine dexmedetomidine infusion during CPB. Bulow et al. reported that dexmedetomidine was associated with a significant reduction of IL-1, IL-6, tumor necrosis factor-alpha, and INF-γ levels.[25] This effect resembling remifentanil may affect synergistically and result in present results. Fourth, we selected the only patients who underwent ASD or ventricular septal defect closure for this study. It was not elucidated that this remifentanil effect was beneficial to the patients with complex congenital heart disease, for example, hypoplastic left heart syndrome.
Because these patients have complicated hemodynamic state, remifentanil effect might induce worse outcome in the management of such children. To resolve these limitations, more detail, controlled prospective comparative study is warranted.

**Conclusion**

Remifentanil infusion suppresses increases of blood glucose and lactate levels and may act as vasodilator during CPB in pediatrics. Moreover, any side effect was observed in the current study. However, the remifentanil infusion rate, which is optimal for preventive effect on the elevations of blood glucose and lactate, is unclear. More detail prospective, randomized, controlled study should be taken to elucidate the effect of remifentanil during CPB in children.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. von Dossow V, Luetz A, Haas A, Sawitzki B, Wernecke KD, Volk HD, et al. Effects of remifentanil and fentanyl on the cell-mediated immune response in patients undergoing elective coronary artery bypass graft surgery. J Int Med Res 2008;36:1235-47.

2. Diegeler A, Doll N, Rauch T, Haberer T, Falk V, et al. Humoral immune response during coronary artery bypass grafting: A comparison of limited approach, “off-pump” technique, and conventional cardiopulmonary bypass. Circulation 2000;102 19 Suppl 3:III95-100.

3. Brix-Christensen V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. Acta Anaesthesiol Scand 2001;45:671-9.

4. Anand KJ, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 1990;73:661-70.

5. Falcao G, Ulate K, Kouzekanani K, Bielefeld MR, Morales JM, Rotta AT. Impact of postoperative hyperglycemia following surgical repair of congenital cardiac defects. Pediatr Cardiol 2008;29:628-36.

6. Yates AR, Dyke PC 2nd, Taed R, Hoffman TM, Hayes J, Feltes TF, et al. Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. Pediatr Crit Care Med 2006;7:351-5.

7. Munoz R, Laussen PC, Palacio G, Zienko L, Piercey G, Wessel DL. Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: An early indicator of morbidity and mortality. J Thorac Cardiovasc Surg 2000;119:155-62.

8. Winterhalter M, Brandl K, Rahe-Meyer N, Osthau A, Hecker H, Hagl C, et al. Endocrine stress response and inflammatory activation during CABG surgery. A randomized trial comparing remifentanil infusion to intermittent fentanyl. Eur J Anaesthesiol 2008;25:326-35.

9. Sato K, Maekawa S, Seki R, Yamashita H, Higashibepu N, Okazaki S, et al. Remifentanil prevents hyperglycemia and reduces insulin use during cardiopulmonary bypass in adult cardiac surgery. Masui 2011;60:441-7.

10. Alexander WS, Hilton DJ. The role of suppressors of cytokine signaling (SOCS) proteins in regulation of the immune response. Annu Rev Immunol 2004;22:503-29.

11. Ilangumaran S, Ramanathan S, Rottapel R. Regulation of the immune system by SOCS family adaptor proteins. Semin Immunol 2004;16:351-65.

12. Imoto Y, Kado H, Masuda M, Yasui H. Effects of chlorpromazine as a systemic vasodilator during cardiopulmonary bypass in neonates. Jpn J Thorac Cardiovasc Surg 2002;50:241-5.

13. Fyman PN, Cottrell JE, Kushins L, Castel H. Vasodilator therapy in the perioperative period. Can Anaesth Soc J 1986;33:629-43.

14. Li S, Krawczeski CD, Zappitelli M, Devanajan P, Thiessen-Philbrook H, Coca SG, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: A prospective multicenter study. Crit Care Med 2011;39:1493-9.

15. Vlasselaers D, Mesotten D, Langouche L, Vanhorebeek I, van den Heuvel I, Milants I, et al. Tight glycemic control protects the myocardium and reduces inflammation in neonatal heart surgery. Ann Thorac Surg 2010;90:22-9.

16. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, et al. Early insulin therapy in very-low-birth-weight infants. N Engl J Med 2008;359:1873-84.

17. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: A prospective, randomised controlled study. Lancet 2009;373:547-56.

18. Faustino EV, Bogue CW. Relationship between hypoglycemia and mortality in critically ill children. Pediatr Crit Care Med 2010;11:690-8.

19. Koren G, Barker C, Goresky G, Bohn D, Kent G, Klein J, et al. The influence of hypothermia on the disposition of fentanyl – Human and animal studies. Eur J Clin Pharmacol 1987;32:373-7.

20. Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl – Oxygen anesthesia for coronary-artery operations. Anesthesiology 1980;53:250-3.

21. Dawson PJ, Bjorksten AR, Blake DW, Goldblatt JC. The effects of cardiopulmonary bypass on total and unbound plasma concentrations of propofol and midazolam. J Cardiothorac Vasc Anesth 1997;11:556-61.

22. McFarlan CS, Anderson BJ, Short TG. The use of propofol infusions in paediatric anaesthesia: A practical guide. Paediatr Anaesth 1999;9:209-16.

23. Lake CL, Booker PD. Pediatric Cardiac Anesthesia. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 184-5.

24. Knapik M, Knapik P, Nadzakiewicz P, Misolek H, Saucha W, Walaszczuk M, et al. Comparison of remifentanil or fentanyl administration during isoflurane anesthesia for coronary artery bypass surgery. Med Sci Monit 2006;12:P133-8.

25. Bulow NM, Colpo E, Pereira RP, Correa EF, Waczkau EP, Duarte MF, et al. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. Braz J Med Biol Res 2016;49:e4646.