

Original Article

# *Continuous blood glucose monitoring during pediatric cardiopulmonary bypass*

Nami Kakuta\*, Shinji Kawahito\*\*, Naoji Mita\*, Tomohiro Soga\*\*, Shusuke Yagi\*\*, Shiho Satomi\*, Fumihiko Tada\*\*\*, Hiroyuki Kinoshita\*\*\*\*, Kazumi Takaishi\*\*\*\*\*, Hiroshi Kitahata\*\*\*\*\*

Department of Anesthesiology, Tokushima University Hospital\*

Department of Community Medicine and Human Resource Development, Tokushima University Graduate School of Biomedical Sciences\*\*

Department of Anesthesiology, Shikoku Medical Center for Children and Adults\*\*\*

Department of Anesthesiology, IMS Fujimi General Hospital\*\*\*\*

Department of Dental Anesthesiology, Tokushima University Hospital\*\*\*\*\*

## Abstract

The purpose of this study was to assess the accuracy and efficacy of a continuous blood glucose monitoring system (artificial endocrine pancreas; STG-22, Nikkiso, Co., Ltd., Tokyo, Japan) during pediatric cardiopulmonary bypass. Sixteen pediatric patients scheduled to undergo cardiovascular surgery with cardiopulmonary bypass (6 for atrial septal defects, 8 for ventricular septal defects and 2 for others, age: 7 months to 13 years, body weight 6.4-55.4 kg) were enrolled. The glucose sensor line of the artificial endocrine pancreas was connected to the venous side of the cardiopulmonary bypass circuit and used for continuous blood glucose monitoring. We obtained 66 samples for blood gas assessment from the cardiopulmonary bypass circuit, and i-STAT (Abbott, East Windsor, NJ, USA) was used for conventional blood glucose assessment. Data were analyzed with simple linear regression analysis using the Bland and Altman approach. After cardiopulmonary bypass was started and the aortic artery clamped, the blood glucose level rose markedly to around 300 mg/dl. Blood sampling via the venous side of the cardiopulmonary bypass circuit showed that continuous blood glucose monitoring was stable and reliable even during pediatric cardiovascular surgery with

cardiopulmonary bypass. A close correlation ( $R = 0.97$ ) was observed between continuous glucose measurement and conventional intermittent glucose measurements. The results of this continuous blood glucose monitoring system for cardiopulmonary bypass during pediatric cardiovascular surgery were highly reliable.

**Keywords:** continuous blood glucose monitoring, artificial endocrine pancreas, cardiovascular surgery, cardiopulmonary bypass, children

## Introduction

Hyperglycemia can cause a number of perioperative problems, including cardiac, neurological, and infectious complications<sup>1)</sup>, and often occurs in patients with or without diabetes during cardiovascular surgery, especially during cardiopulmonary bypass. Intensive insulin therapy (IIT) may reduce mortality and morbidity among critically ill patients<sup>2~5)</sup>. While the viability of IIT for children has been reported<sup>6)</sup>, variations in blood glucose levels during cardiopulmonary bypass (CPB) for children are extensive, making control of the blood glucose level difficult. Continuous blood glucose monitoring is essential for strict glycemic control during pediatric cardiovascular surgery. The purpose of this study was to assess the accuracy and efficacy of a continuous blood glucose monitoring system (artificial endocrine pancreas<sup>7, 8)</sup>; STG-22, Nikkiso, Co., Ltd., Tokyo, Japan) during pediatric CPB.

## Methods

This investigation conformed to the principles outlined

---

Received on Jun. 15, 2019; Accepted on Aug. 13, 2019

Corresponding address: Shinji Kawahito  
Department of Community Medicine and Human Resource Development,  
Tokushima University Graduate School of Biomedical Sciences,  
3-18-15, Kuramoto, Tokushima 770-8503, Japan  
Tel: +81-88-633-7181 Fax: +81-88-633-7182  
email: kawahito.shinji@tokushima-u.ac.jp

in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Studies of Tokushima University Hospital, and written informed consent was obtained from the parents or legal guardians of all children. Sixteen pediatric patients scheduled to undergo cardiovascular surgery with CPB were enrolled. The diagnoses of the patients were as follows: six atrial septal defects, eight ventricular septal defects, one pulmonary artery stenosis, one double outlet right ventricle). Complete repairs of these anomalies were performed. The patients' characteristics were as follows: age, 7 months to 13 years 4 months; height, 68.0 to 160.6 cm; weight, 6.4 to 55.4 kg; gender (male/female), 8/8. General anesthesia was induced using sevoflurane, and maintained with sevoflurane, fentanyl and midazolam. The total dose of fentanyl during CPB was from 50 to 100  $\mu\text{g}/\text{kg}$ .

The STG-22 is an original artificial endocrine pancreas with a closed-loop glycemic control system that provides continuous blood glucose monitoring through a glucose sensor electrode, and automatically administers insulin and glucose infusions to maintain appropriate blood glucose levels<sup>7, 8</sup>. The insulin and glucose pumps are computer-regulated based on a targeted blood glucose value determined before operation of the system is started. The STG-22's glucose sensor, which draws blood from the patient at a rate of 2 ml per hour, is capable of continuously measuring the blood glucose level with its glucose sensor, and automatically infuses insulin or glucose to adjust the blood glucose level of the patients in accordance with the target glucose value, in an adaptation of what we call the "closed loop system". This device provides continuous blood glucose monitoring by means of dual lumen catheter blood sampling, a high-quality roller pump and a glucose sensor electrode with a glucose oxidase membrane. The measured blood glucose levels are entered into a computer, and the infusion rate of insulin or glucose is determined by an algorithm. In the present study, we used this device only for glucose monitoring purposes.

We developed a novel blood sampling method utilizing an artificial endocrine pancreas via the cardiopulmonary bypass circuit<sup>9</sup>. The glucose sensor line of the artificial endocrine pancreas (STG-22) was connected to the venous side of the CPB circuit and used for continuous blood glucose monitoring. A radial arterial catheter was also inserted to obtain samples for blood glucose determination. The blood glucose determination was carried out approximately once every thirty minutes, to ensure a stable condition. We obtained 66 samples for blood gas assessment from the CPB circuit. An i-STAT (Abbott, East Windsor, NJ, USA) was used for conventional blood glucose assessment.

The accuracies of continuous glucose measurements

(STG-22) and the conventional intermittent glucose measurements (i-STAT) were compared by a Bland-Altman plot<sup>10, 11</sup>. In addition, the values obtained using the two methods were subjected to correlation analysis. StatView version 5.0 (SAS institute Inc., Cary, NC) was used for the statistical analysis. Values were expressed as mean  $\pm$  SD, and  $P < 0.05$  was considered to be statistically significant.

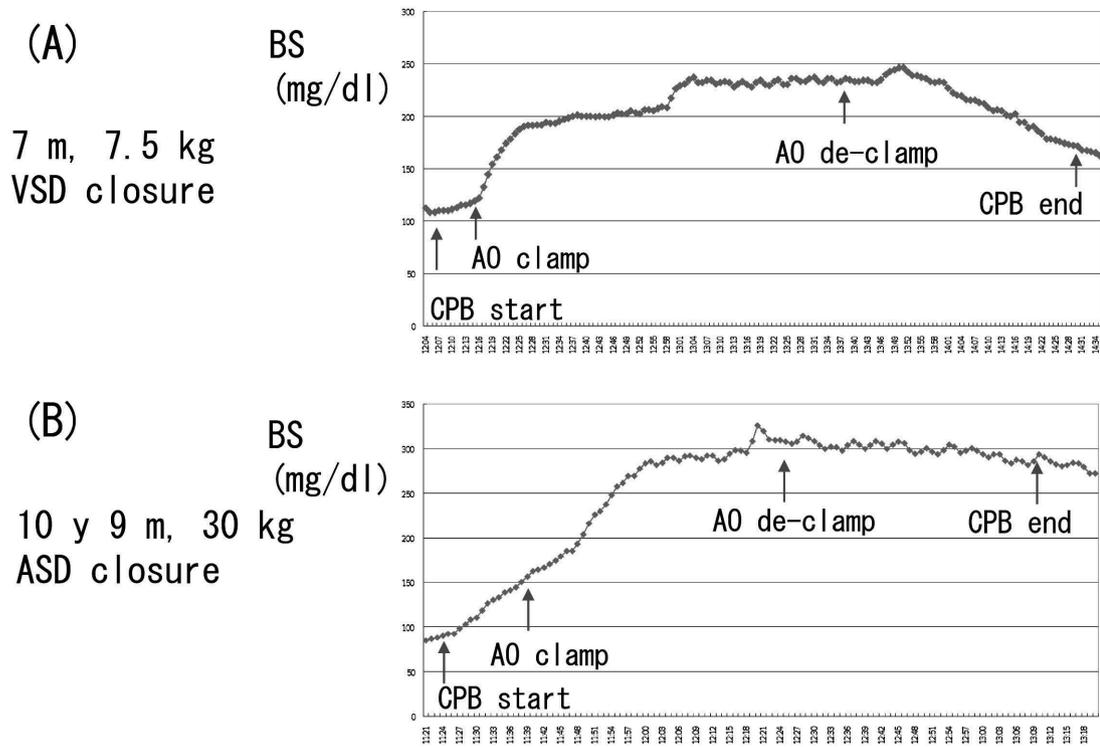
## Results

Blood sampling via the venous side of the CPB circuit showed that continuous blood glucose monitoring was stable and reliable even during pediatric cardiovascular surgery with CPB. There were no complications related to use of the STG-22. Figure 1 shows two typical cases of continuous blood glucose monitoring during cardiovascular surgery with cardiopulmonary bypass. We found that significant hyperglycemia occurred after initiation of the cardiopulmonary bypass using an aortic clamp; the blood glucose level increased markedly (maximum blood glucose concentration:  $255 \pm 72$  mg/dl). After the aortic de-clamp and termination of the CPB, the blood glucose showed a tendency to decrease (**Figure 1A**), but hyperglycemia of around 200 mg/dl persisted in some cases (**Figure 1B**).

A close correlation ( $r = 0.97$ ) was observed between continuous glucose measurement by the STG-22 and conventional intermittent glucose measurements (i-STAT) (**Figure 2, left**). The limits of agreement are indicated by the dotted line – that is, the interval of two standard deviations of the measurement differences either side of the mean difference. Significant agreement was also observed when the differences between the two measurements were plotted against their mean values. Limits of agreement were thought to be clinically acceptable, however, continuous glucose measurement by the STG-22 tended to be lower than conventional intermittent glucose measurements (i-STAT) (fixed bias: 30.0; 95% confidence interval: 24.6 - 35.4) (**Figure 2, right**).

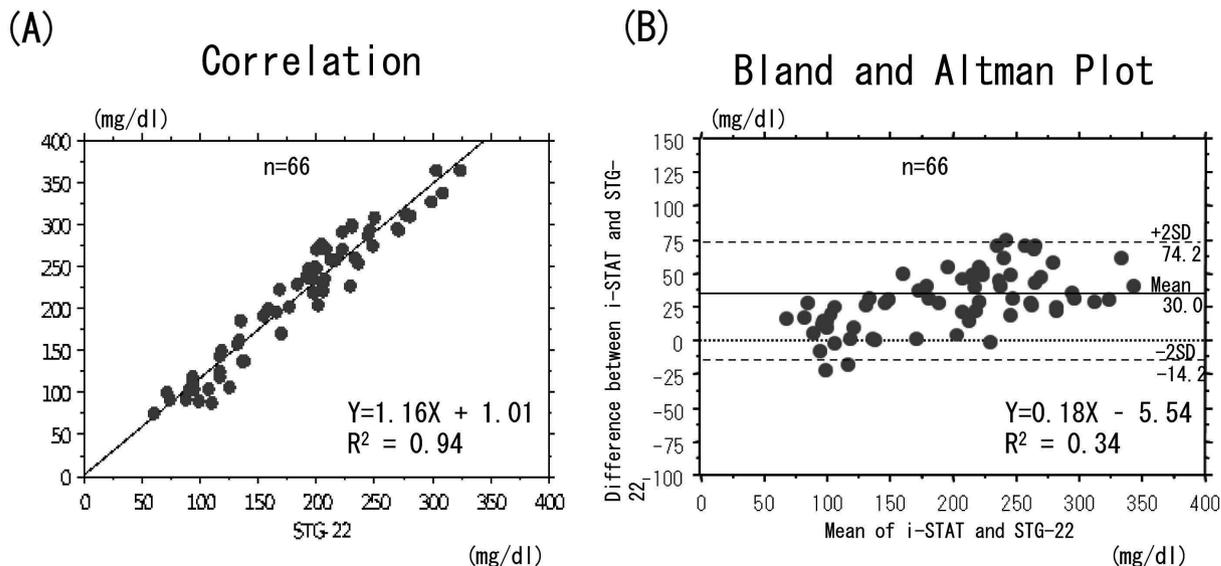
## Discussion

This is the first report of continuous blood glucose monitoring during cardiovascular surgery for pediatric patients. Use of the continuous blood glucose monitoring system during CPB for pediatric cardiovascular surgery was remarkably reliable. During cardiovascular surgery (especially cardiopulmonary bypass), blood glucose levels change dramatically, so continuous blood glucose monitoring is essential for strict glycemic control during pediatric cardiovascular surgery. The artificial endocrine pancreas is currently the only continuous blood glucose monitoring device in the world, and appears to be a useful option for IIT.



**Figure 1 Continuous blood glucose monitoring during pediatric cardiovascular surgery with cardiopulmonary bypass (two typical examples)**

BS: blood sugar, CPB: cardiopulmonary bypass, AO: aorta, VSD: ventricular septal defect, ASD: atrial septal defect



**Figure 2 Accuracy of continuous blood glucose monitoring during pediatric cardiopulmonary bypass**

Left: Correlations between continuous glucose measurements (STG-22) and conventional intermittent glucose measurements (i-STAT).

Right: Differences between the two measurements plotted against their mean (Bland-Altman plot of continuous glucose measurements (STG-22) and conventional intermittent glucose measurements (i-STAT)).

Our ultimate goal is the establishment of a new, superior, perioperative blood glucose control method using an artificial endocrine pancreas during pediatric cardiovascular surgery.

Hyperglycemia can exacerbate a number of perioperative problems, including cardiac, neurologic, and infectious complications<sup>1)</sup>. IIT was reported to reduce mortality and morbidity in critically ill adult patients<sup>2~5)</sup>, especially high-risk cardiac surgery patients. Regarding pediatric patients, some studies have demonstrated that hyperglycemia is a predictor of adverse outcomes in pediatric intensive care units<sup>12, 13)</sup>. Srinivasan et al.<sup>12)</sup> demonstrated that 86% of patients in their pediatric intensive care unit had a glucose value > 126 mg/dl at some point during their stay. In addition, they showed that the duration of hyperglycemia and the peak glucose were associated with mortality. Faustino and Apkon<sup>13)</sup> also demonstrated an association between hyperglycemia and length hospital of stay. The patient population analyzed by Srinivasan et al. did not include any postoperative cardiac patients. Faustino and Apkon's population included cardiac patients in the postoperative period, but there was no subanalysis of this patient population.

In the field of cardiovascular surgery, the importance of controlling postoperative blood glucose values at 200 mg/dl or less has been recognized since the late 1990s<sup>14, 15)</sup>. Since then, many reports regarding the usefulness of intensive insulin therapy during cardiovascular surgery have been published<sup>16~19)</sup>. In a study by Van den Berghe et al., intensive insulin therapy after surgery reduced morbidity and death in critically ill patients, most of whom had undergone cardiac surgery.

Regarding glycemic control during cardiopulmonary bypass, one study analyzed 1,579 adult patients with diabetes who underwent cardiovascular surgery in 2005<sup>20)</sup>. Among patients whose blood glucose levels during cardiopulmonary bypass exceeded 360 mg/dl, the mortality increased from 1.7% to 6%. This is why hyperglycemia of more than 300 mg/dl should be avoided, even temporarily, if a patient has diabetes. Cases with blood glucose levels exceeding 300 mg/dl may be considered rare, but through continuous monitoring we found many cases of blood glucose levels above this value during cardiopulmonary bypass.

Why does hyperglycemia occur during cardiovascular surgery (especially during cardiopulmonary bypass)? One of the main reasons is suppression of insulin secretion. This is caused by a reduction in the pancreatic blood flow, the inhibition of  $\beta$ -cell activity of the pancreas due to hypothermia, and the increased secretion of insulin counter-regulatory hormones. Other reasons are intracellular disorder of glucose use due to peripheral circulatory failure, and inhibition of the glycolytic pathway enzyme due to

hypothermia<sup>21)</sup>. We do not use it in this hospital, the effect of cardioplegia and priming solution including glucose may be thought.

The reliability and accuracy of continuous blood glucose monitoring during and after general surgery with the STG-22 has been verified in several studies, such as those by Yamashita et al.<sup>22, 23)</sup>. We examined it during pediatric cardiovascular surgery with CPB at this time. In our study, the blood glucose levels measured continuously during CPB with the STG-22 correlated strongly with measurements obtained intermittently with a conventional laboratory glucometer. Significant agreement was also observed when the differences between the two measurements were plotted against their mean values, and the results were similar to those obtained from previous reports. The accuracy of STG-22 during pediatric CPB was confirmed. In addition, when we discuss agreement using Bland-Altman plot, evaluation of systematic bias (fixed bias and proportional bias) is essential. Because 95% confidence interval of bias did not include zero, it was considered that fixed bias was present. Regarding proportional bias, it is necessary to perform regression analysis of Bland-Altman plot and examine significance of the coefficient of regression. Because a weak correlation was shown, it was considered that proportional bias was also present in this study. However, proportional bias which is growing big in proportion to a true value is a natural phenomenon, it is clinically acceptable without an extreme difference.

However, our clinical study had some limitations: (1) the sample size was small; (2) the variation of range of age group was too broad from infant to junior high school students; (3) the depth of anesthesia and/or the dose of opioid given during the cardiopulmonary bypass might affect the blood glucose level; and (4) the Bland-Altman plot methods only defines the intervals of agreement, it does not say whether those limits are acceptable or not. Acceptable limits must be defined a priori, based on clinical necessity, biological considerations or other goals<sup>24)</sup>.

In conclusion, we confirmed that the results from a continuous blood glucose monitoring system for CPB during pediatric cardiovascular surgery were highly reliable. Because insulin secretion during CPB decreases due to hypothermia and hypoperfusion, glucose levels change extensively. Continuous monitoring enhances awareness of typical changes in blood glucose levels during cardiovascular surgery for children. This artificial endocrine pancreas facilitates the safe use of IIT during pediatric cardiovascular surgery.

## References

- 1 Kawahito S, Kitahata H, Oshita S: Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. *World J Gastroenterol* 2009; 15: 4137-4142.
- 2 Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Eng J Med* 2001; 345: 1359-1367.
- 3 Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 2003; 31: 359-366.
- 4 Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Eng J Med* 2006; 354: 449-461.
- 5 Van den Berghe G, Wilmer A, Milants I, et al: Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006; 55: 3151-3159.
- 6 Vlasselaers D, Milants I, Desmet L, et al: Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomized controlled study. *Lancet* 2009; 373: 547-556.
- 7 Hanazaki K, Nosé Y, Brunicardi FC: Artificial endocrine pancreas. *J Am Coll Surg* 2001; 193: 310-322.
- 8 Kono T, Hanazaki K, Yazawa K, et al: Pancreatic polypeptide administration reduces insulin requirements of artificial pancreas in pancreatectomized dogs. *Artificial Organs* 2005; 29: 83-87.
- 9 Kawahito S, Higuchi S, Mita N, et al: Novel blood sampling method of an artificial endocrine pancreas via the cardiopulmonary bypass circuit. *J Artif Organs* 2013; 16: 508-509.
- 10 Bland JM, Altman DG: Agreed statistics: measurement method comparison. *Anesthesiology* 2012; 116: 182-185.
- 11 Sedgwick P: Limits of agreement (Bland-Altman methods). *BMJ* 2013; 346: f1630.
- 12 Srinivasan V, Spinella PC, Drott HR, et al: Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med* 2004; 5: 329-336.
- 13 Faustino EV, Apkon M: Persistent hyperglycemia in critically ill children. *J Pediatr* 2005; 146: 30-34.
- 14 Furnary AP, Zerr KJ, Grunkemeier GL, et al: Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 1999; 67: 352-362.
- 15 Golden SH, Peart-Vigilance C, Kao WH, et al: Perioperative glycemic control and the risk of infections complications in a cohort of adults with diabetes. *Diabetes Care* 1999; 22: 1408-1414.
- 16 Furnary AP, Gao G, Grunkemeier GL, et al: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; 125: 1007-1021.
- 17 Lazar HL, Chipkin SR, Fitzgerald CA, et al: Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcome and decreases recurrent ischemic events. *Circulation* 2004; 109: 1497-1502.
- 18 Quattara A, Lecomte P, Manach YL, et al: Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology* 2005; 103: 687-694.
- 19 Lecomte P, Foubert L, Nobels F, et al: Dynamic tight glycemic control during and after cardiac surgery is effective, feasible, and safe. *Anesth Analg* 2008; 107: 51-58.
- 20 Doenst T, Wijeyesundera D, Karkouti K, et al: Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2005; 130: 1144-1150.
- 21 Kawahito S, Kitahata H, Kitagawa T, et al: Intensive insulin therapy during cardiovascular surgery. *J Med Invest* 2010; 57: 191-204.
- 22 Yamashita K, Okabayashi T, Yokoyama T, et al: The accuracy of a continuous blood glucose monitor during surgery. *Anesth Analg* 2008; 106: 160-163.
- 23 Yamashita K, Okabayashi T, Yokoyama T, et al: Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. *Acta Anaesthesiol Scand* 2009; 53: 66-71.
- 24 Giavarina D: Understanding Bland Altman analysis. *Biochem Med* 2015; 25: 141-151.