Removal of prostaglandin E₂ and increased intraoperative blood pressure during modified ultrafiltration in pediatric cardiac surgery

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Objective: We investigated the relationship between serum prostaglandin E₂ and intraoperative blood pressure in pediatric cardiac surgery with modified ultrafiltration.

Methods: In 35 consecutive patients (31.6 ± 26.8 months, 0.4–111 months, 10.9 ± 5.5 kg, 2.9–23.8 kg) who underwent cardiac surgery with modified ultrafiltration, we measured intraoperative serum prostaglandin E₂ changes and effluent prostaglandin E₂, assessed the relationship between serum prostaglandin E₂ and intraoperative hemodynamic parameters, and performed subset analyses to compare patients with low (<10 kg, n = 18) and high (>10 kg, n = 10) weights.

Results: During cardiopulmonary bypass, systolic blood pressure decreased from 80.8 ± 15.2 to 60.5 ± 11.3 mm Hg ($P = .0000002979$) and serum prostaglandin E₂ increased from 16.6 ± 8.7 to 58.8 ± 53.3 pg/mL ($P = .002$). During modified ultrafiltration, although central venous pressure and catecholamine dosage transited at the same levels, systolic blood pressure increased from 60.5 ± 11.3 to 83.4 ± 14.1 mm Hg ($P = .0000002979$) and serum prostaglandin E₂ decreased from 58.8 ± 53.3 to 21.1 ± 11.6 pg/mL ($P = .001$), with negative correlation between serum prostaglandin E₂ and systolic blood pressure ($R = -0.392$, $P = .0000277723$) and 15,700 ± 10,700 pg (1790 ± 2230 pg/kg) prostaglandin E₂ removed during modified ultrafiltration. Decrease in serum prostaglandin E₂ was significantly higher in low-weight patients (51.8 ± 58.4 pg/mL) than in high-weight patients (15.7 ± 30.1 pg/mL).

Conclusion: Removal of prostaglandin E₂ is one reason for increased blood pressure during modified ultrafiltration, with the effect more marked in low-weight patients.

Modified ultrafiltration (MUF) was developed as a method to reduce the adverse effects of cardiopulmonary bypass (CPB) in pediatric patients.¹ In pediatric cardiac surgery with CPB, MUF has been reported not only to reduce total body water and decrease pulmonary vascular resistance but also to increase blood pressure (BP).² The mechanism for the increase in BP during MUF, however, remains unclear. The removal of interleukins 6 and 8³ and endothelin 1⁴ during MUF was reported in previous studies; however, these changes could not explain the increase in BP during a short period of MUF. In this study, we hypothesized that a major cause of the increase in BP is removal of some vasodilator by MUF. We therefore investigated the effects of MUF on the relationship between the serum prostaglandin E₂ (PGE₂) level that is activated through exposure of blood to artificial material during CPB and intraoperative BP in pediatric cardiac surgery.

MATERIALS AND METHODS

In this study, we assessed 35 consecutive patients who underwent pediatric cardiac surgery with CPB and MUF from October 2005 to September

2007. Informed consent to measure the serum PGE₂ level and the PGE₂ level in the MUF discharge had been obtained from the parents. The age, weight, and operative procedure data are shown in Table 1. Exclusion criterion was body weight greater than 25 kg to ensure investigation of a pediatric population.

For pediatric cardiac surgery, we generally use four kinds of CPB circuit adapted for different body weights. In this study, CPB was performed with an SS circuit (priming volume 350 mL/circuit; Senko Medical Co, Ltd, Osaka, Japan; artificial lung baby-RX; Terumo Corporation, Tokyo, Japan) for body weights smaller than 7 kg, an S circuit (priming volume 500 mL/circuit; Senko; artificial lung D-902 Lilliput II; Dideco SpA, Mirandola, Italy) for body weights between 7 and 20 kg, and an M circuit (priming volume 700 mL/circuit; Senko; artificial lung CAPIOX RX-15; Terumo) for body weights greater than 20 kg. The CPB flow was maintained at 2.8 L/(m²/min) during cardiac arrest, and an α -blocker (chlorpromazine) was administered several times to a total dosage of 2 to 4 mg/kg. Initial blood priming was performed when the predicted hematocrit during CPB was lower than 15%, which was the criterion in a previous study.⁵ Blood transfusion during CPB was performed to ensure a hematocrit greater than 30% at the end of the CPB. Cardiac arrest was obtained by crystalloid cardioplegia with added albumin. The CPB time, aortic crossclamp time, and amount of intraoperative blood transfusion are also shown in Table 1.

MUF was performed with a hemoconcentrator (CF04; JMS Co, Ltd, Hiroshima, Japan) connected to the CPB circuit in all cases. After CPB, we performed MUF through aortic and inferior vena caval cannulas with the same routes used for CPB. The blood was taken from the body through the aortic cannulas and hemofiltered. The remaining blood in the CPB reservoir and the hemofiltered blood were returned to the body through the inferior vena caval cannula. The MUF flow was 10 mL/(kg/min), and the time was 15 minutes. Diluted ultrafiltration with 1000 mL crystalloid solution was performed concomitantly during the CPB.

Many chemomediators are increased by an inflammatory reaction during pediatric heart surgery with CPB, and these chemomediators could act as vasodilators. A kallikrein-kinin system is one of the inflammatory systems, and prostaglandin E₂ (PGE₂) is one of the substances produced through

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J Thorac Cardiovasc Surg 2009;137:730-5
0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2008.09.017

Abbreviations and Acronyms

BP	= blood pressure
CPB	= cardiopulmonary bypass
CVP	= central venous pressure
DD	= dopamine dosage
HR	= heart rate
MUF	= modified ultrafiltration
PGE ₂	= prostaglandin E ₂

activation of the kallikrein–kinin system during CPB (Figure 1). PGE₂ has a low molecular weight and thus is removed through the membrane of the filter. We therefore measured the serum PGE₂ level at the following four times (n = 28): before (before CPB) and after (end CPB) the CPB, after the MUF (end MUF), and after the operation (postoperative). Changes in systolic BP measured by an arterial line, central venous pressure (CVP) measured by a central venous catheter, heart rate (HR), and dopamine dosage (DD) were assessed from anesthesia records at the same four times as the measurement of the serum PGE₂ level. Additionally, to confirm that PGE₂ had been removed to MUF discharge, the PGE₂ level in the discharge and the total PGE₂ removed into the discharge during MUF were also investigated (n = 12).

Correlation analyses between the serum PGE₂ level and BP, CVP, HR, and DD and between BP and CVP, HR, and DD were performed. Because the adverse effects of CPB are increased in low-weight patients,^{6–10} we divided the patients into two groups by body weight: less than 10 kg (group L, n = 18) and greater than 10 kg (group H, n = 10). Subset analyses between the two groups were performed.

After collection, blood samples were centrifuged at 3000 rpm for 5 minutes. Plasma was then separated and stored at –70°C until analysis. Discharge samples were treated in the same way as blood samples. The PGE₂ level was measured with a commercially available radioimmunoassay kit (PerkinElmer Life and Analytical Sciences, Inc, Waltham, Mass).

Comparisons between two values were performed with unpaired 2-tailed *t* tests for the means of normally distributed variables and Wilcoxon rank sum tests for skewed data. Correlation coefficients were used to assess the correlations between BP and vasodilator level. A correlation coefficient *R* between –0.30 and 0.30 was considered to indicate a poor correlation. All the statistical analyses were performed with the statistical software package SPSS 12.0 J (SPSS Inc, Chicago, Ill) software for Windows (Microsoft Corporation, Redmond, Wash). All data are expressed as mean ± SD.

RESULTS

The HR increased during CPB from 126 ± 18 beats/min before CPB to 149 ± 24 beats/min at end CPB (*P* = .0000356305), and no significant differences were observed after end MUF CPB (146 ± 21 beats/min postoperative 149 ± 24 beats/min). The CVP showed no significant changes during the procedure (7.8 ± 2.1 mm Hg before CPB, 9.1 ± 3.5 mm Hg at end CPB, 9.4 ± 4.1 mm Hg at end MUF, and 10.3 ± 3.6 mm Hg postoperative). The DD increased from 0.5 ± 1.6 μg/(kg/min) before CPB to 6.5 ± 2.3 μg/(kg/min) at end CPB (*P* = .00000000000000008262). No significant differences, however, were observed after CPB (end MUF 6.3 ± 2.1 μg/[kg/min], postoperative 6.0 ± 1.9 μg/[kg/min]).

The systolic BP decreased during CPB from 80.8 ± 15.2 mm Hg before CPB to 60.5 ± 11.3 mm Hg at end CPB

TABLE 1. Patient profiles

Age (mo, mean ± SD and range)	31.6 ± 26.8 (0.4–111)
Weight (kg, mean ± SD and range)	10.9 ± 5.5 (2.9–23.8)
Cardiopulmonary bypass time (min, mean ± SD and range)	93.7 ± 50.4 (41–300)
Aortic crossclamp time (min, mean ± SD and range)	45.6 ± 29.4 (14–160)
Blood transfusion (mL, mean ± SD and range)	339 ± 269 (0–1045)
Operative procedures (No.)	
Ventricular septal defect closure	14
Atrial septal defect closure	3
Fontan operation	3
Tetralogy of Fallot repair	2
Bidirectional Glenn shunt	2
Ross procedure	1
Tricuspid valve closure	1
Jatene operation	1
Atrioventricular septal defect repair	1
Truncus arteriosus repair	1
Partial anomalous pulmonary venous connection repair	1
Cor triatriatum repair	1
Left ventricle–right atrium shunt closure	1
Doty procedure	1
Pulmonary atresia with intact ventricular septum repair	1
Right ventricular outflow tract stenosis release	1

(*P* = .00000002979). During MUF, however, systolic BP increased significantly to 83.4 ± 14.1 mm Hg at end MUF (*P* = .000000002802). After that, no significant difference was observed between end MUF and postoperative (84.0 ± 14.5 mm Hg) values (Figure 2).

The serum PGE₂ level increased during CPB from 16.6 ± 8.7 pg/mL before CPB to 58.8 ± 53.3 pg/mL at end CPB (*P* = .002). During MUF, however, the serum PGE₂ level decreased significantly to 21.1 ± 11.6 pg/mL at end MUF (*P* = .001); it also showed a tendency to be lower at the postoperative point (15.4 ± 9.7 pg/mL, *P* = .06) than at end MUF (Figure 3). The transitional pattern seen Figure 3 (serum PGE₂) is much like a reversal of the transitional pattern seen in Figure 2 (systolic BP).

The mean amount of the discharge from MUF, the PGE₂ level in the MUF discharge, total PGE₂ in the MUF discharge, and PGE₂ in MUF discharge per body weight are shown in Table 2. During MUF, a large quantity of PGE₂ was removed to the MUF discharge by ultrafiltration.

In correlation analyses, there was a significant negative correlation between serum PGE₂ level and systolic BP (*R* = –0.392, *y* = –0.1801*x* + 79.7, *P* < .001; Figure 4). Although analyses between other parameters were performed, there were no correlations between serum PGE₂ level and diastolic BP, CVP, HR, and DD or between BP (systolic and diastolic) and CVP, HR, and DD. During MUF, the serum

FIGURE 1. Kallikrein-kinin system and prostaglandin E₂.

PGE₂ level was lower and the systolic BP was higher in almost all patients (Figure 5).

In subset analyses, the blood transfusion per body weight (67.7 ± 42.8 mL/kg in group L vs 21.2 ± 29.3 mL/kg in group H), the priming volume per body weight (58.8 ± 17.1 mL/kg in group L vs 35.2 ± 7.0 mL/kg in group H), and the area of CPB circuit per body weight (0.35 ± 0.11 m²/kg in group L vs 0.22 ± 0.05 m²/kg in group H) were all significantly larger in group L than in group H ($P < .001$).

In each group, systolic BP decreased during CPB, from 73.9 ± 10.7 mm Hg in group L and 89.7 ± 15.8 mm Hg in group H before CPB to 57.5 ± 12.1 mm Hg in group L and 64.6 ± 9.3 mm Hg in group H at end CPB ($P = .0000836278984$ in group L and $.00000603$ in group H),

FIGURE 2. Change in systolic blood pressure during operation. Asterisk indicates $P < .01$. MUF, Modified ultrafiltration; CPB, cardiopulmonary bypass; Postop, after operation.

FIGURE 3. Change in serum prostaglandin E₂ level during operation. Asterisk indicates $P < .01$. MUF, Modified ultrafiltration; CPB, cardiopulmonary bypass; Postop, after operation.

and systolic BP in group H was higher than in group L before CPB ($P = .002$). During MUF, systolic BP in each group increased, to 82.4 ± 12.3 mm Hg in group L and 85.2 ± 15.9 mm Hg in group H at end MUF; values were thereafter maintained at the same level to the postoperative measurement (87.1 ± 17.0 mm Hg in group L and 81.9 ± 11.6 mm Hg in group H).

In group L, the serum PGE₂ level increased significantly during CPB from 16.7 ± 8.6 before CPB to 72.8 ± 58.1 pg/mL at end CPB ($P = .000758$); in group H, however, there was no significant difference between values of 15.6 ± 9.2 pg/mL before CPB and 32.5 ± 30.8 pg/mL at end CPB. At end CPB, the serum PGE₂ level was significantly higher in group L than in group H ($P = .02$). In group L, the serum PGE₂ level decreased significantly during MUF to 23.9 ± 12.5 pg/mL at end MUF ($P = .04$); in group H, however, this value was not significantly lower at end MUF (16.2 ± 7.6 pg/mL). After that, no significant differences were observed between end MUF and postoperative values (17.1 ± 11.0 pg/mL in group L and 12.4 ± 5.9 pg/mL in group H).

TABLE 2. Prostaglandin E₂ in the modified ultrafiltration discharge

MUFD (mL)	882 ± 337
PGE ₂ level (pg/mL)	18.8 ± 11.5
PGE ₂ in MUFD (pg)	15,700 ± 10,700
Ratio of PGE ₂ in MUFD to body weight (pg/kg)	1790 ± 2230

All values are mean ± SD. MUF, Modified ultrafiltration discharge; PGE₂, prostaglandin E₂.

FIGURE 4. Correlation between serum prostaglandin E₂ level and systolic blood pressure during operation. There was negative correlation between serum prostaglandin E₂ level and systolic blood pressure ($R = -0.392$, $y = -0.1801x + 79.7$, $P < .01$).

In correlation analyses, although there was a significant negative correlation between serum PGE₂ level and systolic BP in group L ($R = -0.433$, $P < .001$, $y = -0.191x + 82.3$), there was no significant correlation in group H. The decrease in serum PGE₂ during MUF was larger in group L than in group H (51.8 ± 58.4 pg/mL in group L vs 15.7 ± 30.1 pg/mL in group H, $P = .04$), and the amount of PGE₂ in the MUF discharge per body weight was also larger in group L than in group H (3020 ± 2550 pg/kg in group L vs 930 ± 420 pg/kg in group H, $P = .1$) (Figure 6).

DISCUSSION

MUF has been reported to have several clinical benefits: increasing intraoperative BP,^{11,12} reducing the incidence of pleural or pericardial effusion, and shortening hospital stay¹³ and duration of ventilatory support.¹⁴ With regard to the reason that MUF induces these clinical improvements, two major contrasting effects can be suggested, “concentration” or “removal” of some factor or factors in the blood. For example, increases in the hematocrit, fibrinogen, or total plasma protein^{15,16} during MUF would be brought about by concentration, whereas decreases in interleukin 6 or 8 or in tumor necrosis factor α^3 would occur through removal.

Although it has been suggested that the increase in BP during MUF might result in part from improvements in myocardial contractility associated with a reduction in myocardial water content,² the precise mechanism for any

FIGURE 5. Changes in serum prostaglandin E₂ levels and systolic blood pressure during modified ultrafiltration (MUF). In almost all cases, serum prostaglandin E₂ level decreased and systolic BP increased during modified ultrafiltration.

increase in BP remains unclear. During MUF, the removal of serum PGE₂ could decrease cardiac index in response to an increase in cardiac afterload. Although systolic BP increased during MUF in this study, we did not examine whether cardiac index increased. A previous study, however, showed that ventricular systolic function improved during MUF as a result of reduced myocardial edema.¹⁷ We suppose that increased cardiac index would be brought by improved ventricular function despite increased afterload caused by removal of PGE₂ during MUF. An earlier study of ours showed that systolic BP was not correlated with increased hematocrit after MUF, and there was also no correlation between the percentage increases in systolic BP and hematocrit, suggesting that the rise in hematocrit was unlikely to be responsible for the increased BP after MUF.¹¹ To investigate the major reason for the increase in BP during MUF, in this study we therefore paid attention to another effect, the removal of a major vasodilator.

PGE₂ production is stimulated by the kallikrein–kinin system,¹⁸ which is activated through the exposure of blood to artificial materials during CPB.^{19,20} Additionally, PGE₂ is a major intrinsic vasodilator, and a relationship has been reported between increased serum PGE₂ levels and decreased BP in patients with intraoperative hypotension under conditions of CPB²¹ and hemodialysis.²² As in a previous report of coronary artery bypass grafting with CPB in adult patients,²³ our study found that the serum PGE₂ level increased and systolic BP decreased significantly during CPB in pediatric patients. In contrast, during MUF, the

FIGURE 6. Subset analysis by body weight. Asterisk indicates $P < .01$. Group L, Patients with body weight <10 kg; Group H, patients with body weight >10 kg; MUF, modified ultrafiltration; N.S., not significant; CPB, cardiopulmonary bypass; Postop, after operation.

serum PGE₂ level decreased and systolic BP increased significantly. Additionally, with respect to the relationship between serum PGE₂ level and systolic BP, there was a significant negative correlation.

During MUF, we used the JMS CF04 membrane for ultrafiltration; this has a screening coefficient that allows the passage of 90% of molecules 5000 Da in molecular size and 50% of molecules 10,000 Da in molecular size. PGE₂ (352 Da in molecular size) will theoretically be removed almost entirely through the membrane during ultrafiltration. The serum PGE₂ level in our study, however, remained above the reference range even after MUF. Possible explanations for this are that PGE₂ production may be increased under re-warming of body temperature during MUF²⁴ and that limited MUF flow can not ultrafilter all the body's blood.

In this study, a large amount of PGE₂, 15700 ± 10700 pg (1790 ± 2230 pg/kg) was removed by discharge during MUF, while at the same time systolic BP increased. In the light of these results, there is strong evidence that one reason for the decrease in serum PGE₂ is removal by MUF. The predicted total amount of PGE₂ decreased during MUF, however, was as follows: 10.9 (mean body weight in kilograms) $\times 80$ (mean circulated blood in mL/kg) $\times (58.8 - 21.1$ [mean serum PGE₂ level during MUF in pg/mL]) = $32,874$ pg. Therefore about 50% of the predicted total amount of PGE₂ would have been expected to be removed

through the ultrafiltration membrane during MUF in this study. The rest of the decrease in PGE₂ during MUF would have to be due to inactivation or removal by other means, such as short-term inactivation by enzymatic action²⁵ in the lungs,²⁶ excretion to urine,²⁷ and adsorption onto the membrane of the ultrafiltration or artificial CPB circuit, as with cytokine removal by a polymethymethacrylate membrane hemofilter.²⁸ Although in our method of MUF (performed with blood derived from the aorta and returned into the inferior vena cava) the pulmonary to systemic perfusion ratio theoretically could become higher during MUF than after MUF, which might bring about greater lung inactivation of serum PGE₂, we unfortunately have no data on this. Furthermore, we did not measure preoperative PGE₂ level in this study. A previous study of evaluating the serum PGE₂ level, however, showed that mean serum PGE₂ level before oral PGE₂ administration was 45 ± 33 pg/mL in infants 27 ± 9.0 days old with pulmonary atresia and patent ductus arteriosus,²⁹ and mean serum PGE₂ level during the first 2 days after birth was 12.4 ± 6.8 pg/mL in patients with patent ductus arteriosus.³⁰ To investigate the effect of the difference in morphology, we performed another subset analysis of the patients with univentricular morphology ($n = 6$) and biventricular morphology ($n = 22$). The results showed that the increase in serum PGE₂ level and the decrease in systolic BP during CPB tended to be lower in the patients with univentricular morphology than in those with biventricular morphology. We suspect that the reason for the tendency for serum PGE₂ to be lower in the patients with univentricular morphology may be increased pulmonary blood flow from collateral arteries developed as a result of preoperative cyanosis. Further investigation to clarify the mechanism of the decrease in serum PGE₂ level during MUF is therefore warranted.

It has been reported that large priming volumes produce deleterious hemodynamic effects and postoperative cardiopulmonary dysfunction.^{6,7} In our subset analysis by body weight, the amount of blood transfused per body weight, priming volume per body weight, and area of CPB circuit per body weight were larger in group L patients (<10 kg) than in group H patients. Previous studies have demonstrated that increased priming volume^{8,9} or blood product transfusion¹⁰ enhances inflammatory response to CPB. It was suggested that the greater invasiveness of using CPB in low-weight patients would result in an increased serum PGE₂ level from the greater production of PGE₂ that in turn produces a greater decrease in BP. Interestingly, the decrease of serum PGE₂ during MUF was larger in group L than in group H; this because the increased serum PGE₂ levels of the smaller patients decreased to the same level as those of the other patients after MUF. These results suggest that the effect of PGE₂ removal by MUF on increased serum PGE₂ levels would be greater in low-weight patients.

Several limitations of this study should be noted. This study was not randomized and did not have a control group,

because it is our policy that MUF should be performed for all pediatric patients undergoing cardiac surgery with CPB and that the benefits of MUF must be provided to all these patients. In this study, the circuits, priming volumes, morphology, pulmonary to systemic perfusion ratio, age, and weight were not standardized, because the number of patients was not large enough. There were the problems of the relatively small size of the study with a diverse range of anomalies and widely range of age and weight. This was a pilot study to define the effectiveness of the MUF and to examine the removal and reduction in PGE₂ during MUF; standardization of these factors should therefore be performed in the future. Although statistical significance was obtained, the SD of serum PGE₂ at the end of CPB became large, because various types of patients with various ages, body weights, and diagnoses (many pathologies, with univentricular as well as biventricular physiology) were included in our study. An uncontrolled bias may have been induced, because CPB circuits change according to the body surface area of the patient. In this study, the circuits, priming volumes, morphology, and pulmonary to systemic perfusion ratio were not standardized, because the number of patients was not large enough. Although BP is regulated by various vasoactive substances, only PGE₂ was measured in our study, and we did not assess whether the cardiac index might be improved during MUF because of a reduction in cardiac edema.

In conclusion, serum PGE₂ level decreased and systolic BP increased during MUF, with no change in the CVP and DD. There was a negative correlation between intraoperative serum PGE₂ levels and systolic BP. A large quantity of PGE₂ was filtered out during MUF, resulting in a decrease in serum PGE₂. These results suggested that the decrease in serum PGE₂ levels caused by removal of PGE₂ is one of the reasons for the increase in BP seen during MUF. PGE₂ removal by MUF is more effective in low-weight patients and may counteract the more marked increase in serum PGE₂ levels caused by CPB in these patients.

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