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A neutrophil elastase inhibitor, sivelestat, improved respiratory and cardiac function in pediatric cardiovascular surgery with cardiopulmonary bypass

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Abstract

Purpose. Several reports indicate that a neutrophil elastase inhibitor, sivelestat, may have prophylactic efficacy against a systemic inflammatory response after cardiovascular surgery with cardiopulmonary bypass (CPB). We evaluated the clinical pulmonary and cardiac effects of sivelestat.

Methods. We performed a retrospective study of 25 pediatric patients who underwent elective cardiovascular surgery with CPB for ventricular septal defect with pulmonary hypertension. Ten patients received 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ sivelestat; the other is patients were the control group. There were no significant differences in demographic characteristics between the two groups. The $P_{a_{O_2}}$/fractional inspired oxygen ($F_{I_{O_2}}$; P/F) ratio, the respiratory index (RI), and the fractional area change (FAC) of the left ventricle (LV) in the postoperative course were measured.

Results. The P/F ratio was higher in the sivelestat group compared with the control group and there were significant differences between the two groups immediately after weaning form CPB, and at 12 h after weaning from CPB ($P < 0.05$). The RI was lower in the sivelestat group compared with the control group and there were significant differences between the two groups at immediately after weaning from CPB, and at 6 h and 12 h after CPB ($P < 0.05$). The FAC of the LV was significantly better in the sivelestat group and there was a significant difference between the two groups on postoperative day (POD) 3 ($P < 0.05$).

Conclusion. We have shown that pediatric patients who underwent cardiovascular surgery with CPB who received sivelestat had a higher P/F ratio, a lower RI, and better FAC of the LV in the postoperative course.

Key words Neutrophil elastase inhibitor · Sivelestat · Pediatric cardiovascular surgery · SIRS

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Introduction

Cardiopulmonary bypass (CPB) induces a systemic inflammatory response syndrome (SIRS) with the activation of inflammatory cells, the activation of complement, and the release of cytokines or chemokines [1–4]. Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS), which are characterized by an increased-permeability pulmonary edema associated with local and systemic inflammation, are also induced after cardiovascular surgery with CPB and contribute significantly to the postoperative morbidity and mortality [3–5].

Neutrophils and neutrophil elastase play important roles in the endothelial injury and the increased vascular permeability which are characteristics of ALI/ARDS [6,7]. Sivelestat, a neutrophil elastase inhibitor, was developed in Japan [8]. The protective effect of sivelestat in ALI/ARDS, postperfusion lung injury, and ischemia-perfusion lung injury has been demonstrated in several studies [9–11]. Moreover, several clinical studies have demonstrated the usefulness of sivelestat in the treatment of patients with ALI/ARDS [12–16], although there has been a conflicting study regarding its efficacy [17]. Especially, it has been suggested that ALI/ARDS can be alleviated more effectively if sivelestat is used early [12].

Because ARDS following cardiovascular surgery and CPB has been reported to carry a 15% mortality rate [4], it is important in the perioperative management to prevent ALI/ARDS following SIRS induced by CPB. Sivelestat has been shown to reduce both neutrophil elastase levels and interleukin (IL)-8 production, and to preserve neutrophil deformability during simulated extracorporeal circulation [18]. Moreover, it has been shown to attenuate ALI following CPB in an animal model [19]. Several clinical studies have shown the prophylactic efficacy of sivelestat for patients undergoing cardiovascular surgery with CPB [20–22]. However,

these studies evaluated only the respiratory effects of sivelestat, such as the Pa_{O_2}/fractional inspired oxygen ($F_{I_{O_2}}$; P/F) ratio, ventilator setting, and duration of ventilator support. Pulmonary hypertension (PH), which is a characteristic of ARDS [23], decreases right cardiac function and cardiac output. The degree of PH has been demonstrated to correlate with the severity of lung injury [24]. That is, it is suggested that the degree of cardiac function in the postoperative course is associated with the severity of lung injury. Therefore, with the hypothesis that sivelestat could improve respiratory and cardiac functions, we evaluated the effect of sivelestat on these functions after pediatric cardiovascular surgery with CPB.

Methods

After obtaining informed consent from the parents of the patients, we retrospectively studied 25 patients who had undergone elective cardiovascular surgery with CPB for ventricular septal defect (VSD) with PH. Patients who had received ventilator support preoperatively were excluded. Patients were classified into two groups: before and after sivelestat was introduced into our hospital. The control group (15 patients) underwent a standard procedure, and the sivelestat group (10 patients) received a continuous infusion of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ sivelestat after the induction of anesthesia. All patients were operated by the same surgeon.

Anesthesia was induced with nitrous oxide and sevoflurane, and endotracheal intubation was performed with fentanyl (2 $\mu g \cdot kg^{-1}$) and vecuronium (0.2 $mg \cdot kg^{-1}$). Anesthesia was maintained with fentanyl (30–50 $\mu g \cdot kg^{-1}$), isoflurane, or sevoflurane and vecuronium. Ventilation was controlled to maintain Pa_{CO_2} at approximately 40 mmHg, except during total bypass; continuous positive airway pressure was set at 5 cmH_2O. Methylprednisolone (30 $mg \cdot kg^{-1}$) was administered intravenously before CPB. Perioperative inotropic support was provided according to the decision of anesthesiologists, using dopamine, nitroglycerin, and milrinone. Sivelestat was administered until the patients were extubated.

The extracorporeal circuit consisted of a roller pump. Hematocrit levels were maintained at 20% or more throughout CPB. Crystaloid cardioplegia was used for cardiac preservation. The CPB flow rate was more than 2.4 $l \cdot min^{-1} \cdot m^{2-1}$. Hypothermia (30°C) was maintained during CPB. Modified ultrafiltration (MUF) was not performed in any of the patients because the cardiac surgeons in our hospital were not accustomed to MUF.

Demographic characteristics, duration of ventilator support, perioperative pulmonary complications, and duration of stay in the intensive care unit (ICU) were examined. Blood samples for arterial blood gas analysis were drawn regularly in the postoperative course. The P/F ratio and the respiratory index (RI; $A–a_{DO_2}/Pa_{O_2}$) were evaluated. Other blood samples, for examination of the inflammatory response (white blood cells [WBC]) were drawn on postoperative days (PODs) 0, 1, 2, and 3. Cardiac function was assessed by transthoracic echocardiography on PODs 0, 1, 2, and 3. The fractional area change (FAC) of the left ventricle (LV) was taken as an evaluation of cardiac function.

Values are presented as means and SD. Demographic characteristics were evaluated by the Mann-Whitney *U*-test. One-way analysis of variance (ANOVA) as compared with the base value was performed for within-group comparisons. Comparison of the two groups as a function of time was performed by two-way ANOVA with repeated measures. Values were further compared by the use of post-hoc tests with Bonferroni correction. $P < 0.05$ was considered significant.

Results

The preoperative demographic characteristics are summarized in Table 1. The two groups did not differ in terms of age, body weight, anesthesia time, operation time, CPB time, and aortic cross-clamp time. Preoperative FAC of the LV and estimated right ventricular pressure (RVP) did not differ significantly.

Figure 1 shows the values for the P/F ratio. Although the P/F ratio decreased in the postoperative course in

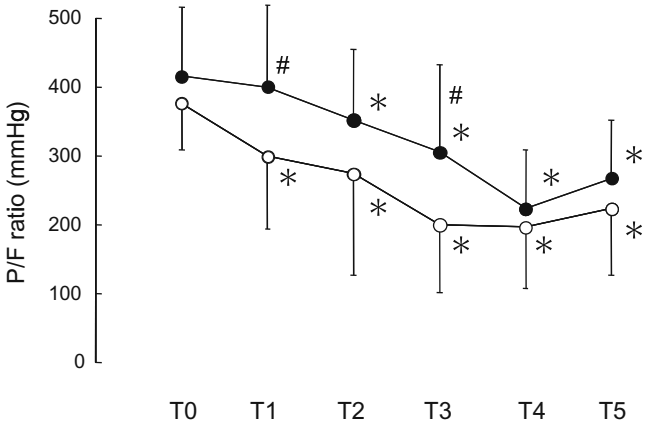

Fig. 1. Time course of changes in the $Pa_{O_2}/F_{I_{O_2}}$ (*P/F*) ratio. All values are means ± SD. * $P < 0.05$ vs initial value (*T0*) in the same group; # $P < 0.05$ vs value obtained at the same time in the control group (*open circles*). *T0*, After induction of anesthesia; *T1*, immediately after weaning from cardiopulmonary bypass (CPB); *T2*, 6 h after weaning from CPB; *T3*, 12 h after weaning from CPB; *T4*, 24 h after weaning from CPB; *T5*, 48 h after weaning from CPB. *Filled circles*, Sivelestat group

Table 1. Patients' demographic data and clinical characteristics

Characteristics	Control group (n = 15)	Sivelestat group (n = 10)	
Age (months)	3.7 ± 2.8	2.9 ± 2.2	NS
Weight (g)	4598.5 ± 1279.1	4236.7 ± 957.4	NS
Anesthesia time (min)	271.2 ± 33.5	264.8 ± 30.0	NS
Operation time (min)	191.4 ± 31.2	176.7 ± 21.5	NS
CPB time (min)	95.9 ± 25.8	82.1 ± 16.0	NS
Ao crossclamp time (min)	55.7 ± 17.5	50.3 ± 11.6	NS
Preoperative RVP/LVP (%)	78.2 ± 18.9	82.5 ± 16.7	NS
Preoperative FAC of the LV (%)	56.0 ± 6.1	57.2 ± 7.2	NS

All values are means ± SD
NS, not significant; CPB, cardiopulmonary bypass; Ao, aortic; RVP, right ventricular peak pressure; LVP, left ventricular peak pressure

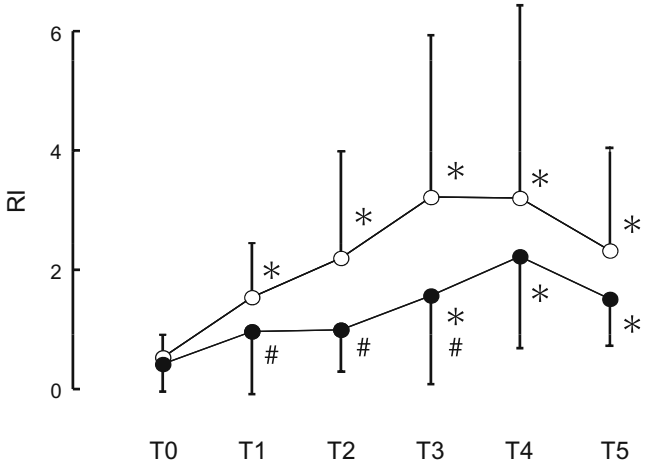

Fig. 2. Time course of changes in the respiratory index (*RI*). All values are means ± SD. * $P < 0.05$ vs initial value (*T0*) in the same group; # $P < 0.05$ vs value obtained at the same time in the control group. *T0*, Preoperative, after induction of anesthesia; *T1*, immediately after weaning from CPB; *T2*, 6 h after weaning from CPB; *T3*, 12 h after weaning from CPB; *T4*, 24 h after weaning from CPB; *T5*, 48 h after weaning from CPB

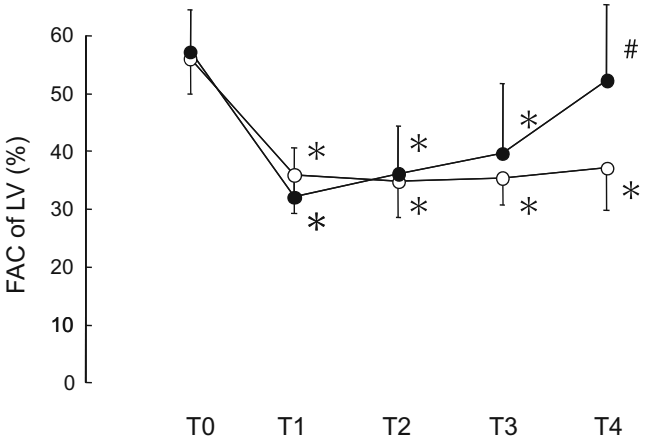

Fig. 3. Time course of changes in the fractional area change (*FAC*) of the left ventricle (*LV*). All values are means ± SD. * $P < 0.05$ vs initial value (*T0*) in the same group; # $P < 0.05$ vs value obtained at the same time in the control group. *T0*, Preoperative; *T1*, postoperative day 0 (POD 0); *T2*, POD 1; *T3*, POD 2; *T4*, POD 3

both groups ($P < 0.05$), it was higher in the sivelestat group compared with the control group and there were significant differences immediately after weaning from CPB (400.9 ± 118.7 vs 299.8 ± 105.5 mmHg; $P < 0.05$) and 12 h after weaning from CPB (305.8 ± 126.9 vs 199.8 ± 98.0 mmHg; $P < 0.05$).

Figure 2 shows the values for the RI. Although the RI increased in the postoperative course in both groups ($P < 0.05$), it was lower in the sivelestat group compared with the control group and there were significant differences immediately after weaning from CPB (0.96 ± 1.05 vs 1.54 ± 0.91; $P < 0.05$), 6 h after weaning from CPB (0.99 ± 0.70 vs 2.19 ± 1.79; $P < 0.05$), and 12 h after weaning from CPB (1.57 ± 1.49 vs 3.21 ± 2.72; $P < 0.05$).

Figure 3 shows the values for the FAC of the LV. Although the FAC of the LV in both groups significantly decreased in the acute phase of the postoperative course ($P < 0.05$), that in the sivelestat group gradually improved and returned to near the preoperative value on POD 3 compared with the control group (52.2 ± 13.1% vs 37.1 ± 7.3%; $P < 0.05$).

Figure 4 shows the values for the WBC count. The count was lower in the sivelestat group compared with the control group in the postoperative course, although the difference between the two groups was not significant.

Figure 5 shows the time course of changes in the rates of ventilator support. The duration of ventilator support tended to be shorter in the sivelestat group compared with the control group, although the difference between the two groups was not significant (2.1 ± 1.0 vs 2.6 ± 2.1 days; $P > 0.05$). The duration of stay in the ICU tended to be shorter in the sivelestat group compared with the control group, although this difference also was not significant (6.1 ± 2.2 vs 11.1 ± 10.2 days; $P > 0.05$).

We had no pulmonary and cardiovascular complications in either of the groups.

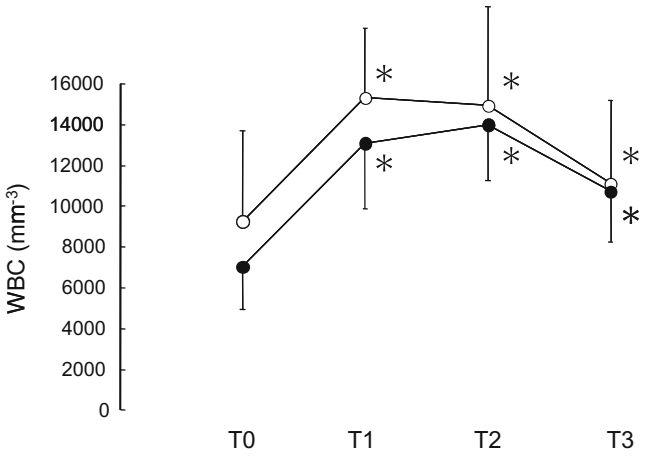

Fig. 4. Time course of changes in white blood cell (*WBC*) count. All values are means ± SD. * $P < 0.05$ vs initial value (*T0*) in the same group. *T0*, POD 0; *T1*, POD 1; *T2*, POD 2; *T3*, POD 3

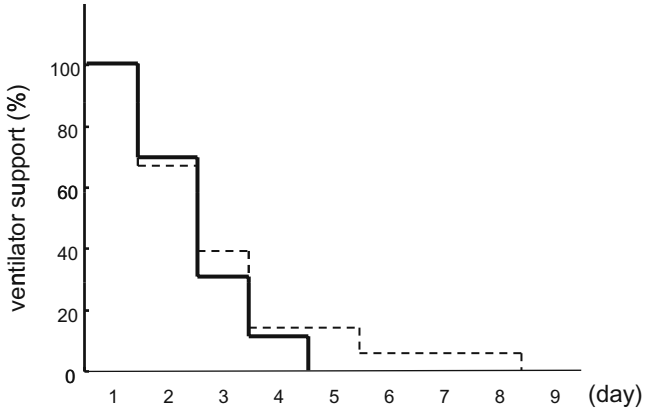

Fig. 5. Time course of changes in rate of ventilator support. *Dashed line*, Control group; *continuous line*, sivelestat group

Discussion

CPB initiates a multifaceted response involving complement activation; neutrophil activation, with degranulation and protease enzyme release; cytokine release; and endothelial cell activation [1,2]. However, this response is accentuated in pediatric patients because of the high circuit surface area-to-blood-volume ratio compared to that in adults [25]. Several studies have summarized the profile of proinflammatory and antiinflammatory cytokines in the response to CPB in children [25–27]. Especially, it is thought that the impairment of cardiovascular and respiratory function correlates with the level of IL-8, as a mediator of the inflammatory response [26], and the degree of organ injury and the clinical outcome depend on the balance between proinflammatory cytokines such as IL-6, IL-8, and tumor necrosis factor-α (TNF-α) and antiinflammatory cytokines such as IL-10 [27]. Accordingly, the efficacy of various antiinflammatory strategies, such as the use of a heparin-coated bypass circuit, ultrafiltration, aprotinin, and steroids has been demonstrated [3,28–34]. Similarly, several studies have demonstrated that sivelestat, a neutrophil elastase inhibitor, has an antiinflammatory effect in cardiovascular surgery with CPB [18,19] and it has also shown prophylactic efficacy against ALI/ARDS following cardiovascular surgery with CPB [20–22]. To confirm these findings, we evaluated the clinical respiratory and cardiac effect of sivelestat in pediatric cardiovascular surgery with CPB.

The P/F ratio and the RI are well established as parameters that quantify impaired respiratory function. Our results showed that although both the P/F ratio and the RI tended to worsen until 24 h after weaning from CPB, regardless of the presence of sivelestat administration, the values in the sivelestat group were better than those in the control group. In patients with preoperative PH, it is possible that the degree of PH can be increased by ALI/ARDS following cardiovascular surgery with CPB. We note that PH, which decreases right cardiac function and cardiac output, is a characteristic of ARDS [23]. In our study, we could not evaluate the degree of PH because the pulmonary artery pressure and RVP in the perioperative period were not measured routinely at our hospital. Moreover, because many patients in both groups were extubated within POD 2, and because the number of samples for arterial blood gas analysis was small after POD 3, we could evaluate the respiratory function only until 48 h after CPB. However, it is thought that neither the P/F ratio nor the RI would have tended to worsen in either group after POD 3, because no pulmonary complications were observed in either of the groups.

In the present study, the FAC of the LV in the sivelestat group improved significantly on POD 3 compared with the value in the control group, although the postoperative FAC of the LV decreased in both groups. Postoperative LV function in pediatric patients who underwent intracardiac repair for VSD has been shown to be low for a few days after the operation and to improve gradually until patient discharge [35]. Moreover, because PH decreases cardiac output and the degree of PH correlates with the severity of lung injury [24], it is possible that LV function is decreased by ALI/ARDS following cardiovascular surgery with CPB. Therefore, it was suggested that, if ALI/ARDS following cardiovascular surgery with CPB could be attenuated by sivelestat, sivelestat would have a beneficial effect on LV function. It has been reported that pediatric patients with postoperative myocardial dysfunction have higher levels of proinflammatory cytokines, which have negative inotropic effects [36,37], than those

without postoperative myocardial dysfunction [38]. Because sivelestat has been shown to reduce the plasma level of IL-8 and neutrophil elastase during CPB [18,21], it is possible that the improved cardiac function in the present study was associated with the antiinflammatory effect of sivelestat.

However, we cannot conclude that the antiinflammatory effects of sivelestat induced the high P/F ratio, the low RI, and the good cardiac contractility in the present study, because cytokines were not measured, and there was no significant difference between the sivelestat and control groups in the WBC counts. It would be desirable to evaluate the association between the two production of proinflammatory cytokines and the effect on respiratory and cardiovascular function after sivelestat administration.

There were no significant differences in the duration of ventilator support and stay in the ICU between the two groups in the present study. The lack of differences between the groups could reflect the fact that the objective disease in the patients in the present study was not complicated and the scale of the study was small.

However, it is suggested that sivelestat administration could be a therapeutic option to improve respiratory and cardiac function after pediatric cardiovascular surgery with CPB, because the P/F ratio, the RI, and the cardiac contractility were better in the sivelestat group than in the control group.

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