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Article

# The Effect of Sivelestat Sodium Hydrate on Severe Respiratory Failure after Thoracic Aortic Surgery with Deep Hypothermia

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Patients who undergo thoracic aortic surgery with deep hypothermia frequently have postoperative respiratory failure as a complication. Severe lung injury in these patients results in a fatal outcome. A specific neutrophil elastase inhibitor, sivelestat sodium hydrate, is an innovative therapeutic drug for acute lung injury. We evaluated the protective effects of sivelestat sodium hydrate on severe lung injury after thoracic aortic surgery with deep hypothermia. From January 2002 to July 2007, 71 consecutive patients underwent thoracic aortic surgery with deep hypothermia. Of these patients, 22 had postoperative respiratory failure with PaO<sub>2</sub>/FiO<sub>2</sub> ratios of less than 150. They were randomly assigned to one of two groups. The first group (Group S, n = 10) was administered sivelestat sodium hydrate continuously at 0.2 mg/kg/h until weaning from mechanical ventilation; the second group (Group C, n = 12) was not administered sivelestat sodium hydrate. The groups were comparable with respect to clinical data. There were no significant differences between the two groups in age, operation duration, total cardiopulmonary bypass time, circulatory ischemia time, cardiac arrest time, intraoperative blood loss, and total transfusion volume. The improvement of pulmonary function was observed in the both groups, but more marked in Group S by statistical analysis using analysis of variance for repeated measurements. Especially, in the early phase, pulmonary function improvement was more marked in Group S. The duration of mechanical ventilation, the length of stay in the intensive care unit, and the length of hospital stay were shorter in Group S, but not significantly. Sivelestat sodium hydrate is a specific neutrophil elastase inhibitor that improves pulmonary function in patients with severe postoperative respiratory failure following thoracic aortic surgery with deep hypothermia. The drug may shorten the duration of postoperative ventilation, intensive care unit stay, and hospital stay.

**Key words:** deep hypothermia, lung injury, neutrophil elastase inhibitor, sivelestat sodium hydrate, thoracic aortic surgery

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## Introduction

Respiratory failure after thoracic aortic surgery with deep hypothermia still remains an important clinical problem despite refinements in surgical technique, cardiopulmonary bypass (CPB) system, and postoperative intensive care. It affects postoperative morbidity and mortality; results in prolonged hospitalization; and increases the cost of treatment. Patients who undergo

**Table 1 Patient demographics and operative procedure**

Variables, mean $\pm$ SD or No.	Group S (n = 10)	Group C (n = 12)	<i>p</i> value
Age, year	72 $\pm$ 7	74 $\pm$ 7	0.49
Sex, male/female	5/5	9/3	0.38
Emergent or urgent / Elective	7/3	6/6	0.41
Diagnosis			0.52
Acute aortic dissection (type A)	6	4	
Distal aortic aneurysm	3	3	
Distal and descending aortic aneurysm	1	3	
Ascending and descending aortic aneurysm	0	1	
Distal aortic aneurysm + AP	0	1	
Operative procedure			0.43
Ascending aortic replacement	4	3	
Total arch replacement	4	4	
Distal arch replacement	1	0	
Total arch + descending aortic replacement	1	4	
Distal arch replacement + CABG	0	1	
Median sternotomy / Concomitant left thoracotomy	8/2	10/2	0.84

AP, angina pectoris; CABG, coronary artery bypass grafting

thoracic aortic surgery with deep hypothermia frequently have postoperative respiratory failure associated with systemic inflammatory response syndrome (SIRS).<sup>1)</sup> A specific neutrophil elastase inhibitor, sivelestat sodium hydrate (SSH), has been reported as a novel therapeutic drug for treating acute lung injury.<sup>2-4)</sup> There are few comparative studies about the clinical effects of this drug on serious lung injury. In this study, we evaluate the protective effects of SSH on severe lung injury after thoracic aortic surgery with deep hypothermia.

## Methods

### Patients

From January 2002 to July 2007, 71 consecutive patients underwent thoracic aortic surgery with deep hypothermia in our hospital and were investigated retrospectively for this study. Of these patients, 22 postoperatively had severe respiratory failure with PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratios of less than 150. The mean age of patients was 73.2  $\pm$  7.1 years and 14 (63.6%) patients were men. An emergent or urgent aortic repair was done in 13 patients (59.1%). Before surgery, the patients were evaluated by computed tomography (CT). In elective surgical cases, 3-dimension CT angiography, aortography, coronary angiography, and pulmonary function were performed preoperatively. The patients with elective surgery had normal pulmonary function (% volume capacity  $\geq$  80% and % forced expiratory volume in 1st second  $\geq$  70%). All patients in this study did not have chronic obstructive

pulmonary disease (COPD) preoperatively. The patients consisted of 10 patients who had a Stanford type A aortic dissection; 6 patients, distal aortic aneurysm; 4 patients, distal and descending aortic aneurysm; 1 patient, ascending and descending aortic aneurysm; and 1 patient, distal aortic aneurysm and angina pectoris. The operative procedures performed were 7 ascending or hemiarch aorta replacement; 8 total arch aorta replacement; 5 total arch and descending aorta replacement; 1 distal arch aorta replacement; and 1 distal arch aorta replacement concomitant with coronary artery bypass grafting. The patients were assigned to one of two groups according to the date of surgery and acceptance of SSH in our institution, July 2004. The first group (Group S, n = 10) was administered SSH continuously at 0.2 mg/kg/h until either weaning from a mechanical ventilator or for a maximal period of 7 days postoperatively. The second group (Group C, n = 12) was not administered SSH. The patient data were comparable between the two groups as shown in **Table 1**. The local ethical committee approved this study, and we obtained informed consent from the patients.

### Operative management and surgical procedure

Standard induction and maintenance of anesthesia was accomplished with a combination of fentanyl, thiamylal, propofol, vecuronium, oxygen with nitrous oxide, and sevoflurane. Each operation was performed through median sternotomy. Four patients had a concomitant left antero-lateral thoracotomy. Before arterial and venous

**Table 2** Operative factor

Variables, mean $\pm$ SD	Group S (n = 10)	Group C (n = 12)	<i>p</i> value
Cardiopulmonary bypass time, min	264 $\pm$ 87	233 $\pm$ 52	0.26
Circulatory arrest time <sup>a</sup> , min	56 $\pm$ 13	54 $\pm$ 20	0.82
Cardiac ischemia time, min	94 $\pm$ 32	92 $\pm$ 30	0.89
Operation time, min	408 $\pm$ 57	413 $\pm$ 82	0.86
Lowest rectal temperature, °C	20.5 $\pm$ 1.2	20.8 $\pm$ 1.1	0.83
Intraoperative bleeding volume, ml	1118 $\pm$ 557	1000 $\pm$ 430	0.52
Transfusion volume <sup>b</sup> , units	13 $\pm$ 6	16 $\pm$ 6	0.23

<sup>a</sup> Circulatory arrest time + retrograde cerebral perfusion time.

<sup>b</sup> Intraoperative and postoperative transfusion volume until 48 hours after surgery.

cannulation, the patients were administered a heparin dose of 400 units/kg for systemic heparinization and to maintain an activated clotting time of more than 400 seconds. The sites used for arterial cannulation were the femoral artery in 8 patients; the axillary artery in 2 patients; the femoral and axillary artery in 2 patients; and the ascending aorta in 10 patients. These arteries and the superior and inferior vena cava were cannulated separately to institute the bypass circuit. Cardiopulmonary bypass (CPB) is routinely instituted at 2.2 to 2.5 L/min/m<sup>2</sup>. Total dose of aprotinin (3.0  $\times$  10<sup>6</sup> kallikrein inhibiting units [KIU]) was administered continuously at 1.0  $\times$  10<sup>6</sup> KIU/hour from the initiation of CPB. A left cardiac venting catheter was inserted through the right upper pulmonary vein or the main pulmonary artery. Cooling was generally proceeded to a rectal temperature of 20°C to 23°C. We accepted 23°C when an ascending or hemi-arch aortic replacement was planned. After core cooling was accomplished, retrograde cerebral perfusion (RCP) and retrograde cold blood cardioplegia were performed - the former, by reversing blood flow in a venous return cannula placed in the superior vena cava; and the latter, by continuously administering retrograde cold blood through a catheter placed in coronary vein. The aortic dissection or the aneurysm was resected, and the aortic stumps were reinforced with Teflon strips. Gelatin-resorcin-formalin (GRF) was used in patients who had undergone aortic dissection. The open anastomosis technique was adopted in all patients. We used the arch first technique in the patients with arch vessel reconstruction. Each replacement was performed with a Dacron prosthesis. Coronary revascularization was an additional procedure performed in 1 patient during rewarming. Patients were rewarmed to a rectal temperature of 34°C before CPB separation. At the termination of CPB, heparin was

neutralized with protamine in a 1:1 ratio. After the operation, the patients were transported to the intensive care unit (ICU), and mechanical ventilation was started. Respiratory weaning was initiated once the patient demonstrated stable hemodynamics and respiratory conditions.

### Statistical Analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation or as a range, and categorical variables are expressed as counts and percentages. All statistical analyses were performed using SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square or Fisher's exact test. Comparisons of P/F ratios at different times were performed using analysis of variance for repeated measurements (repeated measures ANOVA) followed by the Bonferroni test. A *p* value of less than 0.05 was considered significant.

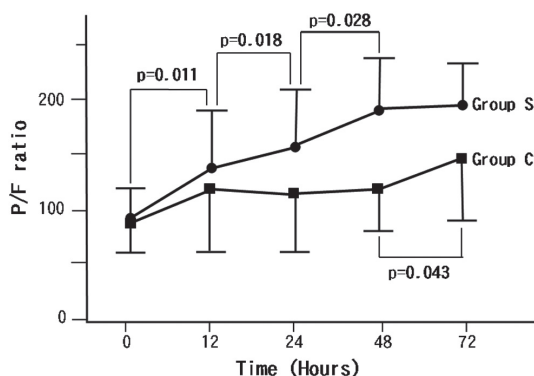
### Results

There were no significant differences between the two groups in gender, age, emergency, total CPB time, circulatory arrest time, cardiac ischemia time, operation time, lowest rectal temperature, intraoperative blood loss, or transfusion volume (**Tables 1** and **2**). And it was showed in **Table 1** that there was no significant deference in the number of patients underwent concomitant left thoracotomy between the two groups. The laboratory data directly after surgery show no significant differences between the two groups (**Table 3**). The P/F ratios directly after surgery were 96  $\pm$  22 and 93  $\pm$  26 in Group S and

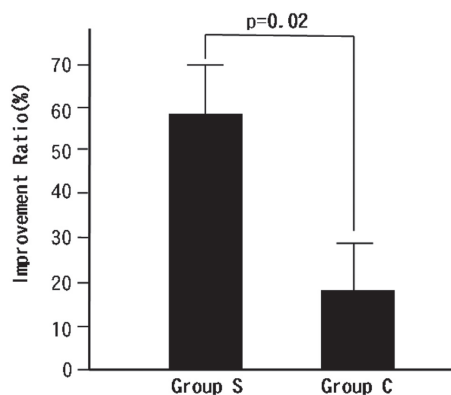
**Table 3** Laboratory data directly after surgery (before SSH administration)

Variables, mean $\pm$ SD	Group S (n = 10)	Group C (n = 12)	<i>p</i> value
WBC, $\times 10^3$ /mm <sup>3</sup>	11.6 $\pm$ 2.7	9.7 $\pm$ 3.7	0.33
Platelet, $\times 10^4$ /mm <sup>3</sup>	9.1 $\pm$ 3.0	8.4 $\pm$ 3.6	0.65
BUN, mg/dl	16 $\pm$ 2.9	19 $\pm$ 7.3	0.15
Creatinine, mg/dl	0.8 $\pm$ 0.3	1.0 $\pm$ 0.6	0.29
Total bilirubin, mg/dl	1.2 $\pm$ 0.4	1.4 $\pm$ 0.6	0.22
ALT, units	55 $\pm$ 46	45 $\pm$ 53	0.53
Cardiac index, L/min/m <sup>2</sup>	2.1 $\pm$ 0.6	2.2 $\pm$ 0.9	0.23

SSH, sivelestat sodium hydrate; WBC, white blood cell; BUN, blood urea nitrogen; ALT, alanine aminotransferase



**Fig. 1** In Group S, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio significantly increased from its baseline value and continued to increase significantly in value at each post-surgical time point of 12 hours, 24 hours, and 48 hours. In Group C, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio significantly increased from its value at 48 hours to its value at 72 hours after surgery.



**Fig. 2** In Group S, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio increased by 59%  $\pm$  10%, while the PaO<sub>2</sub>/FiO<sub>2</sub> ratio in Group C increased by 18%  $\pm$  10% at 24 hours after surgery. The improvement in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio is significantly greater in Group S than in Group C (*p* = 0.02).

Group C, respectively, and were not significantly different. The P/F ratios at 12, 24, 48, and 72 hours postoperatively were 140  $\pm$  53, 159  $\pm$  53, 188  $\pm$  86, and 191  $\pm$  49, respectively, in Group S; and 122  $\pm$  60, 107  $\pm$  45, 121  $\pm$  42, and 145  $\pm$  55, respectively, in Group C. The P/F ratios at each post-surgical time point show no significant differences between the two groups. **Figure 1** shows that the P/F ratio in Group S significantly increases from its baseline value of 96  $\pm$  22 to a value of 140  $\pm$  53 (*p* < 0.05) at 12 hours after surgery, and to a value of 159  $\pm$  53 (*p* < 0.05) at 24 hours after surgery, and to a value of 188  $\pm$  86 (*p* < 0.05) at 48 hours after surgery by statistical analysis using analysis of variance for repeated measurements.

In the early phase, Group S showed a marked improvement in pulmonary function. Further, the P/F ratio in Group S increased by 59%  $\pm$  10%, from the baseline value of 96  $\pm$  22 to a value of 159  $\pm$  53 at 24 hours

after surgery. The P/F ratio in Group C increased by 18%  $\pm$  10%, from a baseline value of 93  $\pm$  26 to a value of 107  $\pm$  45 at 24 hours after surgery. The change in the P/F ratio at 24 hours after surgery versus the baseline ratio value in Group S was a significantly greater change than that in Group C (59%  $\pm$  10% vs. 18%  $\pm$  10%, *p* = 0.02) (**Fig. 2**).

**Table 4** summarizes postoperative complications, including hospital mortality. The in-hospital mortality was 10% (1 of 10 patients) in Group S and 17% (2 of 12 patients) in Group C. The causes of hospital mortality in Group S were respiratory failure due to pneumonia in 1 patient; and in Group C, myocardial infarction in 1 patient and respiratory failure with severe hypoxia in 1 patient. Postoperative complications included stroke in 5 patients, myocardial infarction in 1 patient, renal failure requiring transient hemodialysis in 5 patients,

**Table 4 Postoperative characteristics**

Variables	Group S (n = 10)	Group C (n = 12)	p value
Event, % (n)			
Stroke	20 (2)	25 (3)	1.000
Myocardial infarction	0 (0)	10 (1)	1.000
Wound infection	0 (0)	17 (2)	0.481
Reoperation for bleeding	0 (0)	0 (0)	1.000
Renal failure requiring HD	20 (2)	25 (3)	1.000
Gastrointestinal bleeding	10 (1)	0 (0)	0.455
Hospital mortality	10 (1)	17 (2)	1.000
Outcome, mean $\pm$ SD			
Ventilator time, hours	174 $\pm$ 141	224 $\pm$ 247	0.722
ICU stay, days	18 $\pm$ 17	39 $\pm$ 41	0.054
Hospital stay, days	56 $\pm$ 42	90 $\pm$ 65	0.124

HD, hemodialysis; ICU, intensive care unit

gastrointestinal bleeding in 1 patient, and wound infection in 2 patients. There were no significant differences between the two groups in postoperative complications, including hospital mortality, as shown in **Table 4**.

Furthermore, postoperative outcome data are summarized in **Table 4**. In Group S, the duration of mechanical ventilation was 174  $\pm$  141 hours, the length of stay in ICU was 18  $\pm$  17 days, and the length of hospital stay was 56  $\pm$  42 days. In Group C, the duration of mechanical ventilation was 224  $\pm$  247 hours, the length of stay in ICU was 39  $\pm$  41 days, and the length of hospital stay was 90  $\pm$  65 days. The duration of the ventilation, the ICU stay length, and the hospital stay were shorter in Group S, but this difference was not significant.

## Discussion

Thoracic aortic surgery with deep hypothermia requires time for core cooling and re-warming, and subsequently causes a prolonged CPB time. Kirklin et al. demonstrated that a prolonged CPB time is an additional risk factor for the presumed damaging effect of CPB. They associate the damaging effects, in part, to complement activation.<sup>5)</sup> Cardiopulmonary bypass-induced organ dysfunction remains a clinical problem in certain groups of patients. Although the pathogenesis is multifactorial, it is likely that a pan-endothelial injury, subsequent to widespread humoral and cellular activation, is a major contributor to this process.<sup>6)</sup> It has been suggested that cardiopulmonary bypass causes a systemic inflammatory reaction<sup>1)</sup> through activation of the coagulation and fibrinolytic system, the complement system, neutrophils, and other inflammatory mediators such as cytok-

ines.<sup>7, 8)</sup> This reaction includes endothelial injury and increased microvascular permeability that may result in pulmonary dysfunction with a variable degree of clinical expression.<sup>1, 7)</sup> There is a significant correlation noted between neutrophil activation and the degree of lung dysfunction after CPB.<sup>9)</sup> Neutrophils and neutrophil elastase are believed to play a role in endothelial injury and increased vascular permeability in acute lung injury.<sup>10-12)</sup>

Sivelestat sodium hydrate (SSH), sodium N-[2-[4-(2,2-dimethylpropionyloxy) phenylsulfonylamino] benzoyl] aminoacetate tetrahydrate (ONO Pharmaceutical Co., Osaka, Japan), is a synthetic and specific neutrophil elastase inhibitor.<sup>13)</sup> SSH is a strong inhibitor of neutrophil elastase. The effects of SSH on lung injury have been investigated in several studies.<sup>2-4)</sup>

Ulinastatin, a human urinary trypsin inhibitor, is a famous protease inhibitor that significantly inhibits neutrophil elastase. However, *in vitro* studies indicate that Ulinastatin requires 50 times the concentration than does SSH for 50% inhibition of neutrophil elastase in a clinical use volume.<sup>13, 14)</sup> Aprotinin is also a low-molecular-weight peptide inhibitor of trypsin, kallikrein, and plasmin. Gott and co-workers reported aprotinin has an effect of reduced fibrinolysis and a reduced length of stay.<sup>15)</sup> In those days we had applied aprotinin to thoracic aortic surgery for its ability to reduce postoperative blood loss;<sup>16)</sup> however, in recent years we have not used aprotinin according to some reports<sup>17, 18)</sup> referring to the risk associated with the drug.

The clinical effectiveness of SSH has been reported in cardiac surgery using CPB and in thoracic aortic surgery under deep hypothermia.<sup>19-21)</sup> The patients of these studies, who had an average P/F ratio, did not have very severe respiratory failure, while the patients in our present study had postoperative severe respiratory failure with P/F ratios of less than 150. Bernard et al.<sup>22)</sup> recommended criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The P/F ratio values for ARDS and ALI are defined as less than 200 and 300, respectively. According to the guidelines, the P/F ratio level for weaning from ventilatory support are 200.<sup>23)</sup> In our hospital, the P/F ratio for weaning from ventilator is more than 200, and PaO<sub>2</sub> is more than 80 mmHg. We believe that the weaning level is not as serious as the anoxic level. Therefore, in our study, we settled the severe respiratory failure with P/F ratios of less than 150.

There are some findings that pretreatment with other



neutrophil elastase inhibitors attenuates pulmonary edematous changes in animal models of acute lung injury.<sup>11, 24, 25)</sup> A recent clinical study has suggested the effectiveness of SSH administered prophylactically to patients undergoing total arch replacement.<sup>19)</sup> However, many patients undergoing thoracic aortic surgery with deep hypothermia do not have severe lung injury; therefore, they do not necessarily need a neutrophil elastase inhibitor such as SSH. The administration of SSH is indicated for patients with ALI with SIRS, but not for patients with respiratory failure who have multiple (more than four) organ failure.<sup>22)</sup> Patients in this study matched this criterion, and there was no significant difference between the two groups in laboratory data, as shown in **Table 3**.

The postoperative P/F ratios of Group S improved after surgery compared with those of Group C (**Fig. 1**). The P/F ratio of Group S improved markedly in the early phase, and the improvement at 24 hours after surgery in Group S was significantly higher than that in Group C by repeated measures ANOVA. The improvement of P/F ratios at other post-surgical time points showed no significant differences between the two groups. Meade et al.<sup>26)</sup> report that early extubation may result in shorter ICU stays and an earlier discharge. Extubation after a period of less than 6 hours, as compared with a period of 6 to 24 hours, showed no difference in the length of ICU or hospital stay.<sup>27)</sup> Therefore, extubation after less than 24 hours may be important for a shorter ICU stay and an earlier discharge. Our results (**Fig. 2**) showing that the improvement at 24 hours after surgery in Group S was significantly higher than that in Group C may be remarkable. The duration of mechanical ventilation, length of stay in the ICU and the length of hospital stay in Group S were relatively shorter than these factors in Group C. However, these differences between the two groups were not significant.

In our study, there were four patients with prolonged ventilation due to postoperative stroke and complications of postoperative stroke in five patients. Therefore, the main cause of prolonged mechanical ventilation, excluding respiratory failure, was a depressed level of consciousness due to postoperative stroke. The prolonged ventilation caused by a postoperative stroke may have affected the results of the patients' postoperative course in our study. The incidence of postoperative stroke in each of the groups was 23% (5 of 22). This number may be elevated by many emergent and urgent cases (59%, 13 of 22) in our study. The overall incidence of postoperative

stroke in this series was 13% (9 of 71).

## Study Limitations

Although the patients in this present study were assigned to one of two groups according to the date of surgery and the data were analyzed by a retrospective study, the operations were performed by same surgeons and consistent maneuvers. The patients in this study contain emergency cases, and a few patients in both groups underwent concomitant left thoracotomy. It could be desirable for these cases to be excluded in this study; however, we added these cases to the patients in this study on the statistical examinations. The small sample size of this study may have limited the accuracy of statistical analyses. Thus, we may have been unable to statistically demonstrate the significant effects of SSH on the duration of postoperative ventilation, ICU stay, and hospital stay. Further studies using a larger sample size are needed.

A past study demonstrated that SSH suppresses the production of polymorphonuclear (PMN) elastase and interleukin (IL)-8 in patients with acute lung injury caused by CPB.<sup>21)</sup> Our present study design prevented the examination of the potential relationships between the postoperative respiratory function and the cytokine profile. Past *in vitro* and *in vivo* experimental models have established that SSH can reduce the activity of inflammatory mediators (e.g., neutrophil elastase activity, IL-8 production, and complement levels) during and after CPB. The present study focused upon the clinical effects of SSH on severe lung injury after thoracic aortic surgery with deep hypothermia.

## Conclusions

SSH is a specific neutrophil elastase inhibitor that improves pulmonary function in patients with severe postoperative respiratory failure complications following thoracic aortic surgery with deep hypothermia. The drug may shorten the duration of postoperative ventilation, ICU stay, and hospital stay.

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