

# Effects of pulmonary static inflation with 50% xenon on oxygen impairment during cardiopulmonary bypass for stanford type A acute aortic dissection

## A pilot study

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### Abstract

**Background:** The goal of this study was to investigate the effects of pulmonary static inflation with 50% xenon on postoperative oxygen impairment during cardiopulmonary bypass (CPB) for Stanford type A acute aortic dissection (AAD).

**Methods:** This prospective single-center nonrandomized controlled clinical trial included 100 adult patients undergoing surgery for Stanford type A AAD at an academic hospital in China. Fifty subjects underwent pulmonary static inflation with 50% oxygen from January 2013 to January 2014, and 50 underwent inflation with 50% xenon from January 2014 to December 2014. During CPB, the lungs were inflated with either 50% xenon (xenon group) or 50% oxygen (control group) to maintain an airway pressure of 5 cm H<sub>2</sub>O. The primary outcome was oxygenation index (OI) value after intubation, and 10 minutes and 6 hours after the operation. The second outcome was cytokine and reactive oxygen species levels after intubation and 10 minutes, 6 hours, and 24 hours after the operation.

**Results:** Patients treated with xenon had lower OI levels compared to the control group before surgery ( $P=0.002$ ); however, there was no difference in postoperative values between the 2 groups. Following surgery, mean maximal OI values decreased by 18.8% and 33.8%, respectively, in the xenon and control groups. After surgery, the levels of interleukin-6 (IL-6), tumor necrosis factor alpha, and thromboxane B<sub>2</sub> decreased by 23.5%, 9.1%, and 30.2%, respectively, in the xenon group, but increased by 10.8%, 26.2%, and 26.4%, respectively, in the control group. Moreover, IL-10 levels increased by 28% in the xenon group and decreased by 7.5% in the control group. There were significant time and treatment-time interaction effects on methane dicarboxylic aldehyde ( $P=0.000$  and  $P=0.050$ , respectively) and myeloperoxidase ( $P=0.000$  and  $P=0.001$  in xenon and control groups, respectively). There was no difference in hospital mortality and 1-year survival rate between the 2 groups.

**Conclusion:** Pulmonary static inflation with 50% xenon during CPB could attenuate OI decreases at the end of surgery for Stanford type A AAD. Thus, xenon may function by triggering anti-inflammatory responses and suppressing pro-inflammatory and oxidative effects.

**Abbreviations:** AAD = acute aortic dissection, ALI = acute lung injury, CPB = cardiopulmonary bypass, CT = contrast-enhanced computed tomography, DHCA = deep hypothermic circulatory arrest, ERK = extracellular signal-regulated kinase, FiO<sub>2</sub> = inspired oxygen fraction, IL-10 = interleukin-10, IL-6 = interleukin-6, ITT = intention-to-treat, MDA = methane dicarboxylic aldehyde,

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MPO = myeloperoxidase, MRI = magnetic resonance imaging, OI = oxygenation index, PaO<sub>2</sub> = arterial oxygen tension, PEEP = positive end-expiratory pressure, P<sub>ET</sub>CO<sub>2</sub> = end-tidal carbon dioxide pressure, RI = respiratory index, ROS = oxygen species, ROS = reactive oxygen species, SD = standard deviation, TAOC = total antioxidant capacity, TNF $\alpha$  = tumor necrosis factor alpha, TSOD = total superoxide dismutase, TXB<sub>2</sub> = thromboxane B<sub>2</sub>.

**Keywords:** anesthetics, anti-inflammatory, xenon

## 1. Introduction

Acute lung injury (ALI) after acute aortic surgery with deep hypothermic circulatory arrest (DHCA) is a serious clinical problem, despite refinements in surgical techniques, avoidance of extracorporeal circulation, and intensive postoperative care. This condition affects postoperative morbidity and mortality and can result in prolonged ventilator support, extended hospitalization and intensive care unit stay, and increases in treatment costs. However, few proven effective preventative or therapeutic interventions for ALI exist. The pathogenesis of ALI after thoracic aortic surgery, particularly in patients who have undergone acute aortic dissection (AAD), is complex and remains unknown. However, studies have indicated that ischemia/reperfusion and inflammation are likely to be underlying risk factors.<sup>[1–4]</sup> Reactive oxygen species (ROS) and inflammatory factors may cause injury to endothelial cells and increase microvascular permeability, thereby resulting in lung injury with variable degrees of clinical manifestations.<sup>[5,6]</sup> When treated with a specific neutrophil elastase inhibitor, patients with severe postoperative pulmonary dysfunction following aortic surgery with deep hypothermia had improved outcomes.<sup>[7]</sup> Therefore, reducing inflammation might be a potential therapeutic strategy for treating ALI.

Xenon has been recognized as an ideal anesthetic for hemodynamic stability<sup>[8]</sup> and anti-inflammatory effects.<sup>[9]</sup> It can enhance lipopolysaccharide-induced interleukin-1 beta (IL-1 $\beta$ ) expression in microglia by activating extracellular signal-regulated kinase 1/2,<sup>[10]</sup> inhibiting caspase-3 activation and cytochrome c release from cells,<sup>[11]</sup> and reducing serum levels of the pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF $\alpha$ ) in rats.<sup>[12,13]</sup> In addition, in recent years, it was shown that xenon had neuroprotective, cardioprotective, and renoprotective effects in different animal models subjected to preconditioning, real-time conditioning, and postconditioning.<sup>[14–17]</sup> However, the effects of xenon on respiratory function in patients with Stanford type A AAD during cardiopulmonary bypass (CPB) with DHCA remain unclear.

ALI is a mild form of oxygen impairment (oxygenation index [OI]  $\leq$  300 mm Hg, positive end-expiratory pressure [PEEP]  $\geq$  5 cm H<sub>2</sub>O) that results in the development of bilateral infiltrates, as can be seen on chest radiographs, but does not cause cardiac failure.<sup>[18]</sup> In this study, we demonstrated that the potential effects of pulmonary static inflation with 50% xenon during CPB could attenuate postoperative oxygen impairment and improve pulmonary function in patients with Stanford type A AAD following CPB/DHCA.

## 2. Methods

### 2.1. Study design

We studied the perioperative clinical variables and serological results from 50 subjects who underwent pulmonary static

inflation with 50% oxygen from January 2013 to January 2014, and 50 subjects who underwent pulmonary static inflation with 50% xenon from January 2014 to December 2014 during CPB for Stanford type A AAD in a single-center clinical trial. We were unable to blind researchers to treatments received by the patients, but the patients, inspectors of serum sample, and statistician were blinded to treatments. The clinical trial was registered in the Chinese Clinical Trial Registry (Identifier: ChiCTR-ICR-15006435) and was approved by the Beijing Anzhen Hospital Clinical Research Ethics Committee (Identifier: 2013027). The diagnosis of AAD was confirmed in all of the patients by medical history, chest radiography, transthoracic ultrasound, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Dissection is considered AAD if the time from the onset of symptoms to surgery is 14 days or less. This study only included type A AAD according to the Stanford classification.<sup>[19,20]</sup> Medical quality 50% xenon was provided by WuHan Newradar Special Gas Co. Ltd (WuHan, China).

### 2.2. Subjects

Patients between the ages of 18 and 70 years, who were undergoing emergency surgery in our hospital for type A AAD, requiring CPB and DHCA, were enrolled. Exclusion criteria were coronary heart disease; heart failure; severe cardiac tamponade; unstable hemodynamics; nervous system abnormalities; clinically apparent malperfusion,<sup>[21]</sup> including malperfusion in the lower limb, brain, heart, and kidney; visceral ischemia; and patients who did not provide written informed consent. No patient was prescribed nonsteroidal anti-inflammatory drugs or corticosteroids before or after admission. After written informed consent, 100 patients were blinded to receiving either 50% xenon (xenon group, n=50) or 50% oxygen (control group, n=50).

### 2.3. Trial procedure

Data such as demographics and hemodynamics were recorded immediately after admission. To avoid aortic rupture, systolic blood pressure was controlled between 100 and 120 mm Hg with oral  $\beta$ -blockers and infusion of vasodilators (e.g., nitroprusside) before surgery. In all of the cases, total intravenous anesthesia was performed with a combination of sufentanil and propofol, and the bispectral index (BIS) was maintained at 45% to 55%. After the aorta was cross-clamped and mechanical ventilation was stopped, the lungs were inflated with either 50% xenon (xenon group) or 50% oxygen (control group) to maintain an airway pressure of 5 cm H<sub>2</sub>O. Pulmonary static inflation with 50% xenon or with 50% oxygen was stopped 15 minutes before aortic de-clamping and cardiac resuscitation. Pulmonary parameters were recorded before the operation, and 10 minutes and 6 hours postoperatively. The OI, respiratory index (RI), and dynamic compliance (C<sub>dyn</sub>)/static pulmonary compliance (C<sub>st</sub>)

were calculated based on a fraction of inspired oxygen ( $\text{FiO}_2$ ) of 100%, a PEEP of 5 cm  $\text{H}_2\text{O}$ , a tidal volume of 8 mL/kg, an inspiratory/expiratory ratio of 1:2, and a respiratory rate of 10 times/min. All of the patients were followed prospectively with a telephone interview or in our outpatient clinic at 3 and 6 months after cardiac surgery.

#### 2.4. Outcome

The primary outcome was OI value after intubation and 10 minutes and 6 hours after the operation. The second outcome was cytokine and ROS levels after intubation and 10 minutes, 6 hours, and 24 hours after the operation, as well as in-hospital mortality and 1-year survival.

#### 2.5. Cardiac operation

All of the patients underwent CPB with DHCA and unilateral selective antegrade cerebral perfusion (USACP). When the nasopharyngeal temperature reached 20°C to 25°C, circulatory arrest was instituted, a stent graft was implanted, and a 4-branch prosthetic graft was used for arch replacement in the operation. Valve-sparing root resection (aortic valve plasty, Valsalva sinus plasty, or the David procedure) or composite valve graft replacement was performed according to aortic root subtype (subtype A1, A2, or A3).

#### 2.6. Definitions

The perioperative pulmonary function was represented by OI, RI, Cdyn, and Cst.

$$\text{OI} = \text{PaO}_2 / \text{FiO}_2;$$

$$\text{RI} = \text{P(A-a)O}_2 / \text{PaO}_2;$$

$$\text{Cdyn (mL/cmH}_2\text{O)} = \text{Vt (tidal volume)} / (\text{Ppeak} - \text{PEEP}); \text{ and}$$

$$\text{Cst (mL/mH}_2\text{O)} = \text{Vt} / (\text{Pplat} - \text{PEEP})$$

Hospital mortality included death during hospitalization and death within 30 days of the operation.

#### 2.7. Blood samples

Venous blood (10 mL) was drawn from the central vein catheter immediately after intubation and 10 minutes, 6 hours, and 24 hours after the operation. After rapid centrifugation, plasma was obtained and immediately stored at  $-70^\circ\text{C}$  for further analysis.

#### 2.8. Enzyme-linked immunosorbent assay

Cytokine and thromboxane  $\text{B}_2$  ( $\text{TXB}_2$ ) concentrations in the plasma were assessed in all of the patients using commercially available enzyme-linked immunosorbent assay (ELISA) kits for  $\text{TNF}\alpha$ , IL-6, IL-10, and  $\text{TXB}_2$ . Assays were done in duplicate on a microtiter plate reader at a wavelength of 450 nm. Values are reported as pg/mL of the standardized sample (MULTISKAN MK3 automatic microplate reader, Thermo Fisher Scientific; Westminister, MD).

#### 2.9. ROS measurement

Methane dicarboxylic aldehyde (MDA), myeloperoxidase (MPO), total antioxidation capacity (TAOC), and total superoxide dismutase (TSOD) were evaluated by ultraviolet spectrophotometry (UV-2000 UV Spectrophotometer, Unico Instrument Co., Ltd; Shanghai, China).

#### 2.10. Statistical analysis

The sample size was selected to detect differences in postoperative OI values between the 2 groups. With a 5% (2-sided) type I error rate, based on preliminary experiments, 45 patients per treatment group were needed to detect a 22% difference between treatment groups, assuming a standardized effect size of 0.51 (expected effect size divided by standard deviation [SD] of OI). The power was from 73% to 78% as an autocorrelation from 0.6 to 0.5 accordingly. Assuming a 10% dropout rate, the final sample size was 100 patients (50 patients/group) (Power Analysis and Sample Size, PASS V11.0, NCCS, LLC; Kaysville, UT). All of the data analyses were performed using a commercially available statistical software package (SPSS for Windows, V.18.0; Chicago, IL). Quantitative variables were presented as mean  $\pm$  SD or median (interquartile range [IQR]), and categorical variables were presented as frequencies or percentages. The normally distributed continued variables were compared by the 2-tailed Student's *t* test. When parametric data were not normally distributed, Wilcoxon signed-rank sum tests were used for intergroup comparison. The categorical data were compared using Pearson's chi-squared test or Fisher's exact, as appropriate. Correlations were assessed using Pearson correlation or Spearman's rank correlation. OI was analyzed using repeated measures analysis of variance (ANOVA) with treatment and control as grouping factors and time as a within-subject factor. Perioperative RI, Cdyn, Cst, IL-6, IL-10, TNF, TXB<sub>2</sub>, values of ROS (MDA, MPO, TSOD, TAOC), perioperative hemodynamics, and detection of serum biomarkers (i.e., white blood cells [WBCs], hemoglobin [Hb], platelet [PLT], glutamine [Glu], and lactate [LAC]) were examined in a similar way. Nonparametric and parametric tests were applied to demographics (age, sex, body mass index [BMI], smoking history, hypertension, diabetes), clinical variables (hemodynamics, onset of symptoms to surgery, aortic diameter, left ventricular ejection fraction [LVEF], left ventricular end diastolic diameter [LVEDd], EuroSCORE), surgical variables (surgery time, duration of surgery, intravenous colloid and crystalloid and transfusion), and postoperative factors (intravenous fluids [colloid or crystalloid], blood transfusions, urine volume, seroma drainage, mechanical ventilation time, in-hospital mortality). The Kaplan–Meier method was used to estimate the survival time of patients from the date of operation to last follow-up or death and to demonstrate the effects of xenon on survival at 1 year. Patient data were censored at the date when the patient was last known to be alive. A log-rank test was used to evaluate survival differences between groups. The missing values were less than 10% and were displaced by means according to intention-to-treat rules. *P* values less than 0.05 were considered statistically significant.

### 3. Results

A total of 100 patients undergoing Stanford type A AAD in our hospital were screened for eligibility; 50 patients received 50% xenon and 50 received 50% oxygen. All of the patients fulfilled the evaluation criteria. There were no significant differences between groups regarding patient demographics, pre-operative cardiac function and hemodynamics, operative data, time to extubation, or in-hospital mortality (Tables 1 and 2). More patients in the xenon group needed their blood pressure to be controlled before surgery ( $P=0.009$ ) by oral  $\beta$ -blockers and/or infusion of vasodilators. The median EuroSCORE value was 5 (5, 6) in the xenon group and 5 (5, 5) in the control group ( $P=0.021$ ) prior to surgery.

**Table 1****Subject demographics. Data are given in numbers, percentage, mean  $\pm$  standard deviation, and median (interquartile range, IQR).**

Variables	Control group	Xenon group	P
Number, n	50	50	—
Age, y	45.7 $\pm$ 11.1	48.9 $\pm$ 10.8	0.137
Males, n, %	40 (80)	32 (64)	0.077
Height, cm	170 $\pm$ 8	169 $\pm$ 8	0.691
Weight, kg	74.2 $\pm$ 11.7	75.5 $\pm$ 13.9	0.547
BMI, kg/m <sup>2</sup>	25.6 $\pm$ 3.3	26.1 $\pm$ 3.6	0.326
History of smoking, n, %	28 (56)	21 (42)	0.164
History of hypertension, n, %	34 (68)	40 (80)	0.254
History of DM, n, %	1 (2)	2 (4)	0.558
Time from onset of symptoms to surgery, d	2 (1.5)	2 (1.4)	0.685
Preoperative SBP, mm Hg	113 $\pm$ 19	111 $\pm$ 17	0.563
Preoperative DBP, mm Hg	55 $\pm$ 11	54 $\pm$ 10	0.605
Aortic diameter, mm	51 $\pm$ 8	50 $\pm$ 7	0.164
Vasodilators used n, %	19 (38)	32 (64)	0.010
LVEF, %	62 $\pm$ 11	62 $\pm$ 5	0.899
LVEDd, mm	52 $\pm$ 11	51 $\pm$ 7	0.709
EuroSCORE	5 (5, 5)	5 (5, 6)	0.021

BMI = body mass index, DBP = diastolic blood pressure, DM = diabetes mellitus, EuroSCORE = European system for cardiac operative risk evaluation, IQR = interquartile range, LVEDd = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, SBP = systolic blood pressure.

### 3.1. Effects of xenon on OI and RI values

Patients treated with xenon had lower OI and RI values than the control group before surgery ( $P=0.002$  and  $P=0.004$ , respectively); however, there was no difference in postoperative values between the 2 groups (Table 3). Postoperative OI values decreased in both groups during the study period, with significant time ( $P<0.001$ ) and treatment effects ( $P=0.012$ ), but without a significant difference in the treatment–time interaction ( $P=0.129$ ) (Appendix Fig. 2A, <http://links.lww.com/MD/B589>). In the first fraction (from preoperative to postoperative 10 minutes), there was a mean maximal decrease

in OI of 18.8% and 33.8% in the xenon and control groups, respectively, with a significant difference between groups ( $P=0.021$ ). In paired comparisons, the median RI value in the first fraction increased ( $P=0.005$  for the xenon group;  $P=0.000$  for the control group) by 34.5% and 130% in the xenon and control groups, respectively, with a significant difference between groups ( $P=0.000$ ) (Appendix Fig. 2B, <http://links.lww.com/MD/B589>). Perioperative Cdyn and Cst values were similar in both groups. There was a significant time effect for Cdyn ( $P=0.002$ ), but no effect of time or treatment for Cst (Appendix Fig. 2C and D, <http://links.lww.com/MD/B589>).

**Table 2****Subject perioperative characteristics. Data are given as numbers, percentage, mean  $\pm$  standard deviation, or median (interquartile range, IQR).**

Clinical variables	Control group n = 50	Xenon group n = 50	P
During surgery			
Duration of surgery, min	457 $\pm$ 91	455 $\pm$ 109	0.921
Duration of CPB, min	191 $\pm$ 39	199 $\pm$ 58	0.412
Duration of aortic cross-clamping, min	113 $\pm$ 34	118 $\pm$ 40	0.519
Lowest rectal temperature during CPB, °C	25.8 $\pm$ 1.9	25.6 $\pm$ 1.7	0.681
Intravenous colloid and crystalloid, mL	1953 $\pm$ 1059	1987 $\pm$ 751	0.854
Allogeneic red blood cells, units	2 (0, 4)	2 (0, 4)	0.408
Allogeneic blood plasma, mL	600 (400, 800)	400 (350, 800)	0.576
Allogeneic blood platelet, units	0 (0, 1)	0 (0, 1)	0.617
Urine volume during surgery, mL	1408 $\pm$ 718	1533 $\pm$ 862	0.433
During 24 h following surgery			
Intravenous colloid and crystalloid, mL	3643 $\pm$ 774	3903 $\pm$ 872	0.119
Allogeneic red blood cells, units	2 (0, 3)	2 (0.75, 4)	0.148
Allogeneic blood plasma, mL	200 (0, 400)	200 (0, 400)	0.339
Urine volume, mL	2912 $\pm$ 950	2903 $\pm$ 970	0.962
Seroma volume of drainage, mL	666 $\pm$ 430	663 $\pm$ 352	0.961
Postoperative LVEF, %	59 $\pm$ 6	61 $\pm$ 5	0.093
Mortality-adjusted postoperative mechanical ventilation duration, h*	16.5 (14.75, 36) (n = 42)	21.25 (13.5, 44.25) (n = 46)	0.545
Survival cases with tracheotomy n, %	3 (6.7%)	0 (0%)	0.080
In-hospital mortality, n, %	5 (10)	4 (8)	0.357
1-y survival rate	86.7 $\pm$ 5.1%	89.1 $\pm$ 4.6	0.954

CPB = cardiopulmonary bypass, IQR = interquartile range.

\* Survival cases without tracheotomy.

**Table 3**  
**Subject intraoperative and postoperative data concerning lung function.**

Clinical variables <sup>#</sup>		Control group (n=45)	Xenon group (n=46)	P
OI (PaO <sub>2</sub> /FiO <sub>2</sub> )	Preoperative	325 ± 113	256 ± 90	0.002
	Postoperative 10 min	215 ± 90 <sup>**</sup>	208 ± 96 <sup>**</sup>	0.708
	Postoperative 6 h	220 ± 102	190 ± 84	0.141
RI (P (A-a)O <sub>2</sub> /PaO <sub>2</sub> )	Preoperative	0.93 (0.68,1.66)	1.71 (1.06,2.56)	0.004
	Postoperative 10 min	2.14 (1.62,3.35) <sup>**</sup>	2.30 (1.49,4.13) <sup>*</sup>	0.555
	Postoperative 6 h	2.43 (1.14,4.18)	2.82 (1.68,4.86)	0.163
Dynamic pulmonary compliance, C <sub>dyn</sub> , mL/cm H <sub>2</sub> O	Preoperative	49.5 ± 14.1	43.6 ± 8.8	0.020
	Postoperative 10 min	48.5 ± 14.5	48.0 ± 11.5	0.868
	Postoperative 6 h	47.0 ± 24.3	42.4 ± 11.5	0.270
Static pulmonary compliance, C <sub>st</sub> , mL/cm H <sub>2</sub> O	Preoperative	231 ± 117	225 ± 107	0.820
	Postoperative 10 min	212 ± 129	252 ± 142	0.166
	Postoperative 6 h	234 ± 176	219 ± 149	0.680

OI=oxygation index, RI=respiratory index.

<sup>#</sup>Living cases, compared to baseline.

<sup>\*</sup>P<0.05.

<sup>\*\*</sup>P<0.001.

### 3.2. Effects of xenon on inflammatory mediators

Patients treated with xenon had higher levels of IL-6 and TXB<sub>2</sub> compared to the control group before surgery ( $P=0.000$ , respectively). Moreover, postoperative 6 and 24 hours, xenon patients had slightly higher serum IL-10 levels ( $P=0.008$  and  $P=0.001$ , respectively). At postoperative 10 minutes and 24 hours, TXB<sub>2</sub> levels were lower in the xenon group than in the control group ( $P=0.001$  and  $P=0.019$ , respectively). There were significant time and treatment-time effects for IL-6 ( $P=0.000$  and  $P=0.000$ , respectively), IL-10 ( $P=0.000$  and  $P=0.001$ , respectively), TNF $\alpha$  ( $P=0.012$  and  $P=0.025$ , respectively), and TXB<sub>2</sub> ( $P=0.000$  and  $P=0.001$ , respectively) (Appendix Fig. 3A–D, <http://links.lww.com/MD/B589>). In the first fraction, IL-6, TNF $\alpha$ , and TXB<sub>2</sub> levels decreased by 23.5%, 9.1%, and 30.2%, respectively, in the xenon group, but levels increased by 10.8%, 26.2%, and 26.4%, respectively, in the control group. In the first fraction, IL-10 expression increased by 28% in the xenon group and decreased by 7.5% in the control group. In the second (postoperative 10 minutes to postoperative 6 hours) and third fractions (postoperative 6 to 24 hours), IL-6, IL-10, TNF $\alpha$ , and TXB<sub>2</sub> levels were similar in both groups. In addition, the perioperative serum level of prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) was relatively stable, with no significant differences between groups. These data are summarized in Table 4.

### 3.3. Effects of xenon on ROS levels

Xenon patients had higher serum levels of MDA and MPO ( $P=0.002$  and  $P=0.005$  respectively) before surgery, and higher serum TSOD levels towards the end of follow-up (treatment effect,  $P=0.000$ ). There was a significant time and treatment–time interaction effect for MDA ( $P=0.000$  and  $P=0.050$ , respectively) and MPO ( $P=0.000$  and  $P=0.001$ , respectively) (Appendix Fig. 4A and B). The perioperative value of TAOC and TSOD increased in both groups during the study period, with a significant time effect ( $P=0.000$  and  $P=0.000$ , respectively), but without a significant difference in treatment–time interaction effects ( $P=0.757$  and  $P=0.134$ , respectively) (Appendix Fig. 4C and D). These data are summarized in Table 4.

### 3.4. Effects of xenon on survival

Among the 100 subjects, 9 died after surgery in the hospital and 9 patients were lost to follow-up. A complete 12-month follow-up was performed in the remaining 82 patients discharged from the hospital during outpatient clinic visits and/or by telephone. In the control group, 5 patients died in the hospital (2 by perioperative hemorrhage and 3 by severe multiple organ failure) and 1 died due to gastrointestinal hemorrhage after 3 months. In the xenon group, 4 patients died in the hospital because of severe multiple organ failure and 1 died due to ventricular fibrillation after 6 months. The Kaplan–Meier survival curve showed that there was no difference in survival rates at 1 year between the 2 groups ( $86.7 \pm 5.1\%$  in the control group;  $89.1 \pm 4.6\%$  in the xenon group,  $P=0.954$ ) (Fig. 1).

### 3.5. Effects of xenon on additional variables

There was no overall treatment effect between groups regarding hemodynamics, WBC and PLT counts, and Glu and LAC levels. However, time-dependent changes in WBC and PLT counts, and blood concentrations of Glu and LAC were seen in both groups.

## 4. Discussion

This is the first study to highlight the effects of pulmonary static inflation with 50% xenon on postoperative oxygen impairment during CPB for treatment of Stanford type A AAD. Although perioperative OI and RI values were not significantly different between the xenon and control groups, xenon treatment attenuated the decreased OI value and increased RI at varying degrees at the end of surgery. Our data also demonstrate that pulmonary static inflation with 50% xenon during CPB triggered anti-inflammatory responses and suppressed pro-inflammatory and oxidative effects compared to pulmonary static inflation with 50% oxygen in the complex clinical setting of AAD surgery. However, the exposure time with 50% xenon was approximately 100 minutes in our study, and there was limited impact on lung protection, which may account for the lack of difference in OI values and inflammation 6 hours after the operation between groups.

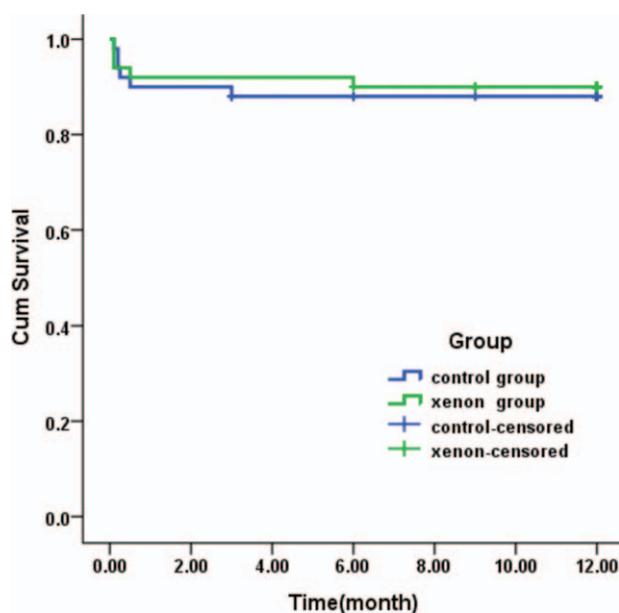
**Table 4****Subject intraoperative and postoperative data regarding hemodynamics, cytokines, and reactive oxygen species.**

Clinical variables		Control group (n=50)	Xenon group (n=50)	P
SBP, mm Hg	Preoperative	112±25	111±17	0.886
	Postoperative 10 min	116±16	114±18	0.644
	Postoperative 6 h	124±24	128±23	0.336
	Postoperative 24 h	132±13	133±20	0.756
DBP, mm Hg	Preoperative	53±12	53±11	0.998
	Postoperative 10 min	60±11	58±10	0.380
	Postoperative 6 h	62±10	62±10	0.737
	Postoperative 24 h	65±11	64±10	0.910
HR, beats/min	Preoperative	76±13	75±16	0.791
	Postoperative 10 min	90±14	94±15	0.145
	Postoperative 6 h	91±14	94±14	0.386
	Postoperative 24 h	91±14	95±12	0.095
Hb, g/L	Preoperative	12.8±1.2	12.5±1.4	0.271
	Postoperative 10 min	10.3±1.9	9.9±2.0	0.271
	Postoperative 6 h	10.8±1.9	10.6±2.0	0.568
	Postoperative 24 h	10.0±1.5	9.9±1.5	0.780
WBC, 10 <sup>9</sup> /L	Preoperative	9.82±4.15	9.45±2.86	0.609
	Postoperative 10 min	11.13±4.89	11.41±3.85	0.757
	Postoperative 6 h	10.36±3.35	10.09±3.36	0.706
PLC, 10 <sup>9</sup> /L	Preoperative	179±70	175±69	0.778
	Postoperative 10 min	115±53	106±43	0.336
	Postoperative 6 h	109±60	94±49	0.151
Glu, mg/dL	Preoperative	133±61	125±21	0.369
	Postoperative 10 min	194±44	204±66	0.341
	Postoperative 6 h	231±66	247±65	0.228
	Postoperative 24 h	199±47	202±49	0.859
LAC, mmol/L	Preoperative	1.42±1.33	1.31±0.84	0.621
	Postoperative 10 min	3.80±2.86	5.13±3.49	0.039
	Postoperative 6 h	3.63±2.78	4.47±3.37	0.181
	Postoperative 24 h	2.24±0.94	2.34±1.02	0.623
IL-6, pg/mL	Preoperative	51.6±18.3	71.6±30.1	0.000
	Postoperative 10 min	57.2±15.9	54.8±23.1**	0.551
	Postoperative 6 h	47.9±14.4	50.0±13.7	0.458
	Postoperative 24h	47.6±17.1	47.3±12.1	0.935
IL-10, pg/mL	Preoperative	95.4±63.1	80.5±64.4	0.244
	Postoperative 10 min	88.3±56.0	103.0±39.8**	0.134
	Postoperative 6 h	59.8±57.6	84.1±27.6	0.008
	Postoperative 24 h	56.3±52.9	87.8±39.9	0.001
TNF $\alpha$ , pg/mL	Preoperative	60.3±34.6	52.9±20.8	0.200
	Postoperative 10 min	76.1±56.2*	48.1±22.8	0.001
	Postoperative 6 h	53.7±36.4	47.2±22.9	0.289
	Postoperative 24 h	58.3±35.4	44.1±22.7	0.019
PGI <sub>2</sub> , pg/mL	Preoperative	32.5 (22.9,69.2)	49.2 (21.6,99.3)	0.352
	Postoperative 10 min	27.8 (17.3,62.6)*	26.4 (20.1,45.8)**	0.639
	Postoperative 6 h	27.1 (15.9,46.6)	30.9 (22.2,42.3)	0.238
	Postoperative 24 h	29.2 (15.7,46.7)	31.5 (22.9,46.7)	0.352
TXB <sub>2</sub> , pg/mL	Preoperative	110±66	179±116	0.000
	Postoperative 10 min	139±129	125±34**	0.453
	Postoperative 6 h	112±95	109±30	0.822
	Postoperative 24 h	100±53	101±30	0.892
MDA, nmol/mL	Preoperative	2.76±0.55	3.23±0.86	0.002
	Postoperative 10 min	3.23±0.448**	3.17±0.92	0.718
	Postoperative 6 h	2.93±0.54	2.89±0.85	0.823
	Postoperative 24 h	2.57±0.45	2.53±0.89	0.780
MPO, units/L	Preoperative	34.7±13.3	44.3±19.9	0.005
	Postoperative 10 min	48.3±12.7**	43.7±18.6	0.149
	Postoperative 6 h	40.1±15.1	37.4±18.1	0.441
	Postoperative 24 h	30.4±12.7	39.7±13.5	0.001
TAOC, units/mL	Preoperative	7.53±1.61	7.26±2.55	0.524
	Postoperative 10 min	8.22±1.46	8.11±2.04	0.763
	Postoperative 6 h	8.54±1.61	8.35±2.18	0.618
	Postoperative 24 h	8.87±1.67	9.13±1.78	0.448
TSOD, units/mL	Preoperative	96±40	128±47	0.000
	Postoperative 10 min	107±31	142±64	0.001
	Postoperative 6 h	118±32	160±56	0.000
	Postoperative 24 h	135±36	194±71	0.000

DBP=diastolic blood pressure, Glu=glucosamine, Hb=hemoglobin, HR=heart rate, IL-10=interleukin-10, IL-6=interleukin-6, LAC=lactic acid, MDA=methane dicarboxylic aldehyde, MPO=myeloperoxidase, PGI<sub>2</sub>=prostaglandin I<sub>2</sub>, PLC=platelet count, ROS=reactive oxygen species, SBP=systolic blood pressure, TAOC=total antioxidation capacity, TNF $\alpha$ =tumor necrosis factor  $\alpha$ , TSOD=total superoxide dismutase, TXB<sub>2</sub>=thromboxane B<sub>2</sub> compared to baseline, WBC=white blood cells.

\*P<0.05.

\*\*P<0.001.



**Figure 1.** Kaplan–Meier curves showing 1 year survival of subjects requiring 50% xenon inflation of the lung during CPB vs patients who received 50% oxygen. CPB = cardiopulmonary bypass.

The mechanisms underlying AAD are complex,<sup>[19,22,23]</sup> and aortic dissection is the end stage of different pathological processes that stress the aortic wall. Recent studies have shown that inflammation plays an important role in aortic dissection.<sup>[24–26]</sup> After the onset of AAD, proinflammatory cytokines are secreted from leukocytes and infiltrate the aortic wall, causing a systemic inflammatory response. The pulmonary microcirculation is a natural reservoir for leukocytes,<sup>[27]</sup> which leads to the accumulation of cytokines, toxic mediators, and alveolar fluid.<sup>[28]</sup> Inflammatory responses and ischemia/reperfusion injury occurs during cardiac surgery requiring CPB.<sup>[29]</sup> Thus, the 2-hit hypothesis of ALI indicates that the initial insult by AAD and a second insult by the CPB result in an exaggerated response after surgery.

Recently, a randomized controlled clinical trial demonstrated the feasibility and safety of balancing xenon anesthesia for coronary artery bypass graft surgery during CPB<sup>[30]</sup>; however, the mechanisms underlying xenon function remain unknown. According to the 2-hit hypothesis of ALI, xenon plays an important role in postconditioning for the first-bit and preconditioning for the second-bit. Furthermore, the combination of xenon and mild hypothermia seems to be synergistic for neuroprotection.<sup>[31–33]</sup> Other studies have been conducted showing that atelectasis is produced to a much larger extent after CPB, resulting in increases of intrapulmonary shunting and postoperative hypoxia.<sup>[34,35]</sup> Thus, positive airway pressure methods during CPB, such as pulmonary static inflation, improve postoperative gas exchange variables.<sup>[36]</sup> The possibility that xenon insufflation simply prevented alveolar collapse better than oxygen, is quite likely because solubility, and therefore, absorption is very limited as opposed to oxygen. Finally, pulmonary static inflation with 50% xenon was processed during the cooling period in DHCA, which enhanced the properties of xenon and improved lung function after surgery.

Higher serum proinflammatory cytokine levels indicate higher morbidity in preoperative ALI in AAD,<sup>[4,37]</sup> whereas the primary biological function of serum IL-10 is to attenuate inflammatory responses and prevent impairment of endothelial dysfunction.<sup>[38]</sup> TXB<sub>2</sub> is the stable metabolite of TXA<sub>2</sub>,<sup>[39,40]</sup> a pro-inflammatory mediator. After the onset of AAD, the production of TXB<sub>2</sub> by aggregated PLTs was increased and further activated by surgery. In this study, we compared the inflammatory profile between the xenon and control groups. Interestingly, we found that IL-6, TNF $\alpha$ , and TXB<sub>2</sub> levels were significantly reduced and anti-inflammatory IL-10 levels were significantly increased after 50% xenon inflation compared to 50% oxygen inflation during CPB. Measuring the serum levels of MDA, MPO, TAOC, and TSOD is a reliable method for assessing the balance between pro-oxidants and antioxidants in the blood. Higher levels of MDA and MPO are indicative of oxidative stress. In our study, when compared to baseline, MDA and MPO levels decreased in the xenon group and increased in the control group 10 minutes postoperatively, demonstrating that xenon treatment attenuates oxidative stress.<sup>[41]</sup>

Previous experiments have demonstrated that xenon can induce impairment of neural function after CPB combined with cerebral air embolism in rats.<sup>[42]</sup> However, Casey and colleagues<sup>[43]</sup> reported that xenon does not generate more gaseous microemboli when compared to air or oxygen in an in vitro CPB circuit. In a clinical trial for delivering xenon to patients undergoing coronary artery bypass graft surgery during CPB, there were no clinical neurologic injuries and no differences in serum levels of S100- $\beta$  and total number of emboli or temporal distribution between the 2 groups.<sup>[30]</sup> During anesthesia, CPB, and surgery, the generation of intravenous gas bubbles was limited. In addition, in our study, up to 1–2 L xenon was used per patient for pulmonary static inflation, only a little of which was delivered into the gas inflow of the CPB circuit. Moreover, the xenon bubbles were completely reabsorbed in the absence of a xenon source in the range of 10 to 15 minutes.<sup>[44]</sup> Thus, we discontinued xenon delivery before 15 minutes of de-clamping to avoid undesirable effects of xenon.

By the retrospective examination, 78.49% of patients undergoing treatment for Stanford type A AAD were found to have pre-operative hypoxemia, and only 70% of patients underwent the surgical procedure within 48 hours whereas it was within 21 days for the others.<sup>[3]</sup> The method of pulmonary static inflation with 50% xenon during CBP is easy to operate and effectively attenuates decreased OI and increased RI at the end of surgery, which may save more lives.

#### 4.1. Study limitations

The present study had several limitations. One major limitation of this study was that it was not a randomized clinical trial, and as such, was susceptible to certain types of bias. In addition, it was conducted at only 1 university center, the number of cases was small, and the patients were followed up for a relatively short period time. Therefore, it may not have been adequately powered for the measurements performed. Furthermore, because only subjects with Stanford type A AAD were included, biased effects due to the variable effects of AAD-related medication cannot be excluded, although they are not expected. Thus, differences between groups regarding baseline cytokines levels have to be regarded as a reactivity of the variable extent of AAD, which was unknown at grouping. Moreover, the noble gas xenon was only

administered during the cooling period of CPB. This was a short time period, so any potential advantages of xenon with respect to organ protection characteristics could have been masked during surgery or with postoperative interventions. Finally, although 50% xenon was used to inflate pulmonary pressure to 5 cm H<sub>2</sub>O during CPB, the effective intra-alveolar concentration of xenon was not assessed. Additional studies are needed to evaluate the relationship between this concentration and inhaled xenon concentration during CPB.

## 5. Conclusions

Pulmonary static inflation with 50% xenon during CPB attenuated the decreased OI and increased RI values at the end of surgery for Stanford type A AAD. The mechanism underlying the role of xenon function may be to trigger anti-inflammatory responses and suppress pro-inflammatory and oxidative effects. However, the advantages of xenon could have been underestimated due to limited exposure time.

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