Original Article

Inflammation is related to preoperative hypoxemia in patients with acute Stanford type A aortic dissection

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Background: Preoperative hypoxemia is a frequent complication of acute Stanford type A aortic dissection (ATAAD). The aim of the present study was to determine which factors were associated with hypoxemia.

Methods: A series of data were collected in a statistical analysis to evaluate preoperative hypoxemia in patients with ATAAD. After retrospectively analyzing data for 172 patients, we identified the risk factors for preoperative hypoxemia. Hypoxemia was defined by an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of 200 or lower. Subsequent to identifying the patient population, a prospective study was conducted using ulinastatin as a preoperative intervention. The ulinastatin group received ulinastatin at a total dose of 300,000 units prior to surgery. All the pertinent factors were investigated through univariate and multiple logistic regression analysis.

Results: The factors associated with preoperative hypoxemia in ATAAD comprised the following: body mass index (BMI) ≥25; white blood cell count (WBC) and neutrophil counts; levels of C-reactive protein (CRP), D-dimer, and interleukin-6 (IL-6); ATAAD involving the celiac trunk, renal artery, or mesenteric artery. Logistic regression analysis showed that CRP and IL-6 levels were independent predictive factors. We found that ulinastatin effectively could improve oxygenation, since compared to the control group the oxygenation in the ulinastatin group was significantly improved.

Conclusions: Systemic inflammatory reactions played a vital role in preoperative hypoxemia after the onset of ATAAD. The oxygenation of the patient could be improved significantly by inhibiting the inflammatory response prior to surgery.

Keywords: Acute Stanford type A aortic dissection (ATAAD); hypoxemia; preoperative risk factors

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Introduction

Acute Stanford type A aortic dissection (ATAAD) is an age-dependent cardiovascular disease associated with high morbidity and mortality because of its potentially fatal complications (1,2). The overall mortality rate of ATAAD is about 10.3% in China (3). ATAAD not only involves the cardiovascular system but can cause multi-organ failure (4). Although the methods of diagnosis, detection, and treatment have been continuously improving, ATAAD remains one of the most severe diseases of the aorta (5). Patients with ATAAD often suffer from acute lung injury (ALI), and hypoxemia is the most typical symptom in patients with ALR. Hypoxemia is defined by an arterial

partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of 200 or lower (6). ALI is caused by various factors that result in injury to the alveolar epithelial and capillary endothelial cells, resulting in acute hypoxic respiratory insufficiency. The pathophysiological characteristics include the imbalance between ventilation and blood flow (6).

The mechanisms underlying preoperative hypoxemia and the cause of lung injury in ATAAD remain elusive. There have been no studies describing relationships between preoperative hypoxemia and ATAAD. In the present study, we established a model to predict the risk factors of ALR before surgery, and then tried to determine the predictors of preoperative hypoxemia, to improve early treatment of hypoxemia in ATAAD.

Materials and methods

Materials

Risk factors for preoperative hypoxemia

Included in this study were 172 consecutive patients with ATAAD who received treatment in the Department of Cardiothoracic Surgery at Shanghai Changhai Hospital between January 2013 and February 2015. The mean age of patients was 51.4±12.7 years, including 135 male patients. Preoperative hypoxemia was defined by an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of 200 or lower. PaO_2 was obtained from the arterial blood gas. FiO_2 was equal to 21 plus 4× the oxygen flow (7).

The patients were retrospectively divided into group A (preoperative hypoxemia, n=77) and group B (preoperative non-hypoxemia, n=95).

Prospective study of hypoxemia before surgery

Included in this part of the study were 55 consecutive patients with ATAAD who received treatment in the Department of Cardiothoracic Surgery at Shanghai Changhai Hospital from February 2015 to September 2015. According to a computer-generated sequence, patients were prospectively randomized into two groups: the ulinastatin group (C group, n=17) and the Control group (D group, n=38). The ulinastatin group received ulinastatin at total doses of 300,000 units before surgery. All the patients underwent cardiopulmonary bypass with induction of deep hypothermic circulatory arrest.

Methods

We collected patient data including age, sex, height, weight, current smoking, current drinking, and history of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), coronary disease, and Marfan syndrome. White blood cell (WBC) counts, neutrophil and platelet counts, and alanine aminotransferase (ALT), glutamic oxaloacetic transaminase (AST), C-reactive protein (CRP), D-dimer, prothrombin time (PT), creatinine (Cr) and interleukin-6 (IL-6) levels were all measured in our laboratory. The left ventricular ejection fraction (LVEF), presence of pericardial effusion, presence of pleural effusion and presence of aortic valve insufficiency were determined via echocardiography. Contrast-enhanced aortic computed tomography (CT) was used to see whether dissection involved the celiac trunk, renal artery (unilateral or bilateral), or mesenteric artery. These data were collected before surgery.

Patient data were collected during surgery including the ECCT (extracorporeal circulation time), AACT (arrest aortic clamping time), and the DHCA (deep hypothermic circulatory arrest). Red cell concentrations for the patients were calculated during surgery and in the first 24 hours postoperatively.

This study was approved by Changhai Hospital Clinical Research Ethics Committee (2016LC0118-08).

Statistical analysis

All statistical analyses were performed using the SPSS 21.0 software package. The continuous data are expressed as mean ± SD. The normally distributed variables were analyzed using the Student's *t*-test, and the non-normally distributed variables were analyzed using the Wilcoxon rank sum test. The qualitative data were analyzed using the chi-square test or Fisher's exact test. $P<0.05$ was considered statistically significant. If single factors between the two groups were statistically significant, then these factors were tested using the multivariate binary logistic regression analysis to predict the independent risk factors. The odds ratios (OR) and the 95% confidence intervals (CIs) were also calculated.

Results

Risk factors for preoperative hypoxemia (retrospective analysis)

According to the level of preoperative hypoxemia, the

Table 1 Analysis of basic information and medical histories of the patients in groups A and B

Variable	A group (n=77), n (%)	B group (n=95), n (%)	P value
Men	60 (77.9)	75 (78.9)	0.871
Age ≥60 years	19 (24.7)	28 (29.5)	0.483
BMI ≥25	27 (35.1)	19 (20.0)	0.026
Current smoking	30 (38.9)	32 (33.7)	0.474
Current drinking	5 (6.5)	9 (9.5)	0.477
History of diabetes	7 (9.1)	12 (12.6)	0.461
History of hypertension	54 (70.1)	60 (63.2)	0.336
History of coronary disease	2 (2.6)	2 (2.1)	1.000
History of COPD	3 (3.9)	2 (2.1)	0.811
Marfan syndrome	3 (3.9)	11 (11.6)	0.067

BMI, body mass index.

172 consecutive patients were retrospectively divided into group A (preoperative hypoxemia, n=77) and group B (preoperative non-hypoxemia, n=95). As shown in *Tables 1* and *2*, the data were collected, including age, sex, height, weight, current smoking, current drinking, and history of hypertension, diabetes, coronary disease, and Marfan syndrome. In addition, WBC, neutrophil and PLT counts, and ALT, AST, CRP, D-dimer, PT, Cr and IL-6 levels were determined in our laboratory. LVEF, presence of pericardial effusion, presence of pleural effusion, and presence of aortic valve insufficiency were determined by echocardiography. Contrast-enhanced CT of the aorta was used to determine if the dissection involved the celiac trunk, the renal artery, or the mesenteric artery. It was found that BMI ≥25, WBC and neutrophil counts, CRP, D-dimer and IL-6 levels, and dissection involving the celiac trunk, renal artery, or mesenteric artery were all associated with preoperative hypoxemia in ATAAD. Multivariate binary logistic regression analysis confirmed that serum CRP levels (OR 1.034, CI, 1.008–1.061; P=0.010) and IL-6 (OR 1.050; CI, 1.003–1.100; P=0.036) levels were independently associated with preoperative hypoxemia in ATAAD (*Table 3*).

Protective effect of ulinastatin on patients with ATAAD (prospective study)

A prospective study was conducted next, in which 55 patients were randomized into two groups: the ulinastatin group (C group, n=17) and the control group (D group, n=38). As shown in *Table 4*, the relative facts during the perioperative period were no different between the two groups. However, postoperative hypoxemia was significantly different (χ^2=4.771; P=0.029).

Discussion

ATAAD can cause fatal complications and high mortality (8). Surgery remains the primary treatment option (8). Dissection complicated by lung injury, especially after surgery, is not only life-threatening, but may prolong the length of ventilator support and the stay in the ICU (9).

In our study, according to the diagnostic criteria for acute respiratory distress syndrome (ARDS) established by the American–European Consensus Conference, hypoxemia was defined as a PaO_2/FiO_2 ratio ≤200 (P/F ratio) (10). Patients with ATAAD often have hypoxemia before surgery. The results of our study showed that preoperative hypoxemia was associated with a variety of factors.

Obesity by itself could easily induce respiratory system-related diseases (11) and is a known of cause obstructive sleep apnea and obesity hypoventilation syndrome. These diseases and disorders are closely associated with hypoxemia. Aizawa *et al.* (12) found that obesity was a risk factor for young-onset ATAAD and postoperative hypoxemia, both of which could prolong the length of intubation and ICU stay. The high-fat content in the pleura and chest walls in obese patients can reduce chest wall and lung compliance, lung volume and thoracic breathing and limit diaphragmatic activity, eventually leading to hypoxia (13). Therefore, obesity can be a potential risk factor used to predict hypoxemia (14). BMI ≥25 kg/m^2 could easily lead to hypoxemia. To prevent pulmonary atelectasis in obese patients, sputum aspiration should be performed positively during and after surgery. Maintaining airway patency and performance of regular X-ray examinations are also needed.

When ATAAD occurs, the coagulation and fibrinolytic systems are activated. Fibrinogen turns into fibrin which participates in the formation of a thrombus. Increased circulating D-dimer levels are reported to be correlated with adverse outcomes in various clinical settings (15). The detection interval of the D-dimer test in our hospital is 0.01–16 μg/mL, and therefore only D-dimer levels above 16 μg/mL were counted in this study. We know that the normal level of serum D-dimer is less than 0.5 mg/L. The D-dimer level in all 172 patients was

Table 2 Analysis of laboratory tests, echocardiography, CTA of the patients in groups A and B

Variable	A group (n=77)	B group (n=95)	T/Z/χ^2 value	P value
Laboratory test				
ALT (U/L)[a], $\bar{x}\pm s$	33.24±17.77	31.31±20.74	T=0.635	0.526
AST (U/L)[a], $\bar{x}\pm s$	34.20±17.11	31.94±19.72	T=0.770	0.442
WBC (10^9/L)[a*], $\bar{x}\pm s$	12.97±3.71	10.50±3.49	T=4.427	<0.01
Neutrophils (10^9/L)[a*], $\bar{x}\pm s$	10.95±3.47	8.64±3.40	T=4.322	<0.01
HAT (%)[a], $\bar{x}\pm s$	37.18±4.26	36.78±4.60	T=0.574	0.567
PLT (10^9/L)[a], $\bar{x}\pm s$	146.99±65.59	167.52±91.85	T=−1.650	0.101
Cr (μmol/L)[a], $\bar{x}\pm s$	81.22±19.97	78.30±21.39	T=1.974	0.357
PT (s)[a], $\bar{x}\pm s$	14.79±1.22	14.68±1.68	T=0.255	0.799
D-dimer (μg/mL)[c*], median (interquartile range)	11 (7, 16)	8 (5, 12)	Z=−2.698	0.007
CRP (mg/L)[a*], $\bar{x}\pm s$	105.18±63.81	44.90±32.04	Z=6.072	<0.01
IL-6 (μg/L)[a*], $\bar{x}\pm s$	93.66±76.91	48.78±22.94	Z=3.971	<0.01
Echocardiography				
EF valve (%)[a], $\bar{x}\pm s$	57.39±7.12	56.93±7.36	Z=0.416	0.678
Pericardial effusion[b], (n, %)	13 (16.9)	24 (25.3)	χ^2=1.769	0.184
Pleural effusion[b], (n, %)	5 (6.5)	9 (9.5)	χ^2=0.51	0.477
Aortic valve insufficiency[b], (n, %)	42 (54.5)	48 (50.5)	χ^2=0.28	0.600
Aortic CTA				
Involve celiac trunk[b*], (n, %)	10 (12.9)	4 (4.2)	χ^2=4.38	0.036
Involve mesenteric artery[b*], (n, %)	12 (15.6)	6 (6.3)	χ^2=3.90	0.048
Involve renal artery (single side)[b*], (n, %)	24 (31.2)	14 (14.7)	χ^2=6.67	0.010
Involve renal artery (both sides)[b*], (n, %)	9 (11.7)	3 (3.2)	χ^2=4.77	0.029

[a], *t*-test; [b], chi-square test; [c], Wilcoxon rank sum test; *, indicates significant difference between groups. CTA, computed tomography angiography; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; HCT, hematocrit; PLT, platelets; Cr, creatinine; PT, prothrombin time; CRP, C-reactive protein; IL-6, interleukin-6.

Table 3 Multivariate logistic regression analysis of preoperative hypoxemia in acute Stanford type A aortic dissection

Variable	Odds ratio (95% CI)	P value
IL-6 (μg/L)	1.050 (1.003–1.100)	0.036
CRP (mg/L)	1.034 (1.008–1.061)	0.010
D-dimer (μg/mL)	1.188 (0.995–1.419)	0.057
WBC (10^9/L)	1.257 (0.920–1.718)	0.151
Neutrophils (10^9/L)	0.972 (0.867–1.089)	0.626
BMI (kg/m^2)	1.179 (0.940–1.478)	0.154

IL-6, interleukin-6; CRP, C-reactive protein; WBC, white blood cell; BMI, body mass index.

positive (sensitivity of 100%). Sbarouni *et al.* (16) found that a serum D-dimer level higher than 700 ng/mL had 94% sensitivity and 59% specificity for the diagnosis of ATAAD. D-dimer ≥5.67 μg/mL was an important risk factor and was independently associated with ATAAD inpatient deaths (17). D-dimer is a marker of fibrinolysis and coagulation (18). D-dimer may reflect disease severity in ATAAD patients with preoperative hypoxemia.

ATAAD involving the celiac trunk, renal artery (unilateral or bilateral) or mesenteric artery is a risk factor for patients with ATAAD and preoperative hypoxemia. When an ATAAD is formed, large amounts of blood flow into the

Table 4 Comparison of clinical characteristics and findings between groups C and D

Variable	C group (n=17)	D group (n=38)	T/Z/χ^2 value	P value
Preoperative hypoxemia[a] (n, %)	7 (41.2)	12 (31.2)	χ^2=0.478	0.489
Women[a] (n, %)	1 (5.9)	7 (18.4)	χ^2 =0.648	0.421
Age[b] (year), $\bar{x}\pm s$	51.59±9.39	49.71±10.59	T =0.541	0.804
WBC[b] (10^9/L), $\bar{x}\pm s$	12.22±3.38	12.44±4.17	T=−1.90	0.246
Neutrophils[b] (10^9/L), $\bar{x}\pm s$	10.70±2.99	10.39±3.92	T=0.288	0.129
D-dimer[c] (μg/mL), median (interquartile range)	6 (4, 8)	8 (5, 9)	Z=−1.332	0.183
CRP[b] (mg/L), $\bar{x}\pm s$	66.84±40.32	64.97±41.33	Z=−0.299	0.765
IL-6[b] (μg/L), $\bar{x}\pm s$	58.33±33.08	62.05±36.96	Z=−0.173	0.862
Involve celiac trunk[a], (n, %)	2 (11.8)	4 (10.5)	χ^2=0.000	1.000
Involve mesenteric artery[a], (n, %)	1 (5.9)	5 (13.1)	χ^2=0.110	0.740
Involve renal artery[a], (n, %)	3 (17.6)	13 (34.2)	χ^2=0.862	0.353
ECCT[b] (min), $\bar{x}\pm s$	155.31±42.51	153.53±27.93	T=0.177	0.350
AACT[b] (min), $\bar{x}\pm s$	91.71±19.85	90.34±16.25	T=0.268	0.114
DHCA[b] (min), $\bar{x}\pm s$	30.38±7.34	31.94±8.05	T=−0.667	0.823
Red cell concentrates[b] (mL), $\bar{x}\pm s$	2,114.29±810.37	1,917.14±532.74	Z=−1.209	0.227
Postoperative hypoxemia[a]*, (n, %)	4 (23.5)	21 (55.3)	χ^2=4.771	0.029

[a], chi-square test; [b], *t*-test; [c], Wilcoxon rank sum test; *, indicates significant difference between groups. WBC, white blood cell; CRP, C-reactive protein; IL-6, interleukin-6; ECCT, extracorporeal circulation time; AACT, arrest aortic clamping time; DHCA, deep hypothermic circulatory arrest.

false lumen. With the expansion of the dissection, more blood flows into it. This can lead to ventilation/perfusion ratio imbalances. The percentage of ATAAD is defined as the percentage of blood volume in the false lumen to that of the blood in the aorta (19) There is a negative correlation between the ventilation/perfusion ratio and AAD% (r=−0.604) (19). The AAD% in patients with preoperative hypoxemia was higher than that in patients without preoperative hypoxemia (50.8%±10.9% *vs.* 28.0%±11.9%, P<0.01). Systemic inflammatory reactions are associated with this process (19).

Systemic inflammatory reactions play a vital role in this process after the onset of ATAAD. Inflammatory reactions are involved in the development of ATAAD (20). Systemic inflammation can be caused by the ATAAD. Increased plasma inflammatory markers are believed to be significantly associated with ATAAD (21). In our study, we found that the WBC and neutrophil counts were increased, and the serum CRP and IL-6 levels were elevated significantly in patients with ATAAD. A multivariate binary logistic regression analysis confirmed that they were independently associated with preoperative hypoxemia in ATAAD.As an acute phase reactant, CRP is a sensitive and non-specific inflammatory marker (22). CRP ≥11.21 mg/L was a significant risk factor for preoperative hypoxemia and was independently associated with an inpatient risk of death in ATAAD patients (17). Prolonged elevation or re-elevation of CRP may be an important factor to guide clinical interventions (23). IL-6 is known to be secreted at high levels in human aortic disease (24). Tieu *et al.* reported that IL-6production contributes to vascular inflammation which can lead to aneurysm and dissection (25). Plasma concentrations of IL-6 were tested in 64 patients with ATAAD, 98 patients with hypertension alone, and 96 healthy subjects (10.98±2.38 *vs.* 3.79±1.56 and 3.32±1.60 pg/mL, P<0.05, respectively) (20). The expression of IL-6 was obvious in ALR. The IL-6 level in the serum and bronchoalveolar lavage fluid rose significantly in patients with pulmonary injury (26). ATAAD can cause systemic inflammatory response. With the self-destruction and cascade amplification, the inflammatory reaction increases gradually. The inflammatory substances are activated in the lung, which can destroy the integrity of

the alveolar cells, eventually leading to pulmonary edema. The extensive existence of capillary beds in the lung tissue is likely to cause injury.

The early use of beta-blockers could prevent excessive inflammation after ATAAD (27). Appropriate clinical interventions may improve oxygenation, so a further prospective study was conducted. Fifty-five patients were prospectively randomized into two groups: the ulinastatin group (C group, n=17) and the control group (D group, n=38). Compared to the control group, the postoperative hypoxemia of patients in the ulinastatin group was significantly improved. Ulinastatin is a broad-spectrum protease inhibitor. It has been used widely in patients with acute inflammatory disorders (28). Ulinastatin stabilizes the lysosomal membrane and inhibits the release of hydrolytic enzymes in vivo. It also inhibits the generation of myocardial inhibitory factor, reducing the production of oxygen free radicals and inhibiting the excessive release of various inflammatory mediators. It is widely used in the treatment of SIRS and other diseases (29,30). The protective mechanism of ulinastatin can be attributed to the inhibited production of pro-inflammatory cytokines (31), The effect of ulinastatin on respiratory function after CPB under DHCA could improve oxygenation (32).

However, the mechanism of preoperative hypoxemia remains unclear. To the best of our knowledge, there is no published study reporting on patients with ATAAD and preoperative hypoxemia. Generally, long- term smoking and smoking history can damage alveolar epithelial cells and the trachea and bronchial epithelial cells, resulting in pulmonary function damage (33). However, we failed to find a significant difference between the two groups in our study. Our research shows that acute inflammatory response may play a vital role in this process.

Conclusions

Hypoxemia is a complication in patients with ATAAD. BMI, systemic inflammatory response, D-dimer level, and the extent of dissection are risk factors for preoperative hypoxemia, of which inflammatory response is the independent predictive factor. Appropriate clinical interventions may play a virtual role in the prevention and treatment of hypoxemia in the perioperative period.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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