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Changes in the concentrations of mediators in exhaled breath condensate during cardiac valve replacement under cardiopulmonary bypass and their relations with postoperative acute respiratory distress syndrome

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Abstract

To investigate the changes in the concentrations of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and 8-iso-prostaglandin $F_{2\alpha}$ (8-isoPGF$_{2\alpha}$) in exhaled breath condensate (EBC) in patients undergoing cardiac valve replacement under cardiopulmonary bypass (CPB) and its relationship with postoperative acute respiratory distress syndrome (ARDS).

A prospective, case–control study was performed on 55 patients undergoing elective cardiac valve replacement under cardiopulmonary bypass, between November 2017 and May 2019. According to the diagnosis of postoperative ARDS, the patients were divided into ARDS group and control group. We compared the clinical characteristics, outcomes, respiratory mechanics, oxygenation parameters, and mediators in the 2 groups immediately after tracheal intubation (T_1), at the end of CPB (T_2), and 2 hours (T_3) and 6 hours (T_4) after CPB, and calculated the receiver operating characteristic curve (ROC), sensitivity, and specificity of the corresponding mediators.

ARDS occurred in 29 patients after CPB. The ARDS group exhibited prolonged postoperative ventilator support, time to extubation, length of stay in the ICU, and postoperative length of stay. The peak airway pressure (P_{peak}) and plat airway pressure (P_{plat}) at T_4 were higher in the ARDS group compared with the control group. The alveolar-arterial oxygen partial pressure [$P_{(A\text{-}a)}O_2$] and respiratory index (RI) were higher and PaO_2/FiO_2 was lower in the ARDS group at $T_{2–4}$ compared with the control group. The levels of EBC and serum mediators in the ARDS group were significantly higher at $T_{2–4}$ compared with those in the control group. All the mediators in EBC were correlated significantly with those in the serum in the ARDS group ($r = 0.7314$, 0.898, 0.8386, 0.792) and control group ($r = 0.6093$, 0.8524, $r = 0.7828$, $r = 0.6575$) ($P < .001$). Meanwhile, the area under the curve (AUC) of IL-8 in EBC was significantly lower at T_2 and the AUC of IL-6 in EBC was significantly higher at T_4 than in serum ($P < .05$). In addition, all of the mediators in EBC had a certain accuracy in diagnose of postoperative ARDS.

EBC analysis could be used to predict the high incidence of ARDS after cardiac valve replacement under CPB.

Abbreviations: 8-isoPGF$_{2\alpha}$ = 8-iso-prostaglandin $F_{2\alpha}$, ARDS = acute respiratory distress syndrome, AUC = area under the curve, CPB = cardiopulmonary bypass, EBC = exhaled breath condensate, IL-6 = interleukin-6, IL-8 = interleukin-8, $P_{(A\text{-}a)}O_2$ = alveolar-arterial oxygen partial pressure, P_{peak} = peak airway pressure, P_{plat} = plat airway pressure, RI = respiratory index, ROC = receiver operating characteristic curve, TNF-α = tumor necrosis factor-α.

Keywords: acute respiratory distress syndrome, cardiac valve replacement, cardiopulmonary bypass, exhaled breath condensate, mediator

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1. Introduction

Cardiac operation alone with cardiopulmonary bypass (CPB) can cause complex inflammatory reactions and oxidative stress responses, which lead to a series of complications. Acute respiratory distress syndrome (ARDS) is one of the main complications after CPB and has high morbidity and mortality rates.[1] Currently, diagnosis of ARDS is performed via arterial blood gas measurements, bronchial lavage fluid analyses, and chest X-ray, which are indirect and lag behind in terms of clinical development.[2] Collection of exhaled breath condensate (EBC) is a noninvasive method that can be used to detect biomarkers from the airway. Interleukin [IL]-6, IL-8 are early markers of tissue damage sensitive material and tumor necrosis factor-α (TNF-α) is an inflammatory mediator of the earliest and most important process of inflammation.[3] The 3 inflammatory factors are among the most promising biomarkers for predicting the morbidity and mortality of ARDS.[4] 8-iso-prostaglandin $F_{2\alpha}$ (8-isopg$F_{2\alpha}$) is a sensitive indicator that reflects oxidative stress and is accepted as a biomarker of ARDS.[5] However, whether the mediators measured in EBC are associated with pulmonary inflammation or oxidative stress remains unclear. Thus, a new method for the early prediction of ARDS induced by CPB is urgently needed.

The purpose of this study was to investigate the relationship between postoperative ARDS and changes in the concentrations of the mediators of inflammatory factors IL-6, IL-8, and TNF-α and oxidative stress 8-isopg$F_{2\alpha}$ in EBC and serum samples of patients undergoing cardiac valve replacement. We hypothesized that increased levels of inflammatory and oxidative mediators in EBC equate to an increased risk of postoperative ARDS after cardiac valve replacement under CPB.

2. Methods

2.1. Patients

The patients undergoing elective cardiac valve replacement under cardiopulmonary bypass from November 2017 to May 2019 were selected as the study subjects. This study was approved by the Ethics Committee of the First People's Hospital of Nantong (the Second Affiliated Hospital of Nantong University) and the Chinese Clinical Trial Register (reference ChiCTR1800014299). Informed consent was obtained from each patient. Fifty five patients (32 males and 23 females) with statuses of II and III under the American Society of Anesthesiologists (ASA) physical status classification system and scheduled for elective cardiac valve replacement under CPB were enrolled in this study. The patients were prospectively and observationally studied in a single center. Patient age ranged from 34 to 80 years. The exclusion criteria included previous ingestion of anti-inflammatory or antioxidant drugs, systemic active infections, liver and kidney dysfunction, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), history of neurologic disturbance, CPB failure (and thus, repetition of CPB), and reoperation or repetition of CPB after operation.

2.2. Anesthesia and intraoperative management

Patients received routine monitoring in the operating room. Anesthesia was induced with intravenously administered midazolam (0.05 mg/kg), etomidate (0.3 mg/kg), sufentanil (1 ug/kg), and vecuronium bromide (0.15 mg/kg). Endotracheal intubation was performed after the induction of anesthesia. Anesthesia was subsequently maintained with propofol ($4–5\,mg\,kg^{-1}\cdot h^{-1}$), remifentanil ($6–15\,\mu g\cdot kg^{-1}\cdot h^{-1}$), and vecuronium bromide ($0.12–0.15\,mg\,kg^{-1}\cdot h^{-1}$). The ventilator settings consisted of a tidal volume (V_T) of 8 to 10 ml/kg, breathing frequency of 12 to 14 breaths/minute, and an inhale:exhale ratio of 1:2. End-tidal CO_2 was maintained between 30 and 35 mm Hg, and the bispectral (BIS) index was maintained between 40 and 60. Positive end-expiratory pressure (PEEP) was set at $0\,cmH_2O$. FiO_2 0.6 was used during mechanical ventilation and not manipulated until PaO_2/FiO_2 was below 300 mm Hg or SpO_2 was lower than 98%. All patients were transferred to the postsurgical intensive care unit (ICU) after surgery without extubation.

2.3. Collection and analysis of EBC and Blood Samples

The EBC collection device was constructed using a portable glass tube connected to the expiratory port of a ventilator. The glass tube was cooled with a mixture of ice and water to generate temperatures of 0°C. The EBC samples were collected at time points T_1 (immediately after tracheal intubation), T_2 (end of CPB), T_3 (2 hours after CPB), and T_4 (6 hours after CPB). Each collection lasted for 30 minutes, and 1 to 2 ml of EBC was obtained. The samples were stored immediately at −80°C at the end of each collection. Radial artery blood samples (5 ml) were collected from all patients at T_1, T_2, T_3, and T_4 and divided into 2 aliquots. One aliquot (1 ml) was promptly used for blood gas analysis, and the other (4 ml) was centrifuged at 1500 rpm for 10 minutes. The serum was separated and stored at −80°C until analysis.

The levels of IL-6, IL-8, and TNF-α in the EBC and serum samples were measured with an enzyme-linked immunosorbent assay kit (R&D Systems, USA), whereas those of 8-iso-$PGF_{2\alpha}$ were measured with a competitive enzyme immunoassay kit (Abcam, UK). Alveolar-arterial oxygen partial pressure [$P_{(A\text{-}a)}O_2$] and the respiratory index (RI) were calculated in accordance with the following formulas: $P_{(A\text{-}a)}O_2 = [FiO_2 \times (760 - 47) - PaCO_2 \times 1.25] - PaO_2$ and $RI = P_{(A\text{-}a)}O_2 / PaO_2$.

2.4. Definitions of outcome variables

The patients were divided into ARDS and control groups in accordance with the diagnosis of postoperative ARDS. All patients received the same treatment before ARDS was diagnosed, and the same empirical treatments after cardiac surgery were symptomatic treatment, oxygen inhalation, component blood transfusion, use of vasoactive drugs, appropriate dieresis, and so on. Standardized treatments were provided to those who developed ARDS and the treatments were positive control of primary disease and use of lung protective ventilation (Vt 6–8 ml/kg predicted body weight, low plateau pressures and positive PEEP) as soon as possible on the basis of the original treatment.

The patients were considered to have ARDS when they met the 2012 Berlin definition of ARDS.[6] The ARDS patients were classified into mild [200 mm Hg $< PaO_2/FiO_2 \leq$ 300 mm Hg with PEEP or continuous positive airway pressure (CPAP) ≥ 5 cmH_2O], moderate (100 mm Hg $< PaO_2/FiO_2 \leq$ 200 mm Hg with PEEP $\geq 5\,cmH_2O$), and severe ($PaO_2/FiO_2 \leq$ 100 mm Hg with PEEP $\geq 5\,cmH_2O$) in accordance with the oxygenation index.

Pulmonary infections that developed within 3 days after replacement were recorded. Secondary outcome measures, including the time of postoperative ventilator support, time to extubation, length of stay in the ICU, post-ICU ventilator use and postoperative length of stay, were recorded.

2.5. Statistical analysis

Statistical analysis was performed with GraphPad Prism version 7.00 (GraphPad Software, USA). The data following normal distribution were presented as mean ± SD, the data with non-normal distribution were presented as medians and interquartile ranges (IQRs), and the counting data were expressed as number or percentage. Independent sample *t* tests were used for the comparison between 2 non-normally distributed groups, and the Mann–Whitney *U* test was used to compare the data of the 2 groups for variables that were not normally distributed. Repeated measures of analysis of variance and Tukeys multiple comparison test were adopted to compare repeated measures. The Chi-Squared test or Fisher exact probability method was utilized to compare differences in rates. The relationships between the inflammatory or oxidative mediators in the EBC and serum samples were analyzed using Pearson correlation coefficients. The receiver operating characteristic curve (ROC) and the AUC was used to compare the diagnostic performance of different parameters. MedCalc 19.0.7 software (MedCalc, Ostend, Belgium) was used to compare different diagnostic tests. Results were considered statistically significant when $P < .05$.

3. Results

3.1. Clinical characteristics and outcomes of patients

Fifty five patients participated in this study, and 29 of them suffered from ARDS after cardiac valve replacement under CPB. Among the 29 patients, 22 suffered mild ARDS, 6 had moderate ARDS, and 1 had with severe ARDS. The 2 groups did not differ in terms of gender, age, height, weight, ASA statuses, New York Heart Association (NYHA) statuses, surgery type ratio, operation duration, CPB duration, block duration, bleeding amount, transfusion volume, pulmonary infections, and mortality ($P > .05$). The time of postoperative ventilator support, time to extubation, length of stay in the ICU, post-ICU ventilator use and postoperative length of stay in the ARDS group were extended compared with those in the control group ($P < .05$). One patient selected in the ARDS group was died at 4 d after CPB, so the postoperative length of stay of that patient was not calculated. The basic clinical characteristics and outcomes of all patients in this study are shown in Table 1.

3.2. Mean arterial pressure and heart rate of patients

The variables of the mean arterial pressure and heart rate of patients in the 2 groups at different time points did not significantly vary between the 2 groups ($P > .05$) (Fig. 1 A and B).

3.3. Hematologic and biochemistry indicators

The hematologic and biochemistry indicators include white blood cell (WBC), hemoglobin (Hb), platelet (PLT), blood urea nitrogen (BUN), creatinine (Cr), natrium (Na), kalium (K), and albumin (ALB). There were no significant differences in all of them between ARDS and control group before the operation ($P > .05$). There were no significant differences in Hb and K between ARDS and control group at 24 hours after operation ($P > .05$). Compared with the control group, the WBC, BUN, Cr, and Na of ARDS group were significantly higher while the Hb and ALB of ARDS group were significantly lower at 24 hours after operation ($P < .05$) (Table 2).

Table 1

Clinical characteristics and outcomes of patients in the 2 groups.

Characteristics and Outcomes	ARDS group n = 29	Control group n = 26	*P*
Gender (male/female)	18/11	14/12	.592
Age (y)	62.31 ± 9.61	58.08 ± 12.39	.160
Height (cm)	167.72 ± 6.83	165.50 ± 6.25	.222
Weight (kg)	72.83 ± 11.25	68.88 ± 8.87	.158
ASA statuses (II/III)	7/22	8/18	.763
NYHA statuses (II/III)	14/15	12/14	>.999
Smoking, n (%)	7 (24.13)	5 (19.23)	.751
Hypertension, n (%)	11 (37.93)	5 (19.23)	.149
Diabetes mellitus, n (%)	4 (13.79)	2 (7.69)	.672
Surgery type (Double valve replacement: Mitral valve replacement: Aortic valve replacement)	7:9:13	9:7:10	.694
Duration of operation (min)	260.17 ± 67.99	273.27 ± 63.94	.467
Duration of CPB (min)	119.34 ± 58.05	109.77 ± 51.69	.523
Duration of block (min)	83.41 ± 52.54	73.88 ± 41.76	.463
Amount of bleeding (ml)	1000 (250)	950 (200)	.146
Transfusion volume (ml)	1350 (300)	1225 (250)	.091
Pulmonary infections, n (%)	4 (13.79)	2 (7.69)	.672
Mortality, n (%)	1 (3.45)	0 (0)	>.999
Time of postoperative ventilator support (h)	12.50 (10.17)	7.83 (3.56)	.029
Time to extubation (h)	17.50 (7.58)	12.75 (7.19)	.007
Length of stay in ICU (d)	1.83 (1.08)	1.60 (0.79)	.008
Post-ICU ventilator use, n (%)	11 (37.93)	1 (3.85)	.003
Postoperative length of stay (d)	12 (5) (n = 26)	11 (3)	.049

The data following normal distribution was presented as mean ± SD, the data with non-normal distribution were presented as medians and interquartile ranges (IQRs).
ARDS = acute respiratory distress syndrome, ASA = American society of anesthesiologists, CPB = cardiopulmonary bypass, ICU = intensive care unit, NYHA = New York heart association.

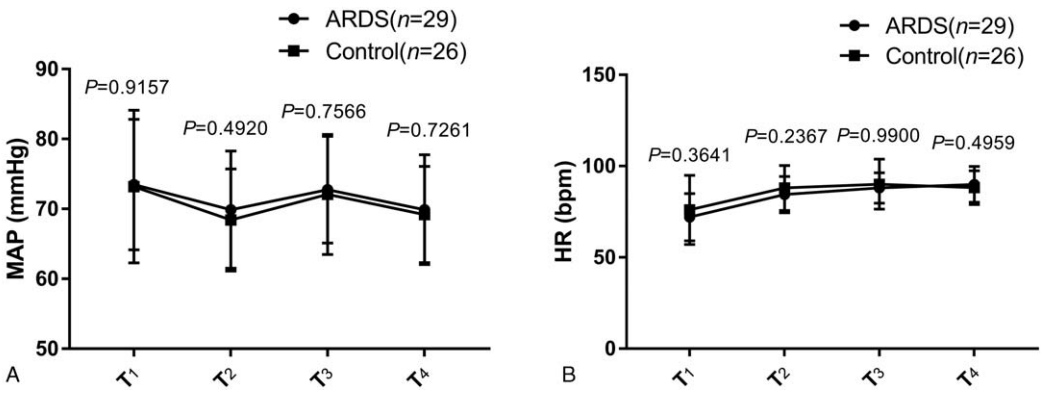

Figure 1. Comparison of mean arterial pressure and heart rate. A, Comparison of mean arterial pressure between the ARDS group and control group. B, Comparison of heart rate between the ARDS group and control group. ARDS = acute respiratory distress syndrome, HR = heart rate, MAP = mean arterial pressure.

3.4. Respiratory mechanics and oxygenation parameters

The respiratory mechanics and oxygenation parameters include tidal volume (VT), peak airway pressure (Ppeak), plat airway pressure (Pplat), PaO_2/FiO_2, $P_{(A\text{-}a)}O_2$, and RI. There was no significant difference in VT between ARDS and control group ($P > .05$). Compared with the control group, the Ppeak and Pplat of ARDS group were significantly higher at T_4 ($P < .001$), the PaO_2/FiO_2 of ARDS group was significantly lower at $T_{2–4}$ ($P < .001$), the $P_{(A\text{-}a)}O_2$ of ARDS group was significantly higher at $T_{2–3}$ ($P < .001$) and T_4 ($P = .003$), and the RI of ARDS group was significantly higher at T_2 ($P = .012$), $T_{3–4}$ ($P < .001$)) (Fig. 2A-E).

3.5. Concentration of mediators in serum and EBC samples

The time course of the levels of mediators, including IL-6, IL-8, TNF-α, and 8-isopg$F_{2\alpha}$, in the serum and EBC samples (Fig. 3A-H) showed that the mediators in serum and EBC were significantly higher in the ARDS group at $T_{2–4}$ compared with the control group ($P < .05$), and the levels of all mediators in EBC and serum were increased at $T_{2–3}$ relative to T_1, and decreased at T_4 relative to T_3 ($P < .05$).

3.6. Correlation analysis of mediators in EBC and serum samples

Spearman correlation analysis found that the levels of IL-6, IL-8, TNF-α, and 8-isopg$F_{2\alpha}$ in EBC were correlated significantly with those in the serum in the ARDS group ($r = 0.7314$, $P < .0001$; $r = 0.898$, $P < .0001$; $r = 0.8386$, $P < .0001$; $r = 0.792$, $P < .0001$) and control group ($r = 0.6093$, $P < .0001$; $r = 0.8524$, $P < .0001$; $r = 0.7828$, $P < .0001$; $r = 0.6575$, $P < .0001$) (Fig. 4A-H).

3.7. The association between levels of mediators and postoperative acute respiratory distress syndrome

The ROC curves of mediators including IL-6, IL-8, TNF-α, and 8-isopg$F_{2\alpha}$ at different time point (Fig. 5A-F, Table 3) showed that, the AUC of the IL-8 in EBC was significantly lower at T2 than in serum ($P = .026$), the AUC of the IL-6 in EBC was significantly higher at T4 than in serum ($P = .001$). There was no significant difference in AUC between mediators in EBC and serum samples at the other time points ($P > .05$). However, all of the mediators in EBC had a certain accuracy in diagnose of postoperative ARDS ($P < .05$).

4. Discussion

ARDS is a potentially life-threatening complication in patients undergoing cardiac surgery. Efforts should be made in order to identify those at higher risk aimed at decreasing the likelihood of developing this ominous condition and improve survival rates.[7] EBC collection is a new, noninvasive method of studying the composition of fluid in the airway lining. Analysis of pulmonary biomarkers in EBC has been proven to be useful in characterizing

Table 2

Comparison of hematologic and biochemistry indicators in the 2 groups.

	Pre-operation			24 h after operation		
Indicators	**ARDS group n = 29**	**Control group n = 26**	**P**	**ARDS group n = 29**	**Control group n = 26**	***P***
WBC (x10^9/L)	5.65 ± 1.43	5.74 ± 1.45	.820	15.59 ± 4.40	10.25 ± 3.08	<.001
Hb (g/L)	149.48 ± 16.90	148.31 ± 18.93	.809	102.38 ± 12.36	98.46 ± 11.14	.224
PLT (x10^9/L)	186.41 ± 44.13	185.73 ± 49.47	.957	86.72 ± 21.31	107.08 ± 21.40	<.001
BUN (mmol/L)	5.59 ± 1.49	5.57 ± 1.45	.956	9.79 ± 3.03	7.65 ± 1.62	.005
Cr (μmol/L)	72.52 ± 16.08	71.27 ± 16.62	.778	102.45 ± 31.95	86.5 ± 18.92	.031
Na (mmol/L)	138.83 ± 2.57	139.04 ± 2.86	.782	143.43 ± 3.74	140.01 ± 2.38	<.001
K (mmol/L)	4.10 ± 0.30	4.09 ± 0.36	.919	4.30 ± 0.42	4.29 ± 0.32	.898
ALB (g/L)	39.49 ± 3.54	39.07 ± 3.73	.667	33.46 ± 4.07	36.41 ± 3.93	.009

The data following normal distribution was presented as mean ± SD.

ARDS = acute respiratory distress syndrome, ALB = albumin, BUN = blood urea nitrogen, Cr = creatinine, Hb = hemoglobin, K = kalium, Na = natrium, PLT = platelet, WBC = white blood cell.

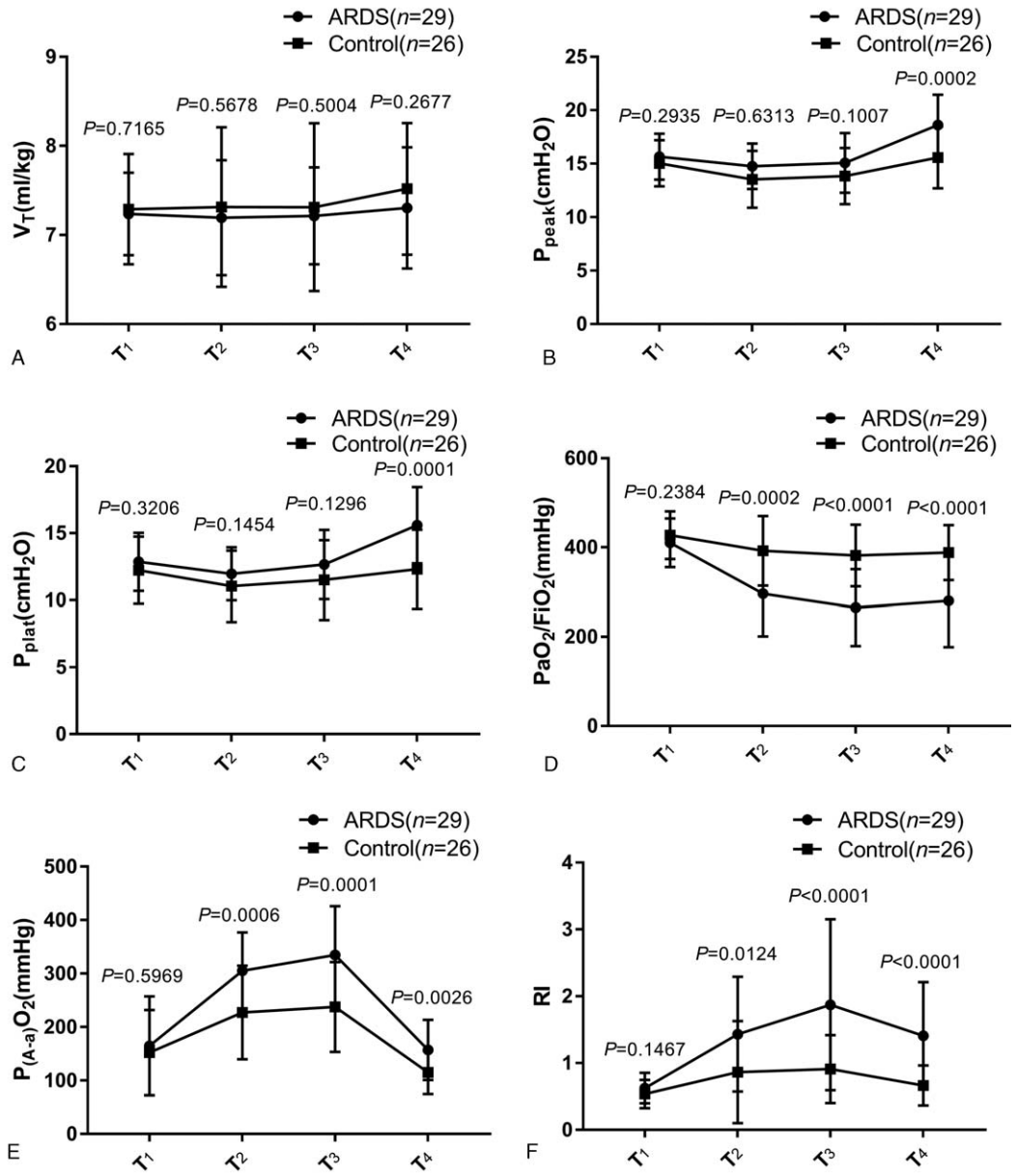

Figure 2. Comparison of mean respiratory mechanics and oxygenation parameters (V_T, P_{peak}, P_{plat}, $P_{(A-a)}O_2$, PaO_2/FiO_2 and RI). A, Comparison of V_T between the ARDS group and control group. B, Comparison of P_{peak} between the ARDS group and control group. C, Comparison of P_{plat} between the ARDS group and control group. D, Comparison of $P_{(A-a)}O_2$ between the ARDS group and control group. E, Comparison of PaO_2/FiO_2 between the ARDS group and control group. F, Comparison of RI between the ARDS group and control group. ARDS = acute respiratory distress syndrome, P_{peak} = peak airway pressure, P_{plat} = plat airway pressure, $P_{(A-a)}O_2$ = alveolar-arterial oxygen partial pressure, RI = respiratory index, V_T = tidal volume.

the pathophysiology of pulmonary diseases and monitoring of airway inflammation.[8,9] In our study, we compared the concentrations of IL-6, IL-8, TNF-α, and 8-isopg$F_{2\alpha}$ in the patients undergoing cardiac valve replacement, calculated the correlation of them between EBC and serum. Then the ROC curves were used to evaluated the association between levels of mediators and postoperative ARDS. We choose these mediators because of they can predict the morbidity and mortality of ARDS.[4] IL-6 function as a promoter of inflammatory reaction and was associated with development of lung injury. IL-8 can promote neutrophil degranulation, release elastase, endothelial injury, microcirculation of blood stasis, tissue necrosis, and organ function injury.[3] TNF-α is an important cytokine and its concentration can reflect the degree of systemic inflammatory response after CPB.[10] 8-isopg$F_{2\alpha}$ is a sensitive indicator of oxidative stress.[11] We found that the levels of IL-6, IL-8, TNF-α, and 8-isopg$F_{2\alpha}$ increased after CBP and decreased at 6 hours after CPB in both EBC and serum, and the patients who were diagnosed as ARDS related to a higher level of these mediators. We also found the trends of these mediators in EBC were closely related to their trends in serum and most of the mediators had medium diagnostic value in diagnose of ARDS. The IL-6 in EBC at 6 hours after CPB had high diagnostic value and it was significantly higher in EBC than in the serum at that time point. But the IL-6 in serum at 6 hours after CPB and the 8-isopg$F_{2\alpha}$ in serum at the end of CPB and 6 hours after CPB only had low

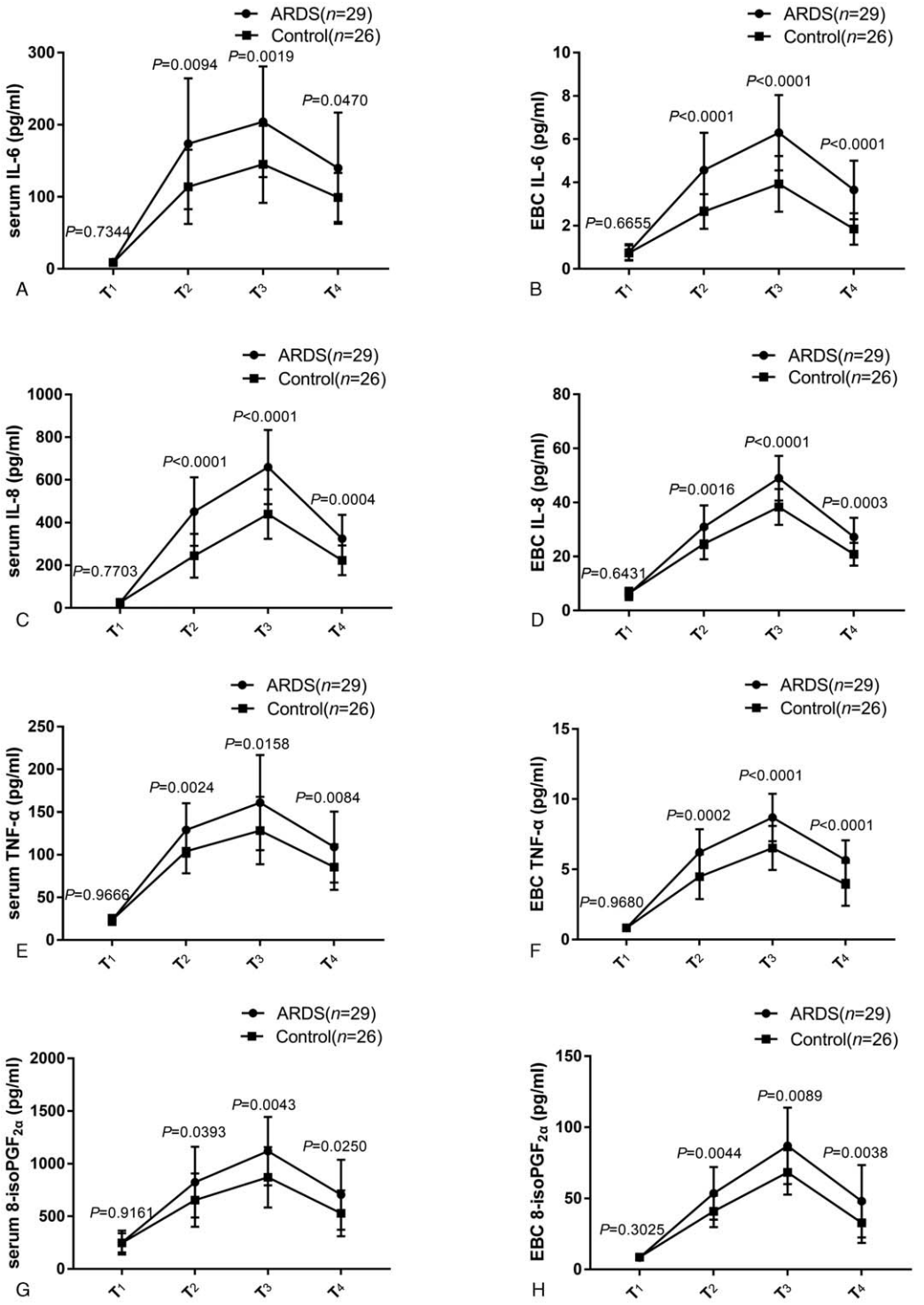

Figure 3. Comparison of serum and EBC levels of IL-6, IL-8, TNF-α and 8-isopg$F_{2\alpha}$. A, Comparison of serum level of IL-6 between the ARDS group and control group. B, Comparison of EBC level of IL-6 between the ARDS group and control group. C, Comparison of serum level of IL-8 between the ARDS group and control group. D, Comparison of EBC level of IL-8 between the ARDS group and control group. E, Comparison of serum level of TNF-α between the ARDS group and control group. F, Comparison of EBC level of TNF-α between the ARDS group and control group. G, Comparison of serum level of 8-isopg$F_{2\alpha}$ between the ARDS group and control group. H, Comparison of EBC level of 8-isopg$F_{2\alpha}$ between the ARDS group and control group. 8-iso$PGF_{2\alpha}$ = 8-iso-prostaglandin $F_{2\alpha}$, ARDS = acute respiratory distress syndrome, EBC = exhaled breath condensate, IL-6 = interleukin-6, IL-8 = interleukin-8, TNF-α = tumor necrosis factor-α.

diagnostic value. Therefore, we considered that EBC collection and evaluation are valuable for the prediction and diagnosis of ARDS, and sometimes may be more sensitive than serum.

Besides that, we compared the outcomes between ARDS and non-ARDS patients and found patients who suffered from ARDS experienced prolonged postoperative ventilator support, time to

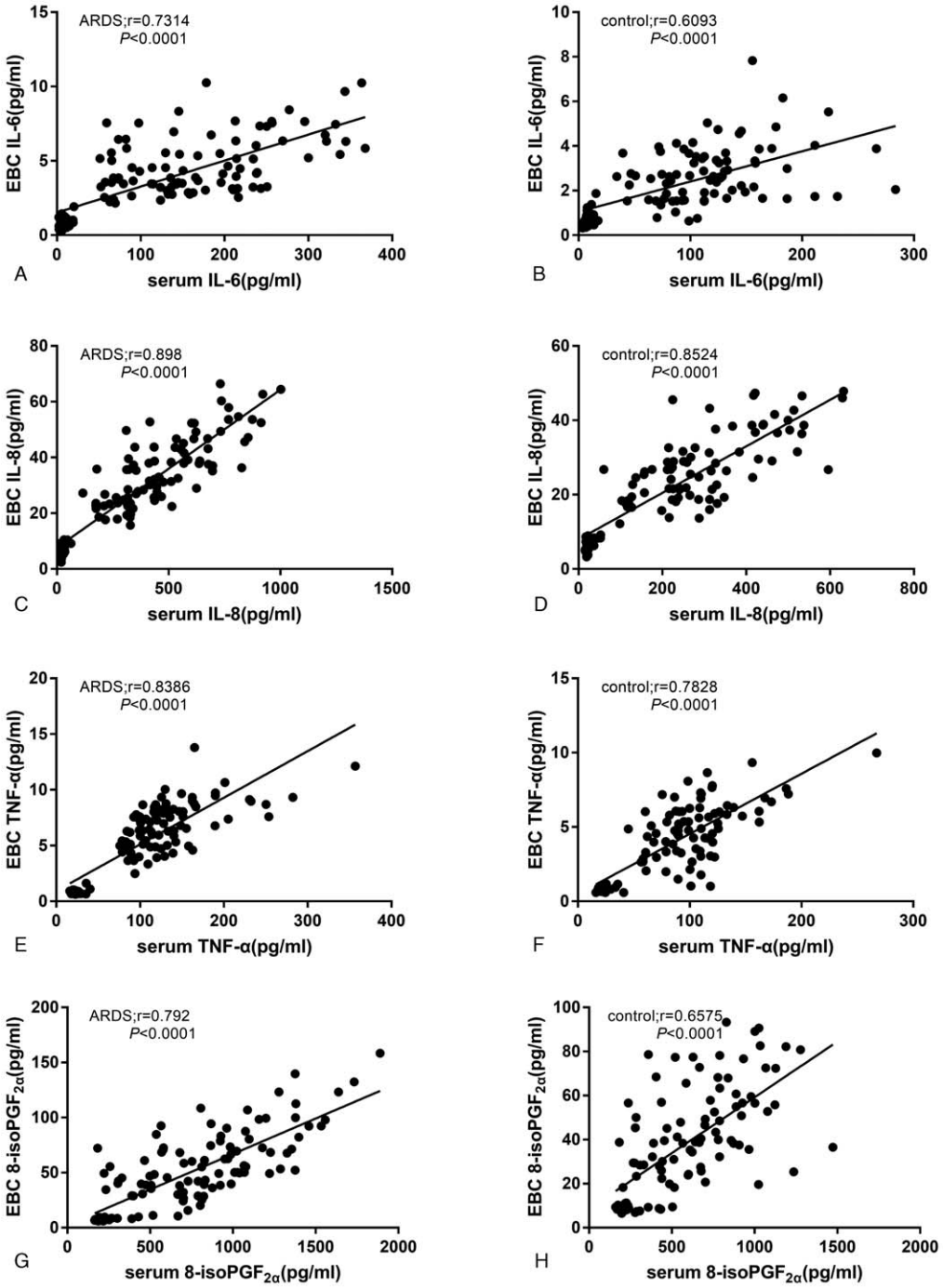

Figure 4. Correlations of EBC levels of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ with levels in serum in the ARDS group and control group. A, Correlation of EBC levels of IL-6 with levels in serum in the ARDS group. B, Correlation of EBC levels of IL-6 with levels in serum in the control group. C, Correlation of EBC levels of IL-8 with levels in serum in the ARDS group. D, Correlation of EBC levels of IL-8 with levels in serum in the control group. E, Correlation of EBC levels of TNF-α with levels in serum in the ARDS group. F, Correlation of EBC levels of TNF-α with levels in serum in the control group. G, Correlation of EBC levels of 8-isopgF$_{2\alpha}$ with levels in serum in the ARDS group. H, Correlation of EBC levels of 8-isopgF$_{2\alpha}$ with levels in serum in the control group. 8-isoPGF$_{2\alpha}$ = 8-iso-prostaglandin F$_{2\alpha}$, ARDS = acute respiratory distress syndrome, EBC = exhaled breath condensate, IL-6 = interleukin-6, IL-8 = interleukin-8, TNF-α = tumor necrosis factor-α.

extubation, length of stay in the ICU, Post-ICU ventilator use, and postoperative length of stay. These results are consistent with previous studies.[12,13] We also compared the hematologic and biochemistry indicators between them and found the ARDS patients related to higher WBC, BUN, Cr, Na and lower PLT, and ALB at 24 hours after operation. The WBC was significantly raised after operation and was significantly higher in the ARDS patients may be related to infection or systemic inflammatory response. The higher BUN and Cr indicated potential renal injury. The exact reason was unclear, but the disorder caused by CPB was probability involved. The higher level of natrium may be due to improper liquid management, but the patients with

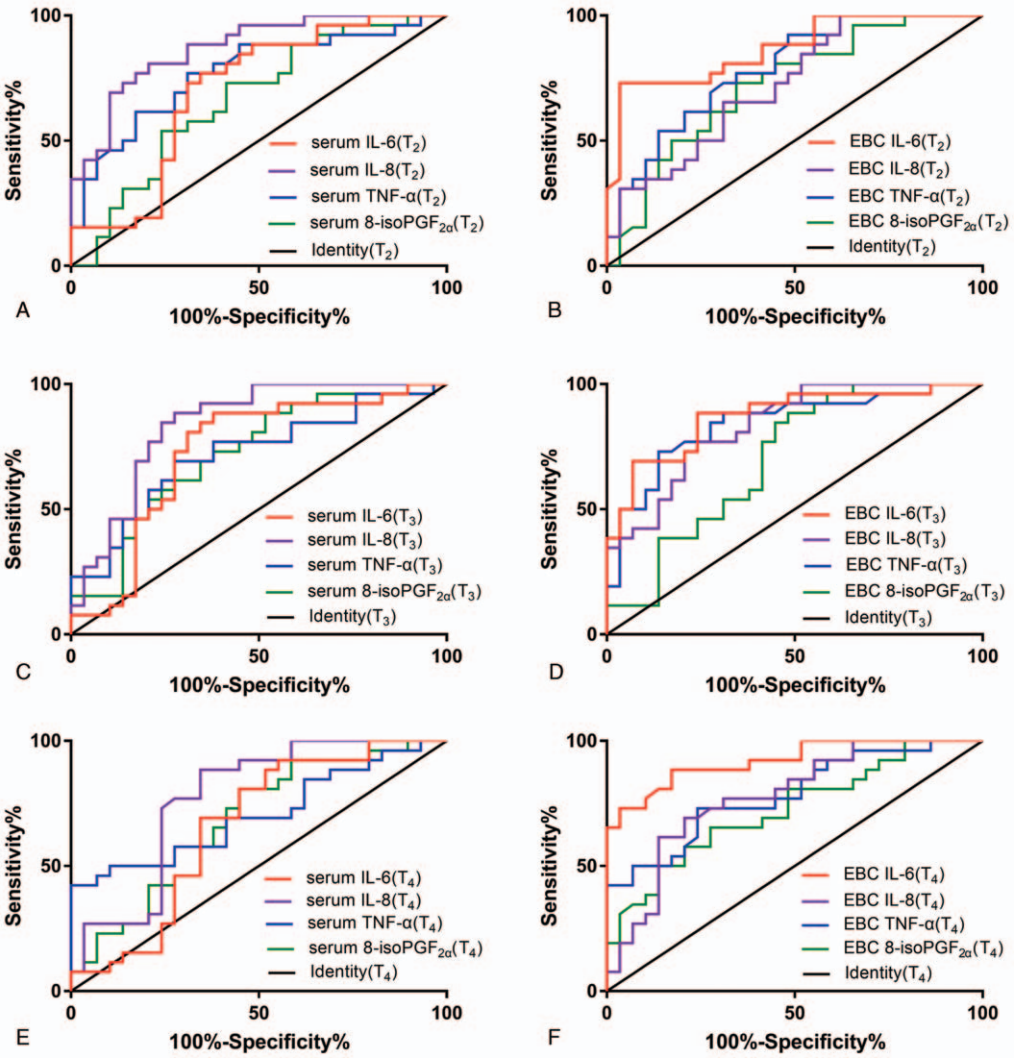

Figure 5. The ROC curves of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in EBC and serum at T_{2-4}. A, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in serum at T_2. B, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in EBC at T_2. C, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in serum at T_3. D, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in EBC at T_3. E, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in serum at T_4. F, The ROC curve of IL-6, IL-8, TNF-α and 8-isopgF$_{2\alpha}$ in EBC at T_4. 8-isoPGF$_{2\alpha}$ = 8-iso-prostaglandin F$_{2\alpha}$, EBC = exhaled breath condensate, IL-6 = interleukin-6, IL-8 = interleukin-8, ROC = receiver operating characteristic curve, TNF-α = tumor necrosis factor-α.

hypernatremia at the conclusion of CPB had longer hospital stays and higher postoperative complication rates.[14] The lower platelet count may be caused by excessive consumption or death of platelet, and a research shows that thrombocytopenia is associated with an increased risk of ARDS.[15] The lower albumin was likely caused by hypermetabolic like postoperative fever or excessive leakage due to pulmonary capillary injury, and albumin may be of great value in predicting and monitoring the severity and course of ARDS in critically patients with or at risk for the syndrome after new onset fever.[16] Pulmonary oxygenation, an important indicator for evaluating lung function when lung injury occurs, may be directly reflected by $P_{(A-a)}O_2$ and RI.[17] In this study, $P_{(A-a)}O_2$ and RI in the ARDS patients were higher than non-ARDS patients after CPB, suggesting that there are more serious damage of oxygenation and lung function in the ARDS patients. The reduction in pulmonary oxygenation and lung function may be caused by the imbalance of the ventilation/blood flow ratio, damage on the alveolar capillary barrier, or increase in inflammatory reactions and oxidative stress responses. The increase in postoperative Ppeak and Pplat in the ARDS patients may be related to the increase of lung water or decrease of pulmonary compliance, and may take part in the occurrence and development of ARDS. The comparison of PaO_2/FiO_2 further suggests a drastic decline in pulmonary ventilation and oxygenation function in the ARDS group. According to the above results, we considered that the ARDS patients were suffered from more damage on oxygenation, lung function, renal function and more disturbance on electrolyte, coagulation function, and nutrition metabolism. And these factors are likely to be the causes of the prolonged postoperative ventilator support, time to extubation, length of stay in the ICU, Post-ICU ventilator use and postoperative length of stay in ARDS patients.

However, there are some limitations in our research. The first one is the incidence of ARDS in our research was higher than

Table 3

The ability to predict postoperative acute respiratory distress syndrome of different variables.

Time	Mediator (pg/ml)	AUC	95% CI	*P*	Cut-off	Sensitivity	Specificity
T_2	Serum IL-6	0.703	0.564–0.819	.005	137.34	65.5	76.9
	EBC IL-6	0.868	0.750–0.944	< .001	2.92	96.6	73.1
	Serum IL-8	0.870	0.778–0.962	< .001	316.26	79.3	80.8
	EBC IL-8*	0.724	0.591–0.857	.001	32.64	37.93	100
	Serum TNF-α	0.771	0.643–0.898	< .001	110.27	69.0	76.9
	EBC TNF-α	0.786	0.668–0.905	< .001	6.32	51.7	92.3
	Serum 8-isopg$F_{2\alpha}$	0.664	0.519–0.810	.027	787.78	58.6	73.1
	EBC 8-isopg$F_{2\alpha}$	0.721	0.585–0.857	.001	45.38	65.5	73.1
T_3	Serum IL-6	0.728	0.591–0.839	.002	186.53	62.1	88.5
	EBC IL-6	0.871	0.754–0.946	< .001	5.04	75.9	88.5
	Serum IL-8	0.841	0.734–0.948	< .001	537.67	72.4	88.5
	EBC IL-8	0.835	0.732–0.938	< .001	43.23	75.9	76.9
	Serum TNF-α	0.719	0.580–0.857	.002	126.53	72.4	69.2
	EBC TNF-α	0.842	0.733–0.950	< .001	7.31	86.2	73.1
	Serum 8-isopg$F_{2\alpha}$	0.720	0.584–0.857	.002	1127.53	48.28	88.46
	EBC 8-isopg$F_{2\alpha}$	0.704	0.565–0.844	.004	82.64	51.7	88.5
T_4	Serum IL-6	0.656	0.516–0.779	.041	132.6	44.8	92.3
	EBC IL-6*	0.921	0.816–0.977	< .001	2.64	82.8	88.5
	Serum IL-8	0.771	0.642–0.900	< .001	312.56	65.5	88.5
	EBC IL-8	0.778	0.654–0.902	< .001	21.86	79.3	69.2
	Serum TNF-α	0.706	0.563–0.848	.005	75.35	100	42.31
	EBC TNF-α	0.784	0.663–0.906	< .001	4.87	75.9	73.1
	Serum 8-isopg$F_{2\alpha}$	0.676	0.533–0.820	.016	677.38	55.2	80.8
	EBC 8-isopg$F_{2\alpha}$	0.725	0.590–0.860	.001	32.24	72.4	65.4

8-isop$GF_{2\alpha}$ = 8-iso-prostaglandin $F_{2\alpha}$, AUC = area under the curve, CI = confidence interval, EBC = exhaled breath condensate, IL-6 = interleukin-6, IL-8 = interleukin-8, TNF-α = tumor necrosis factor-α.
* Compared to the mediators in serum, the AUC of IL-8 was significantly lower at T_2, the AUC of IL-6 was significantly higher at T_4 in EBC(all $P < .05$).

article reports (ranges from 0.4%–20%).[7] But it was lower than the report of Liu, et al.[2] The different incidences may be caused by differences in design methodology of the studies, study populations, different ARDS definitions, and uses of preventive measures such as the use of intraoperative cell saver, use of leukocyte filtration, use of ultrafiltration, use of conservative fluid management, use of protective drugs, use of early extubation, use of lung protective ventilation and so on. Our diagnoses were made by 1 certain cardiac surgeon according to the patients condition and examination results concluded transthoracic echocardiography, coronary angiography, X-rays, blood gas analysis, N-terminal pro-brain natriuretic peptide (NT-Pro-BNP), et al. We considered that the possible causes of ARDS were systemic inflammatory response syndrome caused by surgical trauma, CPB, multiple blood transfusion, and infections.[18] Patients undergoing cardiac surgery are particularly sensitive to lung damage due to these causes because cardiac operation alone with CPB can induce pulmonary ischemia/perfusion (I/R),[19] the exposure of blood to abnormal surfaces and conditions would lead to inflammatory reactions and oxidative stress responses.[20] Multiple blood transfusion can lead to transfusion related acute lung injury and infection is one of the most common reasons of ARDS. These factors can also explain the previous results in our study. Therefore, we must implement measures to prevent postoperative ARDS on the basis of the early detection of the EBC levels of biomarkers and it is our future research direction. The second limitation is the small sample size, which may cause the differences with the reported research. As we know, age, weight, smoking, hypertension, diabetes mellitus, duration of CPB, amount of bleeding, and transfusion volume are risk factors of ARDS. Although, the data of them were larger in ARDS patients, there were no significantly difference between the ARDS and non-ARDS patients. The third one is the patients were followed up only until discharge, and no statistical comparison was performed for long-term complications and mortality. The last one, EBC detection is not instantaneous, and this delay may have affected the accuracy of the results. And the components of EBC tend to become diluted.[21]

5. Conclusion

Our results suggest that EBC analysis of IL-6, IL-8, TNF-α, and 8-isop$gF_{2\alpha}$ can be used to predict the occurrence of ARDS after cardiac valve replacement under CPB, and sometimes EBC may be more sensitive than serum. However, EBC detection has not been used as a routine method for the diagnosis of ARDS, and its practical value requires further study.

Author contributions

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