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Relation or Influence of RVOTO in the Inflammatory Response to Reoxygenation in Patients with Tetralogy of Fallot

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ABSTRACT

Background: This study evaluated differential inflammatory response to cardiopulmonary bypass reoxygenation in tetralogy of Fallot repair. **Methods:** We performed a retrospective study at a cardiovascular center from 2012 to 2018, including 500 patients aged 1 week–18 years who received complete repair of tetralogy of Fallot. Patients were grouped according to tertiles of preoperative RVOT gradient on echocardiography into mild, moderate, and severe stenosis. We measured the highest perfusate oxygenation (PpO₂) during aortic occlusion as independent variable. Primary outcome was systemic inflammatory response syndrome (SIRS) within 7 days postoperatively or the time of death or discharge. **Results:** Overall, rate of SIRS was 24.2% without significant differences among three groups ($P > 0.05$). Older age, male, and smaller indexed left ventricular end-diastolic volume is independent risk factor of SIRS. There were significant interactions between RVOT stenosis and PpO₂ on SIRS (P interaction = 0.011): higher PpO₂ was associated with a greater SIRS risk among combined moderate and severe stenotic children (OR 1.463 95%CI [1.080, 1.981] per-SD increase, $P = 0.014$) but not among mild stenotic children (OR 0.900 [0.608, 1.333] per-SD increase; $P = 0.600$), independent of covariates. **Conclusion:** The association of PpO₂ with SIRS was modified by RVOT obstruction severity in tetralogy of Fallot repair. (Clinical Trials gov: NCT03568357)

KEYWORDS

Cardiopulmonary bypass; tetralogy of Fallot; hypoxia/reoxygenation injury; systemic inflammatory response syndrome

Abbreviations

CPB:	cardiopulmonary bypass;
PpO ₂ :	perfusate oxygenation;
RVOT:	right ventricular outflow tract;
SIRS:	systemic inflammatory response syndrome;
LVEDV:	left ventricular end-diastolic volume;
CI:	confidence interval.



1 Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) is associated with ischemia-reperfusion injury and inflammatory response [1,2]. For patients with cyanotic heart diseases, sudden reoxygenation during CPB would lead to an extra hypoxia-reoxygenation injury induced by oxygen-derived free radicals and lipid peroxidation, thereby exacerbating the systemic inflammatory response to CPB [3–5]. Additionally, previous clinical and experimental studies indicate that hyperoxemic reoxygenation during CPB is associated with higher risk of critical organ injury and dysfunction by decreasing the adaptation and remodeling capacity compared to normoxemic reoxygenation [6–8].

However, there are no definitive reports regarding the effect of continuous perfusate oxygenation (PpO₂) during CPB and its relationship with right ventricular outflow tract (RVOT) obstruction severity in pediatric patients with tetralogy of Fallot. Given the variety of pathological anatomy of tetralogy of Fallot [9,10], we investigate whether the differences in RVOT obstruction severity modifies the association of PpO₂ with systemic inflammatory response syndrome (SIRS) in complete repair of tetralogy of Fallot, with a particular focus on the effect of interplay between obstruction severity and continuous PpO₂.

2 Materials and Methods

2.1 Research Population and Design

This retrospective study focuses on quantitative evaluation of inflammatory responses of pediatric patients with different RVOT obstruction severities to CPB reoxygenation in complete repair of tetralogy of Fallot at a large cardiovascular tertiary academic medical center. The Institutional Review Board of Tianjin Economic Development Area Cardiovascular Hospital approved this study (2019-0826-3). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from parent and/or guardian of patient.

We screened pediatric patients aged 1 month–18 years who underwent complete repair of tetralogy of Fallot on bypass and were routinely admitted to intensive care unit (ICU) for inclusion between May 2012 and December 2018. Key criteria for exclusion included prematurity, previous palliation either with percutaneous or surgical procedures, severe renal dysfunction requiring dialysis, previous red-cell transfusion during the current admission, and use of extracorporeal membrane oxygenation or intra-aortic balloon pump for treatment of cardiogenic shock, as well as those with incomplete PpO₂ records and missing outcome data, thereby leaving 500 infants and children in the final study population. This study was registered with Clinical Trials. gov No. NCT03568357.

2.2 Patient Characteristics

Patients' baseline clinical variables were collected and extracted from the specialized hospital information system (Java His, BlueCore, Tianjin), including age at surgery, sex, body mass index, body surface area, blood pressure, temperature, heart rate, respiratory rate, leukocyte count, hemoglobin, hematocrit, Tet spell history, percutaneous oxyhemoglobin saturation (SpO₂), right bundle branch block (RBBB), NYHA class, ejection fraction, indexed left ventricular end-diastolic volume (LVEDV), McGoon index, CPB time, and aortic crossclamp time. In addition, procedural factors were also collected including cardioplegia solution, transannular patch, and tricuspid valve detachment.

2.3 Exposure

Given this hypothesis that the differences in RVOT stenosis might have differential influences on inflammatory response to reoxygenation during CPB, we selected the highest value of PpO₂ throughout aortic crossclamp as an independent variable for analysis. CPB is primed with Plasma-Lyte A, followed by the addition of packed red blood cells and fresh frozen plasma to achieve the desired hematocrit of

25% on CPB. At initiation of CPB, flow rates are maintained at approximately 150–200 mL/Kg/min and 100–150 mL/Kg/min for patients weighted <10 kg and >10 kg, respectively, subsequently adjusted according to the patient's core temperature (usually a 20% decrease for core temperatures between 30°C and 34°C and an additional 10% decrease for core temperatures <30°C) following our institute protocol [11]. All patients received standardized a-stat CPB management and standardized critical care management according to our institute.

2.4 Modifying Factor

According to EAE/ASE Recommendations for Clinical Practice on Echocardiographic Assessment of Valve Stenosis [12,13], RVOT obstruction severity was evaluated by the peak instantaneous gradient of RVOT from transthoracic two-dimensional echocardiography [13]. Patients were grouped according to tertiles of the peak RVOT gradient into mild stenotic group (<45 mmHg), moderate stenotic group (45–95 mmHg), and severe stenotic group (>95 mmHg), regardless of the level of obstruction (RVOT, valvar or supravalvar).

2.5 Study Outcome

Primary outcome was SIRS through postoperative day 7, hospital discharge, or death, whichever occurred first. SIRS was determined on the basis of International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics [14], as the presence of at least two of the following four criteria appropriate for age-specific ranges for physiologic and laboratory variables, one of which must be abnormal temperature or leukocyte count: (i) Core temperature of >38.5°C or <36°C measured by rectal, oral, or central catheter probe; (ii) Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period, or for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus; or otherwise unexplained persistent depression over a 0.5-hr time period; (iii) Mean respiratory rate >2 SD above normal for age, the prolonged mechanical ventilation defined as ventilation duration >48 hrs, or unplanned re-intubation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia; (iv) Leukocyte count elevated or depressed for age or >10% immature neutrophils. All outcomes were adjudicated independently by an event collaborative team. Secondary outcomes were mechanical ventilation time, ICU duration, inotropic score [15], vasoactive-inotropic score [15], low cardiac output syndrome, and in-hospital mortality rate.

2.6 Statistical Analysis

Patient characteristics were stratified by RVOT obstruction severity. Continuous data were presented as mean (SD) or median (IQRs) and compared using a *t*-test or Kruskal-Wallis testing depending on distributed characteristics, and categorical data were reported as percentages (%) and compared using χ^2 testing. Because of covariates that were potentially missing not-completely-at-random, covariates were imputed for multivariable analysis by means of single imputation with 10 iterations using all covariates.

The variables affecting primary outcome that were significant ($P < 0.10$) in univariate analysis were included in multivariate logistic regression with backward stepwise analysis. We assessed the association of RVOT obstruction severity with the odd ratio (OR) of SIRS with 95% confidence interval (CI) using adjusted logistic regression model for potential risk factors. We test the interactions between RVOT obstruction severity and PpO₂ with SIRS using interaction terms in a similar adjusted multivariable model. Restricted cubic splines were used to test the functional association of PpO₂ with the probability of SIRS by RVOT obstruction severity. In patients of different RVOT obstruction severity, we also tested the 3-way interaction terms among procedural factors [16]. To investigate the cumulative incidence of

SIRS by age at surgery, we used Kaplan-Meier estimates with age as the time scale by RVOT obstruction severity [17].

All statistical analyses were performed using Stata version 14 (Stata Corp, College Station, TX, USA) and R software (version 3.2.0). *P* values of less than 0.05 were considered statistically significant.

3 Results

Among patients of different RVOT obstruction stenosis, there were similar distributions in terms of sex ($P = 0.109$), respiratory rate ($P = 0.244$), leukocyte count ($P = 0.432$), mean blood pressure ($P = 0.052$), CPB time ($P = 0.740$), crossclamp time ($P = 0.698$), NYHA class ($P = 0.593$), cardioplegia type ($P = 0.999$), the presence of RBBB ($P = 0.133$), McGoon index ($P = 0.053$), and tricuspid valve detachment ($P = 0.125$). However, there were different distributions in terms of age at surgery ($P < 0.001$), body mass index ($P < 0.001$), body surface area ($P = 0.784$), systolic blood pressure ($P = 0.009$), diastolic blood pressure ($P = 0.031$), temperature ($P = 0.028$), heart rate ($P = 0.026$), hemoglobin ($P < 0.001$), hematocrit ($P < 0.001$), Tet spell history ($P = 0.006$), SpO₂ ($P < 0.001$), ejection fraction ($P = 0.039$), indexed LVEDV ($P < 0.001$), and transannular patch ($P = 0.044$) (Tab. 1).

Table 1: Baseline clinical, procedural, and outcome data of patients of different RVOT obstruction severity

	Severe stenotic group	Moderate stenotic group	Mild stenotic group	<i>P</i> value
Covariates				
Age at surgery, month	43.1 (18.6–92.3)	31.8 (13.2–63.6)	22.0 (11.4–42.4)	<0.001
Female, %	76 (45.8%)	80 (47.9%)	62 (37.1%)	0.109
Body mass index, kg/m ²	16.2 (3.3)	15.6 (2.3)	16.1 (2.5)	0.099
Body surface area, m ²	0.59 (0.02)	0.59 (0.02)	0.58 (0.02)	0.784
Temperature, °C	36.5 (0.4)	36.5 (0.3)	36.4 (0.4)	0.028
Heart rate, bpm	115.8 (19.1)	118.1 (18.3)	121.2 (17.6)	0.026
Respiratory rate, bpm	24.5 (4.2)	24.9 (3.1)	25.1 (3.1)	0.244
Systolic BP, mmHg	100.7 (11.5)	98.3 (11.1)	97.0 (11.1)	0.009
Diastolic BP, mmHg	59.4 (11.0)	56.7 (10.5)	56.8 (10.3)	0.031
Mean BP, mmHg	47.8 (7.1)	46.1 (6.8)	46.2 (6.8)	0.052
Leukocyte count, 10 ⁹ /L	8.4 (6.8–10.5)	8.5 (7.0–10.4)	8.9 (7.6–10.9)	0.432
Hemoglobin, g/L	159.0 (140.0–186.0)	148.0 (127.5–171.0)	134.0 (121.0–155.5)	<0.001
Hematocrit, vol%	48.7 (9.8)	44.8 (8.6)	41.6 (8.1)	<0.001
Tet spell history, %	81 (48.8%)	66 (39.5%)	53 (31.7%)	0.006
SpO ₂ , %	78.0 (73.0–86.0)	83.0 (79.5–90.0)	90.0 (80.0–96.0)	<0.001
NYHA class, %				0.593
I–II	152 (91.6%)	157 (94.0%)	157 (94.0%)	
III–IV	14 (8.4%)	10 (6.0%)	10 (6.0%)	
Ejection fraction, %	63.4 (4.4)	62.4 (4.6)	63.6 (4.6)	0.039

(Continued)

Table 1 (continued).

	Severe stenotic group	Moderate stenotic group	Mild stenotic group	<i>P</i> value
Indexed LVEDV, ml/m ²	25.9 (18.5–31.6)	27.9 (21.5–37.2)	27.9 (22.4–38.5)	<0.001
McGoon index	1.7 (1.5–2.0)	1.7 (1.5–2.0)	1.8 (1.5–2.1)	0.053
RBBB, %	17 (10.2%)	22 (13.2%)	11 (6.6%)	0.133
Cardioplegia solution, %				0.999
Buckberg	53 (31.9%)	53 (31.7%)	53 (31.7%)	
del Nido:	113 (68.1%)	114 (68.3%)	114 (68.3%)	
Transannular patch, %	103 (62.0%)	94 (56.3%)	81 (48.5%)	0.044
Tricuspid valve detachment, %	26 (15.7%)	29 (17.4%)	40 (24.0%)	0.125
Crossclamp time, min	84.5 (65.8–107.2)	93.0 (69.8–112.0)	85.0 (61.0–109.0)	0.698
CPB time, min	121.0 (92.5–155.0)	129.0 (97.5–161.5)	117.0 (87.0–155.5)	0.740
Modifying factor				
PpO ₂ , mmHg	261.0 (208.0–323.8)	266.0 (210.0–305.5)	256.0 (210.5–307.0)	0.565
Outcome				
SIRS, %	45 (27.1%)	39 (23.4%)	37 (22.2%)	0.546
Mechanical ventilation time, min	22.5 (12.5–66.5)	20.0 (8.0–46.0)	21.0 (9.5–75.0)	0.803
ICU duration, hrs	69.0 (44.0–140.0)	67.0 (42.0–98.0)	49.0 (43.2–117.8)	0.890
Inotropic score	8.0 (5.5–12.0)	8.0 (5.0–11.0)	7.5 (5.0–11.0)	0.413
Vasoactive-inotropic score	10.0 (6.0–14.0)	9.0 (6.0–14.0)	9.0 (5.0–12.1)	0.566
LCOS, %	28 (16.9%)	27 (16.2%)	21 (12.6%)	0.504
In-hospital mortality, %	4 (2.4%)	1 (0.6%)	2 (1.2%)	0.358

Note: Continuous data are presented as mean (SD) or median (IQR) and dichotomous data are presented as counts (%). RVOT = right ventricular outflow tract; BP = blood pressure; SPO₂ = percutaneous oxyhemoglobin saturation; LVEDV = left ventricular end-diastolic volume; RBBB = right bundle branch block; CPB = cardiopulmonary bypass. PpO₂ = perfusate oxygenation; SIRS = systemic inflammatory response syndrome; ICU = intensive care unit. LCOS = low cardiac output syndrome.

The hospital outcomes for all the study patients are listed in [Tab. 1](#). Overall, the rate of SIRS was 24.2% without significant differences among the groups (22.2%, 23.4%, and 27.1% for mild, moderate and severe stenotic groups, respectively, $P > 0.05$). PpO₂ were comparable among the groups (median 256.0 [IQR 210.5–307.0], 266.0 [210.0–305.5], and 261.0 [208.0–323.8] in mild, moderate and severe stenotic group; $P > 0.05$). Besides, there were no significant differences between groups in terms of mechanical ventilation time, ICU duration, inotropic score, vasoactive-inotropic score, low cardiac output syndrome, and in-hospital mortality (all $P > 0.05$).

Risk factor analysis for SIRS with univariate logistic regression model revealed that older age, male, lower heart rate, lower SpO₂, higher systolic, diastolic and mean blood pressure, higher hemoglobin, higher hematocrit, inferior NYHA classification, and lower indexed LVEDV were potential risk factors for SIRS (all with $P < 0.10$) ([Tab. 2](#)). Notably, neither RVOT obstruction stenosis (mild stenosis [reference 1.000]; moderate stenosis OR 1.221 95%CI [0.743,2.004], $P = 0.430$; severe stenosis OR 1.307 [0.792,2.155], $P = 0.295$) nor PpO₂ as continuous variable (OR of 1.152 [0.937,1.415] per-SD

increase, $P = 0.179$) was significant factor affecting the development of SIRS. Multivariate logistic regression analysis showed that only older age (OR of 1.017 [1.011,1.023] per-month increase, $P < 0.001$), male (OR 1.896 [1.186,3.032], $P = 0.008$), and smaller indexed LVEDV (OR of 0.971 [0.951,0.991] per-unit increase, $P = 0.005$) is independent risk factor for developing SIRS (Tab. 2).

Table 2: Logistic regression analysis for systemic inflammatory response syndrome

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age at surgery, month	1.016 (1.011, 1.021)	<0.001	1.017 (1.011, 1.023)	<0.001
Sex, %		0.066		0.008
female	1.0		1.0	
male	1.485 (0.974, 2.265)		1.896 (1.186, 3.032)	
Body mass index, kg/m ²	0.956 (0.884, 1.035)	0.270	—	—
Temperature, °C	1.024 (0.582, 1.802)	0.934	—	—
Heart rate, bpm	0.988 (0.977, 0.999)	0.034	0.997 (0.981, 1.014)	0.736
Respiratory rate, bpm	0.981 (0.924, 1.042)	0.539	—	—
Systolic blood pressure, mmHg	1.020 (1.001, 1.038)	0.037	0.999 (0.974, 1.024)	0.915
Diastolic blood pressure, mmHg	1.025 (1.005, 1.045)	0.013	0.885 (0.749, 1.046)	0.153
Mean blood pressure, mmHg	1.037 (1.007, 1.069)	0.015	1.229 (0.955, 1.582)	0.109
Leukocyte count, 10 ⁹ /L	1.016 (0.948, 1.088)	0.651	—	—
Hemoglobin, g/L	1.014 (1.007, 1.020)	<0.001	0.994 (0.970, 1.018)	0.625
Hematocrit, vol%	1.047 (1.025, 1.070)	<0.001	1.037 (0.946, 1.137)	0.432
Tet spell history, %		0.765		
Absence	1.0		—	—
Presence	0.938 (0.617, 1.427)		—	—
SpO ₂ , %	0.984 (0.965, 1.003)	0.097	1.012 (0.984, 1.042)	0.403
NYHA class, %		0.089		
I–II	1.0		1.0	
III–IV	0.398 (0.137, 1.153)		2.535 (0.800, 8.036)	0.114
Ejection fraction, %	1.006 (0.962, 1.052)	0.794	—	—
Indexed LVEDV, ml/m ²	0.978 (0.962, 0.995)	0.013	0.971 (0.951, 0.991)	0.005
McGoon index	0.906 (0.534, 1.537)	0.714	—	—
RVOT stenosis, %				
Mild	1.0		—	—
Moderate	1.221 [0.743,2.004]	0.430	—	—
Severe	1.307 [0.792,2.155]	0.294	—	—
Right bundle branch block, %		0.283		
Absence	1.0		—	—
Presence	0.662 (0.312, 1.406)		—	—

(Continued)

Table 2 (continued).

	Univariate analysis		Multivariate analysis	
Blood cardioplegia solution, %		0.435		
Buckberg	1.0		—	—
del Nido	1.195 (0.764, 1.870)		—	—
Transannular patch, %		0.788		
Absence	1.0		—	—
Presence	0.945 (0.627, 1.426)		—	—
Tricuspid valve detachment, %		0.286		
Absence	1.0		—	—
Presence	1.314 (0.795, 2.170)		—	—
Aortic crossclamp time, min	1.001 (0.995, 1.006)	0.819	—	—
CPB time, min	1.002 (0.998, 1.005)	0.427	—	—
PpO2 per-SD	1.152 (0.937, 1.415)	0.179	—	—

Note: Variables with $P < 0.10$ by univariate analysis were subjected to multivariate analysis. The multivariate logistic regression analysis was set with entry and removal P values of 0.10 and 0.15, respectively.

OR = odd ratio; CI = confidence interval. RVOT = right ventricular outflow tract; SpO2 = percutaneous oxyhemoglobin saturation; LVEDV = left ventricular end-diastolic volume; CPB = cardiopulmonary bypass; PpO2 = perfusate oxygenation; SD = standard deviation.

Overall, the association of PpO2 modelled as continuous variable with SIRS was assessed before and after adjusting for baseline and clinical covariates (Tab. 3). After adjustment for potential risk factors, there was a marginal significant interaction between different stenosis severity and continuous PpO2 on SIRS ($P_{\text{interaction}} = 0.061$): higher PpO2 was associated with a trend toward a greater risk of SIRS among moderate stenotic children (adjusted OR 1.493 [0.946,2.354] per-SD increase, $P = 0.061$; Fig. 1B) and severe stenotic children (adjusted OR 1.438 [0.903,2.290] per-SD increase, $P = 0.126$; Fig. 1C) but not among mild stenotic children (adjusted OR 0.900 [0.608,1.333] per-SD increase; $P = 0.600$; Fig. 1A).

Table 3: Association of PpO2 with systemic inflammatory response syndrome by overall and by RVOT obstruction severity

	Per-SD increase OR (95%CI)	P value	P for interaction
Overall			
Unadjusted	1.152 (0.937, 1.415)	0.179	—
Adjusted for covariates*	1.164 (0.926, 1.462)	0.192	—
By RVOT obstruction severity			
Unadjusted			0.056
Mild stenotic children	0.855 (0.620, 1.180)	0.342	
Moderate stenotic children	1.314 (0.895, 1.929)	0.163	
Severe stenotic children	1.525 (1.025, 2.270)	0.037	
Adjusted for covariates*			0.061
Mild stenotic children	0.900 (0.608, 1.333)	0.600	
Moderate stenotic children	1.493 (0.946, 2.354)	0.085	
Severe stenotic children	1.438 (0.903, 2.290)	0.126	

(Continued)

Table 3 (continued).

	Per-SD increase OR (95%CI)	<i>P</i> value	P for interaction
By RVOT obstruction severity			
Unadjusted			0.019
Mild stenotic children	0.855 (0.620, 1.180)	0.342	
Major stenotic children	1.414 (1.073, 1.864)	0.014	
Adjusted for covariates*			0.018
Mild stenotic children	0.900 (0.608, 1.333)	0.600	
Major stenotic children	1.461 (1.072, 1.992)	0.016	

Note: *Adjusted for age, sex, heart rate, SpO₂, systolic, diastolic and mean blood pressure, hemoglobin, hematocrit, NYHA classification, and indexed LVEDV.

OR = odd ratio; CI = confidence interval. RVOT = right ventricular outflow tract; SpO₂ = percutaneous oxyhemoglobin saturation; LVEDV = left ventricular end-diastolic volume.

After a similar multivariable adjustment, however, a significant interactions between RVOT stenosis and PpO₂ on SIRS was found when combining severe and moderate stenotic groups into an integral major stenotic group ($P_{\text{interaction}} = 0.0108$): higher PpO₂ was associated with a greater SIRS risk among major stenotic children (adjusted 1.463 [1.080,1.981] per-SD increase, $P = 0.014$; [Fig. 1D](#)) but not among mild stenotic children ([Fig. 1A](#)).

RVOT stenotic differences in the association between continuous PpO₂ and SIRS were further accentuated in procedural differences after adjusting for baseline clinical covariates: cardioplegia type (Buckberg vs. del Nido: multivariable $P_{\text{interaction}} = 0.020$ and 0.243 , respectively), transannular patch (absence vs. presence: multivariable $P_{\text{interaction}} = 0.019$ and 0.566 , respectively), or tricuspid valve detachment (absence vs. presence: multivariable $P_{\text{interaction}} = 0.033$ and 0.200 , respectively) ([Fig. 2](#)).

The cumulative incidence of SIRS by age at surgery and how it depends on triple-stenotic categorizations ([Fig. 3A](#)) and dual-stenotic categorizations ([Fig. 3B](#)) was diagrammatically presented. Patients with mild stenosis have the lowest risk probability compared to those with moderate and severe stenosis by triple-stenotic categorizations and those with major stenosis by dual-stenotic categorizations. By triple-stenotic categorizations, patients with moderate and severe stenosis have the lower SIRS-free probability than mild stenotic patients (P for log-rank < 0.001). By dual-stenotic categorizations, patients with major stenosis have the lower SIRS-free probability than mild stenotic patients (P for log-rank = 0.0005).

4 Discussion

This study is the first report that compares PpO₂ and it correlates with SIRS between different RVOT stenotic patients with tetralogy of Fallot using the real-world patient-based data. Findings suggest RVOT stenosis significantly modified the relationship between PpO₂ and SIRS in complete repair of tetralogy of Fallot, with a steeper association between higher PpO₂ and SIRS increase among moderate and severe stenotic children but not mild stenotic children.

Based on previous findings that hyperoxemic reoxygenation is associated with greater hypoxia-reoxygenation injury than did normoxemic reoxygenation in cyanotic and acyanotic individuals [5–8,18], we hypothesized that the differences in RVOT stenosis might have differential influences on inflammatory response to reoxygenation during CPB. While we indeed found higher PpO₂ was associated with a trend

towards increased risk of SIRS, we were surprised to find no significantly statistical differences between PpO₂ and SIRS before and after adjusting potential confounding factors.

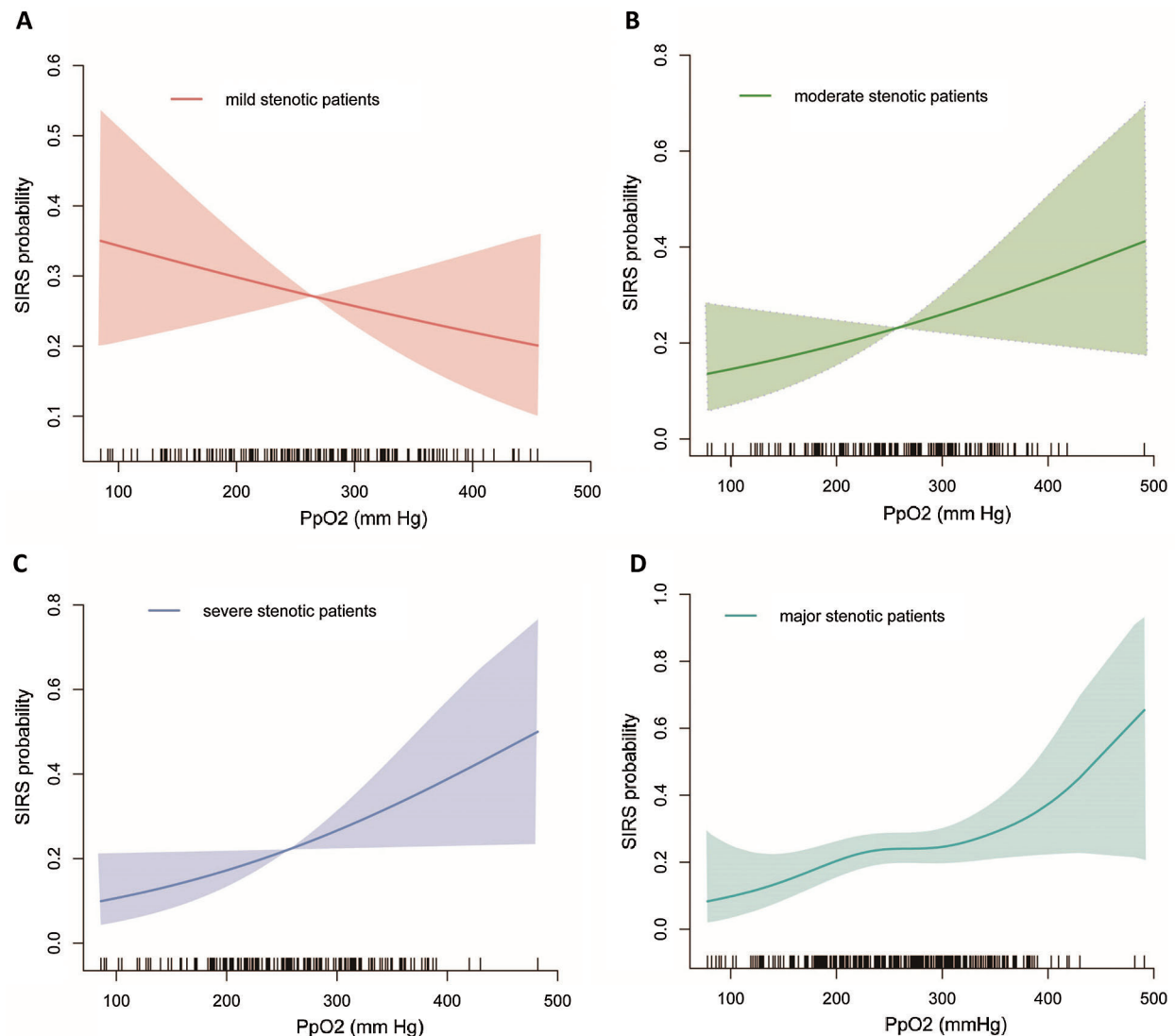


Figure 1: Functional association of PpO₂ with SIRS probability by stenosis

A: SIRS probability with 95%CI among mild stenotic patients alone; B: SIRS probability with 95%CI among moderate stenotic patients alone; C: SIRS probability with 95%CI among severe stenotic patients alone; D: SIRS probability with 95%CI among major stenotic patients alone.

The solid line and shaded areas represent the probability for developing SIRS with 95%CI after adjusting for baseline clinical covariates. PpO₂ = perfusate oxygenation; SIRS = systemic inflammatory response syndrome; CI = confidence interval.

It has been well recognized that RVOT obstruction severity is a major determinant and indicator of hypoxic degree in patients with tetralogy of Fallot [10,19], so we extrapolated that the differences in RVOT stenosis might have differential influences on inflammatory response to reoxygenation. Our findings from interaction analysis showed that higher PpO₂ was associated with a trend toward a greater SIRS risk for moderate and severe stenotic patients but not for mild stenotic patients with a marginal significant interaction. After we combined patients with severe and moderate stenosis into major stenotic

integral, there was a significant interaction between stenosis and PpO₂ on SIRS: higher PpO₂ was associated with a greater SIRS risk among major stenotic patients but not among mild stenotic patients.

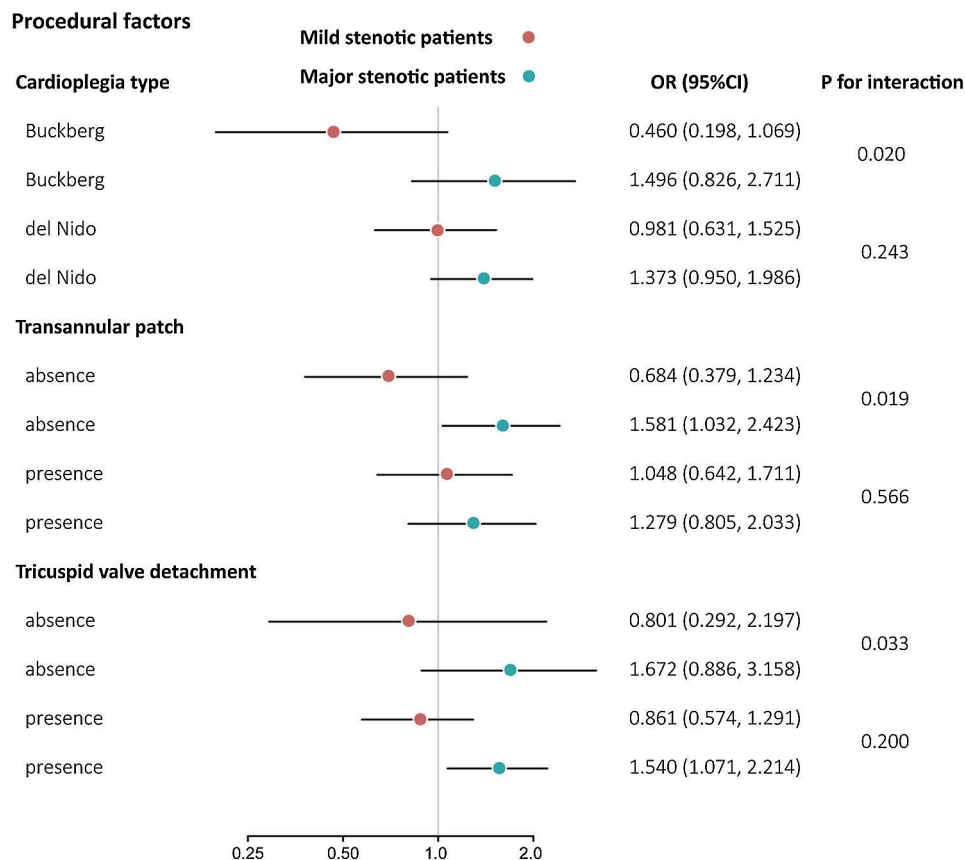


Figure 2: Three-way interaction analysis of PpO₂ on SIRS by procedural factors

The figure represents the OR with 95% confidence interval for each subgroup after adjusting for baseline clinical covariates. PpO₂ = perfusate oxygenation; OR = odd ratio; SIRS = systemic inflammatory response syndrome.

The mechanisms underlying the greater risk of SIRS with PpO₂ increase in major stenotic children than mild stenotic children may relate to intrinsically severer impairment in autoregulatory capacity of systemic organs and systems among major stenotic patients than mild stenotic patients [20,21], thus rendering major organs and systems more susceptible to hypoxia-reoxygenation injury induced by oxygen-derived free radicals and lipid peroxidation when perfused with higher PpO₂ during CPB.

On the contrary to the majority of prior conclusion that hyperoxemic reoxygenation is associated with poor outcome in cyanotic patients, we did not observe the association of higher PpO₂ with greater risk of SIRS in mild stenotic children which is also consistent with Smith's report [22]. The possible explanation is that PpO₂ during CPB in our institute has not yet exceed the critical threshold for mild stenotic children, thereby not leading to significantly negative effect on inflammatory response.

Among mild stenotic group the likely hood of SIRS decreases with increased PpO₂, but in moderate and severe group the likely hood of SIRS increases with increased PpO₂. It highlights differential control of reoxygenation for different stenosis-specific patients with tetralogy of Fallot in CPB management. Not all patients with tetralogy of Fallot should lower PpO₂ levels on bypass. For the mild stenosis patients, a modest increase in PpO₂ level is also beneficial.

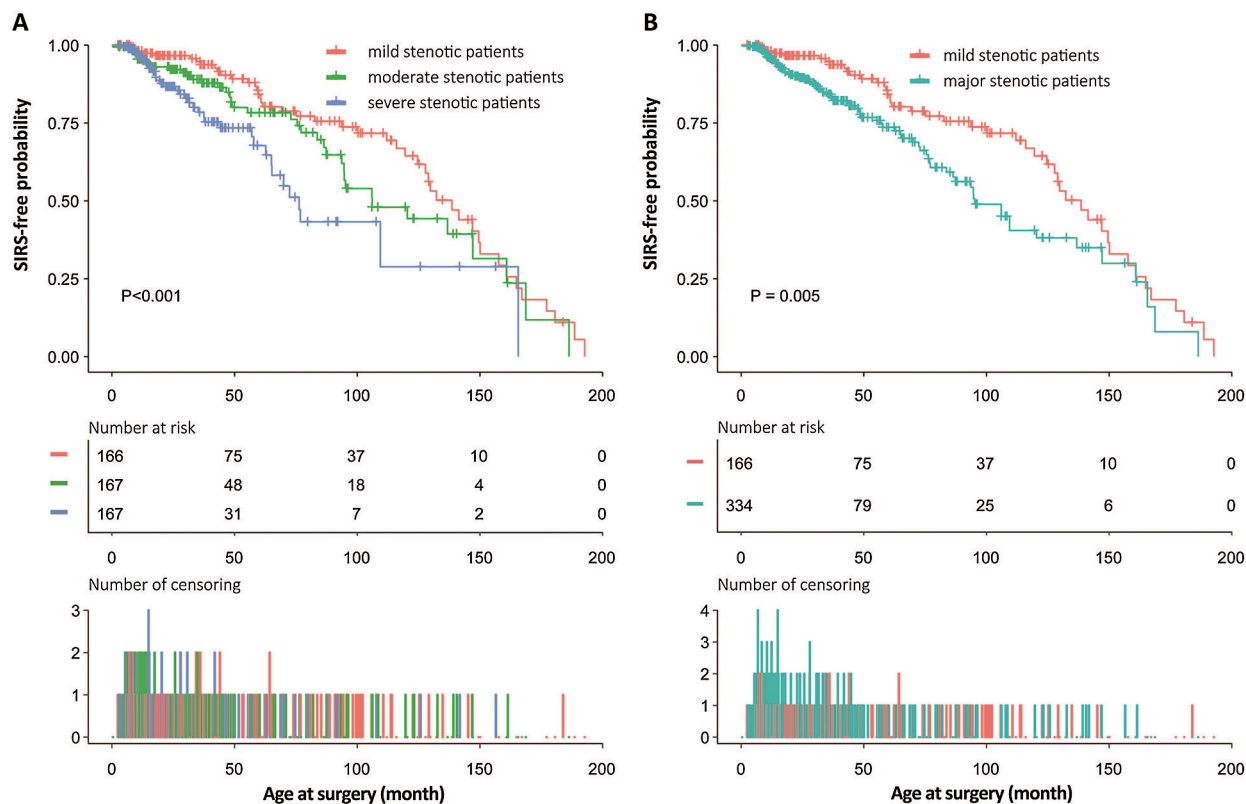


Figure 3: SIRS-free probabilities with increasing age at surgery

A: Kaplan-Meier curves by triple-stenotic categorization; B: Kaplan-Meier curves by dual-stenotic categorization. SIRS = systemic inflammatory response syndrome.

Fig. 3A represents SIRS-free probability by age separately for mild, moderate and severe stenotic patents and how this depends on triple-stenotic categorization.

Fig. 3B represents SIRS-free probability by age separately for mild and major stenotic patents and how this depends on dual-stenotic categorization. For both categorizations, this age gradient is steepest for more stenotic patents.

SIRS, Systemic inflammatory response syndrome.

While our findings are notable, we acknowledge that our observational data from this present study cannot provide conclusive evidence for different PpO₂ cut-offs for mild, moderate, and severe stenotic children and cannot be extrapolated to response to treatment such as conventional oxygenation management [23]. Although we test for three-way interactions among RVOT stenosis, PpO₂ and procedural factors such as repair pathway, transannular patch, and tricuspid valve detachment, the results should be interpreted with caution as we had limited statistical power to assess the stenosis-specific relationships of PpO₂ with SIRS between subgroups due to relatively low patient numbers in those groups.

Based on our hypothesis, it is the highest value of PpO₂ that was regarded as independent variable in the present study, which might overestimate the effect of PpO₂ on SIRS. Results may therefore be considered hypothesis-generating and deserve further study using average value or lowest of PpO₂ as independent variable. It is well known that different CPB strategies including prime constitutes and flow rates may have different effects on inflammatory response and organ functions [24]. In this study, our CPB strategies had little changes during the study period, leading to reducing the impact of prime constitutes and flow rates on the endpoint event. We carefully adjusted our analysis for the potential risk factors selected from available baseline clinical variables; however, residual confounding by unmeasured characteristics cannot be excluded. Taking into consideration the sample cohort age, the generalizability

of our results must be interpreted in the context of demographic and clinical characteristics, especially for old age at surgery in our current study that is different from that of much of the rest of the world.

5 Conclusions

These first data that assess the association of PpO₂ with SIRS between different severities of RVOT obstruction showed that RVOT stenosis significantly modified the relationship between PpO₂ and SIRS in tetralogy of Fallot, with a steeper association between the increase in hyperoxemic reoxygenation and the increase in SIRS probability among moderate and severe stenotic children but not among mild stenotic children. Further studies are needed to determine whether RVOT stenosis-specific PpO₂ cut-offs during CPB for clinical decision-making regarding reoxygenation management in repair of tetralogy of Fallot should be considered.

Data Sharing: The data are available on request from the corresponding author.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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