Reperfusion pulmonary edema in children with tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries undergoing unifocalization procedures: A pilot study examining potential pathophysiologic mechanisms and clinical significance

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Objective: Children with tetralogy of Fallot (TOF), pulmonary atresia (PA), and major aortopulmonary collateral arteries (MAPCAs) are at risk for reperfusion pulmonary edema (RPE) after unifocalization procedures to reconstruct the central pulmonary arteries. The purpose of this study was to determine the incidence of RPE, describe the clinical course of patients with RPE, and explore the mechanism of RPE in this population by measuring plasma biomarkers of alveolar epithelial and endothelial injury and lung inflammation.

Methods: Levels of plasma receptor for advanced glycation end products (RAGE), intercellular adhesion molecule 1 (ICAM-1), and interleukin 6 (IL-6) were measured at baseline and postoperative day (POD) 0, 1, and 2 after unifocalization. A pediatric radiologist reviewed chest radiographs from the same time points and scored each lung segment for the degree of pulmonary edema. A pediatric interventional cardiologist reviewed the preoperative angiograms for each patient and determined the degree of stenosis for each aortopulmonary collateral vessel. RPE was defined as localized pulmonary edema with a pulmonary edema score of at least 2 occurring in the lung segment demonstrating the greatest degree of angiographic stenosis within the first 48 hours after surgery and with resolution by discharge.

Results: Thirty-five patients who underwent 37 unifocalization procedures were enrolled, and 32 patients were included in the analysis. Of these, 16 of 32 (50%) demonstrated evidence of RPE based on our defined criteria. There was no significant difference in RAGE ($P = .60$), ICAM-1 ($P = .34$), or IL-6 ($P = .31$) levels between those with and without RPE at any time point. The mean duration of mechanical ventilation in patients with RPE versus those without was not significantly different (5.1 ± 4.2 vs 5.6 ± 4.5 days, respectively; $P = .57$).

Conclusions: Fifty percent of children with TOF/PA/MAPCAs undergoing unifocalization surgery developed RPE. Levels of plasma biomarkers of alveolar epithelial and endothelial injury and lung inflammation were not increased in patients with RPE compared with those without RPE. The presence of RPE did not affect the duration of respiratory failure and mechanical ventilation. The process of RPE is clinically self-limited and seems unlikely to be associated with vascular changes. (J Thorac Cardiovasc Surg 2014;148:1560-5)

CHD

Tetralogy of Fallot (TOF), pulmonary atresia (PA), and major aortopulmonary collateral arteries (MAPCAs) is a form of cyanotic congenital heart disease in which children are born with TOF plus underdeveloped or absent central pulmonary arteries. Aortopulmonary collaterals provide the only source of pulmonary blood flow, resulting in heterogeneous flow to different lung segments.[1] Surgical repair requires the establishment of controlled blood flow into all lung segments by unifocalizing collateral vessels into the native or reconstructed central pulmonary arteries.[2] Given the propensity for MAPCAs to have highly variable anatomic courses and degrees of stenosis, extensive reconstruction of the collateral vessels is often required. At our institution, we have developed a surgical approach based on the degree of segmental-level stenosis and the presence of true pulmonary arteries that emphasizes early complete unifocalization and intracardiac repair with ventricular septal defect (VSD) closure and placement of a right ventricle-to-pulmonary artery conduit.[3,4]

We recently showed that patients undergoing unifocalization surgery are at risk for the development of reperfusion pulmonary edema (RPE), and that the degree of preoperative angiographic stenosis in MAPCAs was a significant predictor for the development and severity of RPE.[5] RPE

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Abbreviations and Acronyms

ALI = acute lung injury
CPB = cardiopulmonary bypass
ICAM-1 = intercellular adhesion molecule 1
IL-6 = interleukin 6
MAPCA = major aortopulmonary collateral arteries
PA = pulmonary atresia
POD = postoperative day
RAGE = receptor for advanced glycation end products
RPE = reperfusion pulmonary edema
TOF = tetralogy of Fallot
VSD = ventricular septal defect

has been studied in other contexts as well. Lung injury from cardiopulmonary bypass is believed to be related to ischemia-reperfusion mechanisms and can have important clinical implications for infants undergoing congenital heart surgery.[6,7] RPE has also been reported in children with branch pulmonary artery stenosis and selected congenital heart defects after pulmonary artery balloon dilation.[8,9] We hypothesized that children with TOF/PA/MAPCAs undergoing unifocalization surgery may manifest biological evidence of acute lung injury (ALI) similar to adult patients who develop RPE after lung transplant, and we therefore chose to study 3 biomarkers known to have pathophysiologic and prognostic value in adults with ALI. One such molecule is receptor for advanced glycation end products (RAGE), a marker of alveolar type I epithelial cellular injury.[10] RAGE has been shown to correlate with the severity of primary graft dysfunction in adults undergoing lung transplantation. Increased levels of plasma RAGE are a marker of alveolar type I epithelial cell injury and impaired alveolar fluid clearance, and they correlate with the severity of primary graft dysfunction in adults undergoing lung transplant.[11,12] Intercellular adhesion molecule 1 (ICAM-1) is a marker of alveolar epithelial and endothelial injury and alveolar macrophage activation.[13] In children with ALI, ICAM-1 levels early in the course correlate with the duration of mechanical ventilation and survival.[14] Interleukin-6 (IL-6) is a marker of lung inflammation that has been shown to correlate with the degree of pulmonary edema after lung transplant.[15] The primary goals of our study were to describe the incidence and clinical course of RPE in patients with TOF/PA/MAPCAs after unifocalization surgery and to better understand its pathophysiology by assessing plasma markers of alveolar epithelial and endothelial injury and lung inflammation.

METHODS

All patients with TOF/PA/MAPCAs presenting for unifocalization or pulmonary artery revision procedures were eligible for enrollment in this prospective study, including those with additional structural cardiac abnormalities requiring surgical intervention. Patients with single ventricle cardiac anatomy, preoperative respiratory failure, or known infection were excluded. The enrollment period was from May, 2009, to January, 2011.

An experienced pediatric radiologist blinded to the patient's clinical course reviewed a series of chest radiographs for each patient. The radiologist interpreted preoperative, immediate postoperative, postoperative day (POD) 1, and POD 2 radiographs, and scored each for localized pulmonary edema using a scoring system adapted from a previous study assessing pulmonary reperfusion injury in lung transplant recipients.[5,16] The right upper lobe, right middle lobe, right lower lobe, left upper lobe, lingula, and left lower lobe were all scored on a scale from 0 to 3: 0 for normal lung, 1 for minimal opacity not obscuring lung vessels, 2 for opacity partially obscuring lung vessels, and 3 for opacity completely obscuring lung vessels. Lung vascularity and the presence or absence of atelectasis were also recorded. The suitability of the chest radiograph for inclusion in the study was at the discretion of the radiologist, and the radiograph was to be excluded from analysis if the radiologist could not differentiate pulmonary edema from atelectasis.

The degree of stenosis of each MAPCA was determined by an experienced pediatric interventional cardiologist blinded to the patient's postoperative course and was based on a published protocol from our institution.[5] Briefly, the width of the narrowest segment of each MAPCA and the widest downstream segment were measured in millimeters. If a MAPCA branched into multiple segments before the largest downstream segment, the total width of all the downstream segments was used. The stenosis was then reported as a ratio of the width of the narrowest segment to the width of the largest segment downstream. The lung segment with the smallest ratio was considered to be the most at risk for the development of RPE.

For purposes of this study, RPE was defined as localized pulmonary edema with a score of at least 2 occurring in the lung segment with the greatest degree of angiographic stenosis within the first 48 hours after surgery and resolving by hospital discharge. Patients with a pulmonary opacity accompanied by fever and increased levels of inflammatory markers were considered to have pneumonia and were excluded from the analysis. Patients were also excluded for pulmonary hemorrhage, defined as the presence of persistent frankly bloody tracheal secretions in the first 48 hours postoperatively.

Blood samples were collected from each patient's indwelling arterial catheter at 4 time points: preoperative, immediate postoperative, and on POD 1 and 2. The blood was collected in EDTA-treated tubes and centrifuged for 10 minutes at 3000*g*. Plasma samples were then aliquoted and stored at −80°C. Using these samples, the levels of RAGE, ICAM-1, and IL-6 were measured using commercially available enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, Minn).

Partial pressure of oxygen to fractional inspired oxygen (P/F) ratios and alveolar to arterial oxygen gradients (A-a O_2) were calculated daily on POD 0, 1, and 2 for patients undergoing complete intracardiac repair with VSD closure and no residual intracardiac shunt. The A-a O_2 gradient was calculated according to the following equation: $(713 \times Fio_2 - Paco_2/0.8) - Pao_2$ where Fio_2 is the fractional inspired oxygen, $Paco_2$ is the arterial carbon dioxide tension, and Pao_2 is the arterial oxygen tension. The highest P/F values and lowest A-a O_2 gradient measured in the first 48 hours postoperatively were compared between patients with RPE and those without.

Analysis of covariance was used to analyze the impact of RPE on the biomarker levels at the postoperative, POD 1, and POD 2 time points controlling for the baseline level. A generalized estimating equation approach was used to test the impact of RPE on RAGE, ICAM-1, and IL-6, taking repeated measures into account and using an exchangeable correlation matrix. The Student *t* test was used to analyze angiographic stenosis and clinical data. All statistical analyses were performed using commercial software (STATA 12.0, College Station, Tex). The study was approved by the Institutional Review Boards of Stanford University and the University of California, San Francisco.