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.

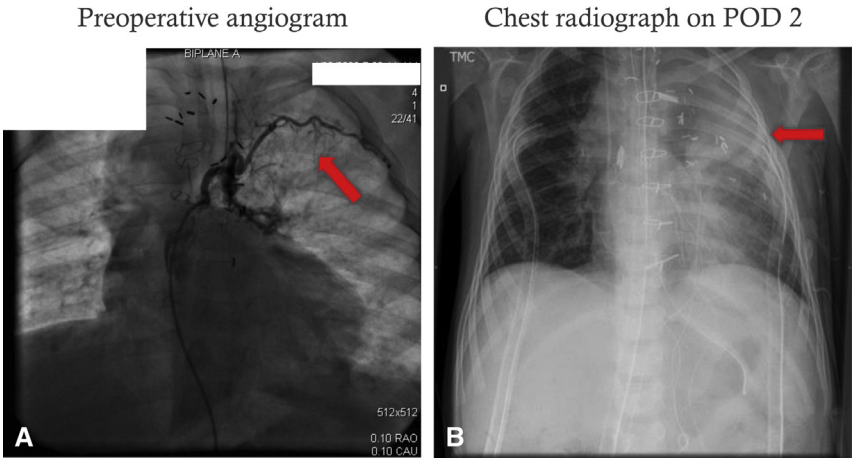

FIGURE 1. Example of long-segment stenosis in the left upper lobe (*arrow* in A) and subsequent reperfusion pulmonary edema in this area (*arrow* in B). *POD*, Postoperative day.

RESULTS

Demographics

Thirty-five consecutive patients undergoing 37 procedures were enrolled during the study period. Five patients were excluded; 1 patient developed postoperative pneumonia and 4 patients had their angiograms performed at other institutions and the images did not provide adequate anatomic definition. No patients were excluded because of suboptimal chest radiographs. There were 16 boys and 16 girls. The median age was 11.5 months (range, 3-132 months) and the median weight was 7.3 kg (range, 4.5-31.2 kg).

Intraoperative Course

The 32 patients included in the analysis underwent 1 of the following 4 types of surgery: complete, single-stage unifocalization with intracardiac repair (n = 12), intracardiac repair as part of a staged unifocalization approach (n = 11), partial unifocalization and aortopulmonary shunt placement without intracardiac repair (n = 7), and unifocalization revision or pulmonary arterioplasty and right ventricle-to-pulmonary artery conduit replacement (n = 2). Two patients undergoing partial unifocalization procedures did not require cardiopulmonary bypass (CPB), and both met the criteria for RPE. In the remaining patients who did require CPB, there was no significant difference in the mean CPB time between patients with RPE (271 ± 146 minutes) compared with those without RPE (274 ± 57 minutes) ($P = .07$). All patients had good biventricular systolic function based on qualitative interpretation of postoperative echocardiograms, and there were no significant residual lesions (VSDs, right ventricular-to-pulmonary artery conduit stenosis or insufficiency, aortopulmonary shunt stenosis, or occlusion). No patients developed clinically detectable postoperative pulmonary hemorrhage.

Criteria for RPE

Review of the chest radiographs for the 32 patients included showed that 16 patients (50%) met the criteria for RPE (a pulmonary edema score of 2 or greater within the first 48 hours postoperatively with resolution by discharge in the lobe of the most significant angiographic stenosis). Of the 16 patients who did not meet the criteria, 7 had a pulmonary edema score greater than 2 in at least 1 lung segment, but the edema was not localized to the lung segment with the most significant angiographic stenosis. The remaining 9 patients did not demonstrate any pulmonary edema and essentially had normal chest radiographs. No chest radiographs were excluded from the analysis.

Amongst the 7 patients with aortopulmonary shunts as their sole source of pulmonary blood flow, 3 developed RPE (43%). The remaining 25 patients had a septated circulation with a right ventricle-to-pulmonary artery conduit as their source of pulmonary blood flow, and 13 patients (52%) developed RPE.

The mean ratio of the narrowest-to-widest segment in the smallest collateral vessels measured on an angiogram in the RPE group was 0.38 ± 0.16, whereas this ratio was 0.31 ± 0.09 ($P = .07$) in those without RPE. An example of RPE in 1 patient is shown in Figure 1. It demonstrates the development of RPE in the left upper lobe lung segment supplied by a significantly narrowed collateral vessel identified on the preoperative angiogram. The stenosis-to-downstream ratio for this collateral vessel was 0.28.

Biomarker Results

Complete biomarker data were available for 8 patients without RPE and 9 patients with RPE. There was insufficient plasma volume for analysis of all 3 biomarkers in the remaining patients. There was no significant difference in RAGE, ICAM-1, and IL-6 levels in patients with and without RPE at any time point (Figure 2, *A-C*). Taking

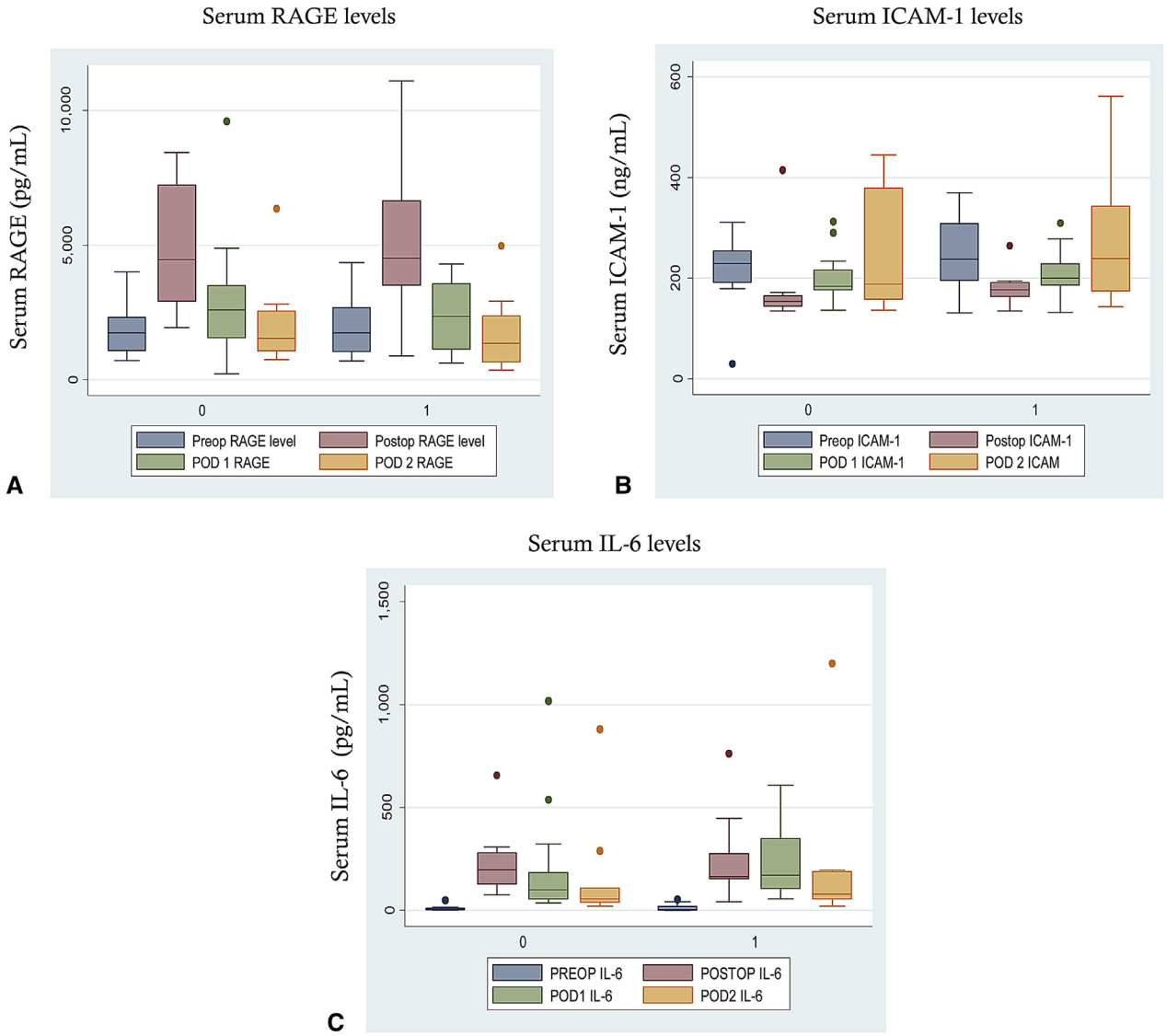

FIGURE 2. Box-and-whisker plots comparing biomarker levels at 4 time points in patients without (0) and with (1) reperfusion pulmonary edema. (*Error bars* represent maximum and minimum values excluding outliers, represented by outside dots. Columns depict 25th percentile, median, and 75th percentile values). A, Serum RAGE levels. B, Serum ICAM-1 levels. C, Serum IL-6 levels. Single outlier value of 4163 pg/mL on POD 2 in reperfusion pulmonary edema group excluded to improve graph visualization. *RAGE*, Receptor for advanced glycation end products; *Preop*, preoperative; *Postop*, postoperative; *POD*, postoperative day; *ICAM-1*, intercellular adhesion molecule 1; *IL-6*, interleukin 6.

repeated measures into account and controlling for baseline preoperative levels, there was no significant difference in the levels of RAGE ($P = .60$), ICAM-1 ($P = .34$), or IL-6 ($P = .31$). Levels of RAGE and IL-6 tended to increase in the immediate postoperative period and then decrease on POD 1 and 2 in both groups, whereas ICAM-1 levels were lower than baseline immediately after surgery and increased back toward baseline on POD 1 and 2.

Clinical Results

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; $P = .57$). Twenty-five patients underwent complete intracardiac repair or unifocalization revision procedures and did not have residual intracardiac shunts, and 13 (52%) demonstrated evidence of RPE. The average P/F ratio of patients with RPE in this group was 216 ± 75, and 241 ± 81 for those without RPE was ($P = .7$). The average A-a O_2 for those with RPE was 206 ± 81 mm Hg and 219 ± 73 mm Hg for those without ($P = .9$). Of the 7 patients who underwent partial unifocalization with pulmonary blood flow supplied by an aortopulmonary shunt, 3 developed RPE.

DISCUSSION

Although RPE has been described in the literature, little is known about its pathophysiology and clinical impact in children with TOF/PA/MAPCAs undergoing unifocalization procedures.[5,8] To our knowledge, this is the first study designed with the explicit goal of understanding the pathophysiology of RPE. Using plasma markers of lung injury that have pathophysiologic and prognostic significance in adults and children with ALI and pulmonary edema after lung transplant, we did not detect a difference in patients with radiographic evidence of lung injury compared with those without in our study population.

One possible explanation is that the extent and severity of pulmonary edema are different in patients with RPE after unifocalization procedures compared with patients with ALI and posttransplant pulmonary edema. Patients with RPE in our population may not develop severe enough alveolar endothelial or epithelial injury and lung inflammation to produce a difference in these biological markers. The definition of ALI includes the presence of bilateral infiltrates on a chest radiograph, indicating that the lungs are diffusely affected.[17] In our patient population, RPE was defined as focal pulmonary edema occurring in a lung region associated with vascular obstruction on angiography. By definition, the degree of lung injury is limited to specific lung segments. Levels of RAGE, ICAM-1, and IL-6 may not have been significantly different between the 2 groups because the degree of pulmonary edema was not extensive enough to cause an important difference in protein expression.

Another potential explanation is that the mechanism by which pulmonary edema develops may be different in our population than in patients with ALI. The pathophysiology of ALI has been found to be related to capillary injury with resultant capillary leak and the development of proteinaceous pulmonary edema.[18-20] Although the possibility of capillary injury cannot be excluded, our patients may have developed hydrostatic edema as a consequence of overperfusion in a previously restricted vascular bed. Patients with significant narrowing of their MAPCAs have decreased blood flow and pressure in the pulmonary microvasculature beyond the narrowings. After unifocalization surgery, blood flow increases through the previously stenotic vessels resulting in increased pressure. The microvasculature cannot immediately restrict flow, and therefore hydrostatic pulmonary edema develops. The pathogenesis of such overperfusion hydrostatic edema was first described by Landolt and colleagues[21] in sheep after pneumonectomy. The lymph-to-plasma ratio in pleural fluid measured from these study sheep was unchanged after increasing pressure and flow to the remaining lung, indicating that capillary leak did not occur.

Hydrostatic pulmonary edema is less clinically severe than edema secondary to lung capillary injury. Hydrostatic pulmonary edema as a pathophysiologic explanation is therefore plausible, given that there was no difference in clinical severity between the 2 groups. There was no difference in the duration of mechanical ventilation between patients with and without RPE, and both groups demonstrated resolution of their pulmonary edema by discharge. In addition, measures of oxygenation, the P/F ratio and A-a O_2 gradient, were similar in patients with and without RPE, indicating that the severity of lung disease may not be clinically significant. The subgroup of our patients undergoing partial unifocalization surgery had surgically placed aortopulmonary shunts to provide pulmonary blood flow and stimulate growth of the pulmonary vasculature before complete intracardiac repair. The pulmonary vascular bed is supplied with systemic-level pressure and flow, and therefore it may be at higher risk for developing hydrostatic pulmonary edema, particularly in segments with low flow preoperatively due to significant vascular restriction. Although only 3 of our patients with this physiology developed RPE, our current pilot study is not powered to detect a difference. Given that patients with pulmonary blood flow via the right ventricle-pulmonary artery conduit developed RPE, it is plausible that the pathophysiology is multifactorial and not related to the pressure of pulmonary blood flow alone. The anatomy, that is, the degree of stenosis, of a vessel before unifocalization may be equally important in determining whether the lung segment develops RPE.

Our study population could be considered at risk for cardiogenic pulmonary edema given that patients were undergoing surgery for congenital heart disease. The pathophysiology of cardiogenic pulmonary edema is different than that of ALI and posttransplant pulmonary edema, and therefore the biological markers of lung injury may also be different. We believe, however, that our study population was at low risk for developing cardiogenic pulmonary edema. Patients with TOF/PA/MAPCAs undergoing unifocalization surgery at our institution are carefully selected for complete intracardiac repair by a well-established surgical algorithm based on low intraoperative pulmonary artery pressures.[3] Previous work from our institution demonstrated that patients typically have good postoperative cardiopulmonary mechanics after repair of TOF/PA/MAPCAs, and that when they develop prolonged postoperative respiratory failure, it is secondary to pulmonary complications.[22] In addition, our patients had either qualitatively normal or only mildly decreased systolic biventricular function on postoperative echocardiography. We defined RPE as focal pulmonary edema in the lung region associated with the greatest angiographic stenosis. If the pulmonary edema did not occur in the area of angiographic stenosis, it was not considered to be RPE. Although patients can experience lung inflammation after CPB, there was no difference in CPB times between the 2 groups.

A recent study from our institution demonstrated that the degree of angiographic stenosis on the preoperative

angiogram correlated with the development of RPE after unifocalization.[5] Our study also demonstrated the trend that RPE developed in patients with more significant angiographic stenosis, although it did not reach statistical significance, likely secondary to the fact that this was a smaller pilot study.

Limitations

We believe this is the first study designed to examine possible pathophysiologic mechanisms of RPE in patients with TOF/PA/MAPCAs undergoing unifocalization surgery. One limitation is that no diagnostic criteria exist for RPE in patients with congenital heart disease undergoing procedures to improve or establish pulmonary blood flow, and little is known about its clinical impact. We defined RPE based on our clinical experience and a recent study from our institution, and chest radiographs were scored using a system of grading adapted from lung transplant recipients.

Another limitation is that we had a small number of patients and the study was likely underpowered to detect a difference in the 3 biological markers of lung injury that we chose to measure. We also had a small number of patients with aortopulmonary shunts relative to patients with right ventricle-to-pulmonary artery conduits, limiting our ability to draw conclusions about the impact of systemic-level pressure on the pulmonary microvasculature. Our study was designed to be a pilot for further investigations aimed at understanding the pathophysiology of RPE in children with congenital heart disease.

In our clinical experience, there is a small population of children who experience severe oxygenation deficits after unifocalization surgery that seem to be associated with RPE. These patients have required veno-venous extracorporeal membrane oxygenation to achieve adequate gas exchange, and they typically have complicated clinical courses. We intend to direct our future efforts at these more severe cases to better understand the pathophysiologic mechanisms of RPE in this unique subpopulation of patients with TOF/PA/MAPCAs.

CONCLUSIONS

Reperfusion pulmonary edema may occur in as many as half of patients with TOF/PA/MAPCAs undergoing unifocalization surgery. Biomarkers of lung injury and the clinical course were not different between children with and without RPE. RPE in our population may be secondary to high-flow, high-pressure hydrostatic pulmonary edema without lung vascular injury. Although we cannot completely exclude the possibility of capillary injury, the process of RPE is clinically self-limited and as such does not seem to involve vascular injury.

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