Factors Associated with Reperfusion Lung Injury After Total Correction of Tetralogy of Fallot

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Abstract

INTRODUCTION: Reperfusion lung injury (RLI) is one of the most common complications after Tetralogy of Fallot (TOF) correction which leads to prolonged hospitalization and significant morbidity. This study aimed to investigate the different factors that may be associated with RLI after TOF correction.

METHODS: All patients who underwent TOF correction from January 2015 to December 2016 in a tertiary cardiovascular referral center were included. Baseline characteristics, echocardiographic and intraoperative findings along with their post-operative course were reviewed. Serial chest radiographs were reviewed and each lung was given a pulmonary edema score prior to and after surgery to determine the presence of RLI. Statistical analysis was performed using Stata SE version 13. Factors associated with RLI were determined using logistic logarithm analysis. The level of significance was set at 5%.

RESULTS: RLI was present in 41 of 114 (36%) patients after TOF correction. Female sex was associated with the development of RLI (OR 2.9; 95% CI 1.29-6.55; p=0.01). Intraoperative use of propofol was a protective factor, with an OR of 0.24 (95% CI 0.07-0.85, p=0.027). We did not identify a significant association between the occurrence of RLI and the factors that reflect the degree of pulmonary stenosis.

CONCLUSION: RLI is common after TOF correction. Female sex increases the odds of its occurrence while intraoperative use of propofol is a protective factor.

KEYWORDS: Tetralogy of Fallot, TOF correction, reperfusion lung injury

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. In a meta-analysis done in 2002, which included 41 studies about TOF, the best estimate of its incidence is 577 cases per million live births.[1] Since the first successful correction of TOF in 1954 by Lillehei and associates in a 10-year-old boy,[2] this condition was studied extensively and its surgical correction was replicated in other conditions.

TOF correction nowadays is done through a transatrial incision for the closure of ventricular septal defect and relief of obstruction to the right ventricular outflow tract[3] while on cardiopulmonary bypass. Reperfusion lung injury (RLI) in the setting of pulmonary artery angioplasty for relief of right ventricular outflow obstruction is a well-recognized entity.[4] It typically manifests as transient pulmonary edema that is localized to an area of increased perfusion of lung tissue that results in impaired gas exchange. It has been thought that this injury is due to increased blood flow to areas of the lung that have been chronically underperfused.[5] Pulmonary injury after cardiopulmonary bypass has led to prolonged hospitalization, intubation and increased cost of hospital stay.[6]

In a study done in 2012 by Maskatia and associates, they reported a 65% incidence of reperfusion injury in patients with TOF – pulmonary valve atresia with major aortopulmonary collateral arteries after unifocalization procedure. They reported that the risk factors for the development of pulmonary reperfusion injury included bilateral unifocalization and the severity of stenosis in collateral arteries.[7]

RLI after TOF correction has been sparsely studied. The aims of this study are to describe the incidence, clinical profile and risk factors for the development of RLI after TOF correction. Based on the results reported by Maskatia and associates, it is hypothesized that post-operative RLI is more likely to develop in TOF cases with more severe pulmonary stenosis, thereby with lower baseline oxygen saturation, higher hematocrit and with history of recurrent admissions for phlebotomy. TOF correction done at an advanced age probably has a higher risk of reperfusion injury since the lungs have been more chronically underperfused. Furthermore, it is hypothesized that prior palliative shunting procedures done to augment pulmonary blood flow will reduce the incidence of RLI provided that the shunt remains patent.

METHODOLOGY

This was a retrospective cohort study conducted in a tertiary referral hospital from January 2015 to December 2016. The study included all pediatric patients (18 years old and below) with TOF who underwent total correction at a tertiary cardiovascular referral center from January 2015 to December 2016. All patients with other medical problems such as pneumonia and Acute Respiratory Distress Syndrome as well as those with incomplete medical records were excluded from the study.

The list of patients with TOF who underwent total correction from January 2015 to December 2016 was obtained from the database and the medical records section. The medical records of the included patients were obtained to determine the following variables: demographic data (age, sex, nutritional status, prior shunting procedures, others); clinical and laboratory data (history of recurrent phlebotomy, maintenance medications, hypercyanotic episodes, pre-operative oxygen saturation and baseline hematocrit); 2D echocardiographic findings (sizes of the main and branch pulmonary arteries, degree of obstruction to right ventricular outflow tract, presence of other sources of pulmonary blood supply and function of both ventricles) and intraoperative findings (type of repair, cross-clamping time, bypass time).

Chest radiographs done preoperatively, immediately after surgery to two days after, and two weeks post-surgery or at discharge from the hospital were assessed by a radiologist to determine who among the patients developed reperfusion injury. The radiologist involved in the study was blinded with regard to the clinical history and subsequent hospital course of the patients. Only the age and hospital number of all included patients were given. The radiographs were scored using a pulmonary edema scoring system used in a previous study which assessed pulmonary reperfusion injury in patients who underwent lung transplantation.[8] In the scoring system, the degree of edema on each lung was assessed using a four-point scale: zero points for a normal lung; one point if with minimal opacity not obscuring lung vessels; two points if with opacity partially obscuring lung vessels; and three points if with opacity completely obscuring lung vessels. The average score of the two lungs was considered the final edema score.

The presence of RLI was defined as a change in pulmonary opacity (i.e., a change in edema score ≥2) appearing immediately after TOF correction that resolved within two weeks or before discharge and was not associated with pulmonary hemorrhage, pneumonia or atelectasis. Patients with pulmonary edema but with clinical courses more compatible with pneumonia (i.e., presence of fever, copious secretions from the endotracheal tube, productive cough, increased C-reactive protein and prolonged duration of pulmonary opacity) or those with a pre-operative radiograph with an edema score >1 were not considered to have RLI. This was done to exclude patients with other causes of pulmonary opacity.

STATISTICAL ANALYSIS

Using Epi Info Version 7, the calculated minimum sample size was 87 based on a 65% incidence of RLI reported among patients with TOF–pulmonary valve atresia with major aortopulmonary collateral arteries who underwent unifocalization procedures[7], using a 10% margin of error and a 95% confidence level.

Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated

as frequency and percent. Factors associated with RLI were determined using logistic regression. The level of significance was set at 5%. Data analysis was performed using Stata SE version[13].

This study was conducted in strict compliance with the ethical principles contained in the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Ethics Review Board (IERB) prior to initiation of the study. Given the retrospective design of the study, the investigators requested that the process of obtaining the informed consent be waived. The risk to privacy was minimal. No sensitive information was obtained. The anonymity of patients was ensured by the investigator.

RESULTS

A total of 130 records of patients with TOF who underwent total correction were retrieved and reviewed. Four were excluded because of incomplete medical records, most of whom did not have intraoperative anesthesia monitoring sheets. Another eight patients were not included because of the lack of baseline work-up of either 2D echo (three patients) or chest radiograph (five patients). Five patients were further excluded due to a different diagnosis (double outlet right ventricle with pulmonary stenosis). Eventually, 114 patients were included in the study. Out of these patients, 36% (n=41) developed RLI. The true incidence had a 95% confidence interval of 27.3% and 45.5%.

Table 1 shows the association of various baseline characteristics with the occurrence of RLI in patients who underwent TOF correction. The age and nutritional status of patients at the time of surgery was not significantly associated with an increased odds of RLI. In contrast, having a prior shunting procedure increased the odds of RLI by 3.69, although this was not statistically significant. Female patients were significantly more likely to develop RLI compared with their male counterparts, with an odds ratio of 2.91 (p=0.009).

The association of clinical and laboratory parameters with the development of RLI is shown in Table 2. No variable was found to be significantly associated with the occurrence of RLI. However, having a history of recurrent phlebotomy and hypercyanotic spells showed a trend towards an increased odds of RLI. On the other hand, pre-operative use of propranolol and having a higher baseline oxygen saturation tended to have a lower odds of reperfusion injury.

Pre-operative echocardiographic sizes of the main and branch pulmonary arteries did not have a statistically significant association with the occurrence of RLI as shown in Table 3. However, smaller right and left pulmonary artery sizes tended to increase the odds of reperfusion injury. The severity of RVOT obstruction was also not significantly associated with the development of RLI. The presence of another source of pulmonary blood flow other than the main and the branch pulmonary arteries (e.g., collaterals and patent ductus arteriosus) carried a trend towards a higher odds of RLI (OR 1.82) but this was not statistically significant. In contrast, an increased McGoon's value tended to lower the odds of RLI but this also did not reach statistical significance. The association of right and left ventricular function with the occurrence of RLI was not established since all of the included patients had good right and left ventricular systolic function prior to surgery.

Table 4 shows that no particular type of RVOT repair had a statistically significant association with the development of RLI. However, MPA and RVOT augmentation, as well as the duration of bypass and cross-clamp had a non-significant trend towards increased odds of RLI.

Out of all the anesthesia used during the operation, only propofol showed a significant association with a lower odds of RLI (OR 0.24), denoting that those who used propofol were 4.17 times less likely to have RLI (p=0.03).

DISCUSSION

This study was a retrospective review of patients who underwent total correction of TOF to determine the incidence and factors associated with RLI. We found that 41 out of 114 (36%) patients developed RLI. Only female sex was associated with a significant increase in the odds of RLI (OR 2.91; p=0.009) while intraoperative use of propofol significantly decreased the odds of having reperfusion injury (OR 0.24; p=0.03). The mechanism by which these factors affect the development of RLI have yet to be determined. Other factors that were investigated failed to show a significant association with the development of RLI.

The study of Maskatia and co-workers showed a strong correlation between the development of RLI and the degree of pulmonary stenosis.[7] In our study, clinical, laboratory and echocardiographic findings consistent with a higher degree of pulmonary stenosis did not demonstrate a significant increase in the occurrence of RLI. In the same way, factors consistent with a milder degree of pulmonary stenosis did not show a significantly lower odds of RLI. Intraoperative factors such as the type of repair of right ventricular outflow obstruction and the duration of bypass and cross-clamp also did not demonstrate a significant association with RLI occurrence.

This study suggests that reperfusion injury does not directly reflect the degree of pulmonary stenosis and is not solely due to increased blood flow in a chronically underperfused lung. Even though the degree of pulmonary stenosis may still play an important role in RLI development as shown by some data trends, we hypothesize that there are other more influential factors that should be evaluated. Post-operative management of fluids, as well as early and aggressive use of diuretics, may have affected the occurrence of RLI. Most of the patients included in the study were given furosemide and other diuretics early in the post-operative period. This may have changed the course of patients that may be considered at high risk of reperfusion injury based on previous studies.

Table 1. Association of demographic factors with the presence of reperfusion lung injury in patients who underwent TOF correction.

Demographic Variables	With RLI (n=41) n,%	Without RLI (n=73) n,%	Odds Ratio	95% CI	p value
Age at TOF					
Less than 5 Years	25 (61)	43 (58.9)	0.9173	0.42 to 2.00	0.829
5 Years and Above	16 (39)	30 (41.1)			
Sex					
Female	20 (48.8)	18 (24.7)	2.9101	1.29 to 6.55	0.010
Male	21 (51.2)	55 (75.3)			
Nutritional status (weight for age)					
Z-Score >+2	1 (2.4)	0 (0.0)	Reference		
Z-score 0 to +2	6 (14.6)	8 (11.0)			
Z-Score 0 to -2	9 (22)	32 (43.8)	0.3214	0.09 to 1.13	0.076
Z-Score <-2	25 (61)	33 (45.2)	0.8658	0.28 to 2.71	0.804
Prior procedures (shunting)					
Present	2 (4.9)	1 (1.4)	3.6923	0.32 to 42.02	0.292
None	39 (95.1)	72 (98.6)			

Table 2. Association of clinical and laboratory findings with the presence of reperfusion lung injury in patients who underwent TOF correction.

Clinical and Laboratory Findings	With RLI (n=41) n,%	Without RLI (n=73) n,%	Odds Ratio	95% CI	p-value
Phlebotomy					
Recurrent	3 (7.3)	3 (4.1)	1.84	0.35 to 9.58	0.468
None	38 (92.7)	70 (95.9)			
Hypercyanotic Spell					
Recurrent	13 (31.7)	18 (24.7)	1.42	0.61 to 3.31	0.418
None	28 (68.3)	55 (75.3)			
Propranolol					
Not maintained	7 (17.1)	20 (27.4)	0.55	0.21 to 1.43	0.217
Maintained	34 (82.9)	53 (72.6)			
Oxygen Saturation					
<60%	3 (7.3)	4 (5.5)	Reference		
60-80%	27 (65.9)	37 (50.7)	0.9730	0.20 to 4.71	0.973
>80%	11 (26.8)	32 (43.8)	0.4583	0.09 to 2.38	0.353
Preoperative Hematocrit					
<60%	27 (65.9)	48 (65.8)	1.0000	0.45 to 2.25	0.991
60-80%	14 (34.1)	25 (34.2)			
>80%	0 (0)	0 (0)	-	-	-

Table 3. Association of pre-operative echocardiographic findings with the presence of reperfusion lung injury in patients who underwent TOF correction.

Echocardiographic Variables	With RLI (n=41) n,%	Without RLI (n=73) n,%	Odds Ratio	95% CI	p-value
MPA Size					
Z-Score >+2	0 (0)	0 (0)	Reference		
Z-score 0 to +2	2 (4.9)	2 (2.7)			
Z-Score 0 to -2	10 (24.4)	18 (24.7)	0.56	0.07 to 4.57	0.585
Z-Score <-2	29 (70.7)	53 (72.6)	0.55	0.07 to 4.09	0.557
RPA Size					
Z-Score >+2	1 (2.4)	0 (0)	Reference		
Z-score 0 to +2	6 (14.6)	12 (16.4)			
Z-Score 0 to -2	26 (63.4)	49 (67.1)	0.91	0.32 to 2.59	0.859
Z-Score <-2	8 (19.5)	12 (16.4)	1.14	0.31 to 4.16	0.840
LPA Size					
Z-Score >+2	1 (2.4)	1 (1.4)	Reference		
Z-score 0 to +2	13 (31.7)	28 (38.4)			
Z-Score 0 to -2	22 (53.7)	37 (50.7)	1.23	0.54 to 2.82	0.622
Z-Score <-2	5 (12.2)	7 (9.6)	1.48	0.40 to 5.50	0.559
RVOT Obstruction					
Mild	0 (0)	1 (1.4)	0.88	0.15 to 5.05	0.890
Moderate	2 (4.9)	3 (4.1)			
Severe	39 (95.1)	69 (94.5)			
Other sources of pulmonary blood flow					
Present	10 (24.4)	11 (15.1)	1.82	0.70 to 4.74	0.222
Absent	31 (75.6)	62 (84.9)			
Right Ventricular Function					
Good (RVEF≥36)	0 (0)	0 (0)	-	-	-
Poor (RVEF<36)	41 (100)	73 (100)			
Left Ventricular Function					
Good (RVEF≥36)	0 (0)	0 (0)	-	-	-
Poor (RVEF<36)	41 (100)	73 (100)			
McGoon's					
<1	1 (2.4)	0 (0)	Reference		
1.0 to 1.5	11 (26.8)	15 (20.5)			
1.6 to 2.0	23 (56.1)	37 (50.7)	0.78	0.31 to 1.95	0.591
>2.0	6 (14.6)	21 (28.8)	0.36	0.11 to 1.17	0.088

MPA, main pulmonary artery; LPA, left pulmonary artery; RLI, reperfusion lung injury; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot

Table 4. Association of intraoperative findings with the presence of reperfusion lung injury in patients who underwent TOF correction.

Intraoperative Variables	With RLI (n=41) n,%	Without RLI (n=73) n,%	Odds Ratio	95% CI	p value
Type of RVOT Repair					
Transannular patch	25 (61)	52 (71.2)	0.63	0.28 to 1.41	0.263
Infundibulectomy	38 (92.7)	69 (94.5)	0.73	0.16 to 3.45	0.696
MPA Augmentation	8 (19.5)	8 (11)	1.97	0.68 to 5.72	0.213
RVOT Augmentation	7 (17.1)	8 (11)	1.67	0.56 to 5.01	0.358
Commissurotomy	0 (0)	1 (1.4)	-	-	-
LPA Augmentation	1 (2.4)	2 (2.7)	-	-	-
Pulmonary Valvotomy	0 (0)	2 (2.7)	-	-	-
Pulmonary Valve Reconstruction (Monocuspal)	0 (0)	1 (1.4)	-	-	-
RPA Augmentation	1 (2.4)	0 (0)	-	-	-
RV to PA Conduit	0 (0)	1 (1.4)	-	-	-
Cross-Clamp Time					
<1 hour	1 (2.4)	2 (2.7)	Reference		
1-2 hours	31 (75.6)	55 (75.3)	1.13	0.10 to 12.94	0.923
>2 hours	9 (22)	16 (21.9)	1.13	0.09 to 14.20	0.928
Bypass Time					
<2 hours	15 (36.6)	32 (43.8)	Reference		
2-3 hours	20 (48.8)	32 (43.8)	1.33	0.58 to 3.06	0.497
>3 hours	6 (14.6)	9 (12.3)	1.42	0.43 to 4.73	0.566
Anesthesia used Intraoperatively					
Sevoflurane	40 (97.6)	70 (95.9)	1.71	0.17 to 17.04	0.646
Midazolam	39 (95.1)	73 (100)	-	-	0.997
Fentanyl	41 (100)	71 (97.3)	-	-	0.998
Rocuronium	40 (97.6)	71 (97.3)	1.13	0.10 to 12.82	0.923
Propofol	33 (80.5)	69 (94.5)	0.24	0.07 to 0.85	0.027
Ketamine	0 (0)	2 (2.7)	-	-	0.998
Atracurium	4 (9.8)	3 (4.1)	2.52	0.54 to 11.87	0.242
Isoflurane	1 (2.4)	3 (4.1)	0.58	0.06 to 5.80	0.646
Morphine	0 (0)	1 (1.4)	-	-	0.998
Oxycodone	0 (0)	1 (1.4)	-	-	0.998

MPA, main pulmonary artery; LPA, left pulmonary artery; PA, pulmonary artery; RLI, reperfusion lung injury; RPA, right pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot

Intraoperatively, the extensiveness of dissection and lung trauma due to retraction may have contributed to the post-operative radiographic picture of reperfusion injury. Mechanical ventilator management in the post-operative period may also have affected our results. Changing ventilator settings, especially positive end-expiratory pressure, can produce dramatic variations in the appearance of pulmonary vasculature in technically identical radiographs. [9]

This study also showed that the use of propofol as an anesthetic agent significantly lowered the risk of RLI. Though no single pathophysiologic mechanism for RLI has been identified, the theory that it is due to inflammatory lung injury characterized by rapid sequestration of neutrophils has been accepted.10 Oxidative stress has also been implicated in the development of RLI.[11] The anti-inflammatory and antioxidative effects of propofol have been studied previously.[12-15] It is possible that these anti-inflammatory and antioxidative effects are responsible for the protection against RLI that propofol seemed to give the patients in the study.

The study has several limitations given its retrospective design. The diagnosis of RLI was based on chest radiographic findings alone and molecular markers for reperfusion were not used. It is possible that the radiographic picture of RLI was caused by a different pathology. Other limitations include: the scoring system used in determining the presence of pulmonary edema had not been validated, factors that were analyzed in the study were limited and there could be other clinical, laboratory, echocardiographic, medical, hemodynamic, intraoperative and postoperative factors that contributed to RLI.

It is suggested that future similar studies focus on the factors contributing to RLI and use more specific molecular markers to definitely diagnose reperfusion injury in addition to chest radiographic findings. Post-operative fluid management as well as ventilatory management, specifically the duration of ventilatory support should be investigated in future studies. A larger sample size is also recommended since the trend of the data in this study seemed to indicate that the degree of pulmonary stenosis might contribute to the development of RLI but did not reach statistical significance.

CONCLUSION

RLI was common in the setting of total correction of TOF with an incidence of 36% in the cohort. Female sex and intraoperative use of propofol were the factors that were identified to increase or decrease the occurrence of RLI, respectively. No significant association between RLI and other laboratory, echocardiographic and intraoperative factors were demonstrated. The cause of RLI in patients after TOF correction is likely multifactorial, thus indicating the need for further related investigations.

REFERENCES

1. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890-1900.
2. Kirklin JW, Blackstone EH, Kirklin JK, et al. Surgical results and protocols in the surgical spectrum of tetralogy of Fallot. *Ann Surg*. 1983;198:251-265.
3. Guolin S, Xuefeng W, Jinjin C, Ruiyan M, Fuping L, Lin C, Yingbin X. Primary repair of tetralogy of Fallot in infants: Transatrial/transpulmonary or transventricular approach. *Asian J Surg*. 2013;36:137-143.
4. Bergersen LJ, Perry SB, Lock JE. Effect of cutting balloon angioplasty on resistant pulmonary artery stenosis. *Am J Cardiol*. 2003;91:185-9.
5. Kreutzer J, Perry SB, Jonas RA, Mayer JE, Castaneda AR, Lock JE. Tetralogy of Fallot with diminutive pulmonary arteries: pre-operative pulmonary valve dilatation and transcatheter rehabilitation of pulmonary arteries. *J Am Coll Cardiol*. 1996;27:1741-7.
6. Su, ZK, Sun Y, Yang YM, Zhang HB, Xu ZW. Lung function after deep hypothermic cardiopulmonary bypass in infants. *Asian Cardiovasc Thorac Ann*. 2003;11:328-31.
7. Maskatia SA, Feinstein JA, Newman B, Hanley FL, Roth SJ. Pulmonary reperfusion injury after the unifocalization procedure for tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collateral arteries. *J Thorac Cardiovasc Surg*. 2012;144:184-9.
8. Anderson DC, Glazer HS, Semenkovich JW, Pilgram TK, Trulock EP, Cooper JD, et al. Lung transplant edema: chest radiography after lung transplantation – the first 10 days. *Radiology*. 1995;195:275-81.
9. Zimmerman JE, Goodman LR, Shahvaru MB. Effect of mechanical ventilation and positive end-expiratory pressure (PEEP) on chest radiograph. *American Journal of Roentgenology*. 1979;133:811-815.
10. Yuan S. Pulmonary reperfusion injury. *Signa Vitae*. 2017;13(1):14-8.
11. Ovechkin AV, Lominadze D, Sedoris KC, Robinson TW, Tyagi SC, Roberts AM. Lung ischemia-reperfusion injury: implications of oxidative stress and platelet-arteriolar wall interactions. *Arch Physiol Biochem*. 2007 Feb;113(1):1-12.
12. Samir A, Gandreti N, Madhere M, Khan A, Brown M, Loomba V. Anti-inflammatory effects of propofol during cardiopulmonary bypass: A pilot study. *Ann Card Anaesth*. 2015 Oct-Dec;18(4):495–501.
13. Mikawa K, Akamatsu H, Nishina K, Shiga M, Maekawa N, Obara H, et al. Propofol inhibits human neutrophil functions. *Anesth Analg*. 1998;87:695–700.
14. Chen RM, Chen TG, Chen TL, Lin LL, Chang CC, Chang HC, et al. Anti-inflammatory and antioxidative effects of propofol on lipopolysaccharide-activated macrophages. *Ann N Y Acad Sci*. 2005 May;1042:262-71.
15. Eroglu A. The Effect of Intravenous Anesthetics on Ischemia-Reperfusion Injury. *Biomed Res Int*. 2014;2014:821513.