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The Role Of Oxidative Stress In The Development And Maintenance Of Pulmonary Hypertension In Children With Congenital Heart Disease

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Abstract: Background: Pulmonary hypertension is a severe and prognostically unfavorable complication of congenital heart disease in children, characterized by progressive pulmonary vascular remodeling and increased perioperative risk. Increasing evidence suggests that oxidative stress plays a significant role in pulmonary vascular dysfunction; however, its contribution to the development and persistence of pulmonary hypertension in pediatric congenital heart disease remains insufficiently defined.

Objective: To investigate the role of oxidative stress in the development and maintenance of pulmonary hypertension in children with congenital heart disease by evaluating key antioxidant defense markers and their association with pulmonary hemodynamic parameters.

Methods: This observational study included children with congenital heart disease stratified according to the presence or absence of pulmonary hypertension based on echocardiographic assessment. Superoxide dismutase activity and total antioxidant status were measured in peripheral blood serum using spectrophotometric methods. Echocardiographic parameters reflecting pulmonary vascular involvement were analyzed in parallel. Intergroup comparisons and correlation analyses were performed using appropriate statistical methods.

Results: Children with pulmonary hypertension demonstrated significantly reduced superoxide

dismutase activity compared with patients without pulmonary hypertension. Total antioxidant status was also lower in the pulmonary hypertension group, indicating depletion of overall antioxidant capacity. Oxidative stress markers were inversely associated with pulmonary artery pressure, suggesting a relationship between impaired antioxidant defense and pulmonary hemodynamic severity. Partial postoperative recovery of antioxidant parameters did not result in complete normalization, indicating persistent redox imbalance.

Conclusion: Oxidative stress, manifested by reduced enzymatic and total antioxidant defense, represents a stable pathogenic component of pulmonary hypertension in children with congenital heart disease. Assessment of antioxidant markers may provide additional insight into pulmonary vascular vulnerability and contribute to improved risk stratification and targeted management strategies in this patient population.

Keywords: Congenital heart disease; Pulmonary hypertension; Oxidative stress; Superoxide dismutase; Total antioxidant status; Pediatric cardiology.

1. Introduction: Pulmonary hypertension represents one of the most severe and prognostically unfavorable complications of congenital heart disease in children. Persistent elevation of pulmonary vascular resistance leads to progressive right ventricular overload, impaired cardiopulmonary adaptation and increased perioperative risk, significantly influencing both short-term and long-term outcomes. Despite advances in early diagnosis and surgical correction of congenital heart defects, pulmonary hypertension continues to develop or persist in a substantial proportion of pediatric patients.

Traditionally, pulmonary hypertension in congenital heart disease has been attributed primarily to prolonged volume and pressure overload of the pulmonary circulation resulting from left-to-right shunting and abnormal cardiac anatomy. However, accumulating evidence suggests that hemodynamic factors alone cannot fully explain the complexity and persistence of pulmonary vascular remodeling observed in affected children. Increasing attention has therefore been directed toward non-hemodynamic mechanisms that contribute to the initiation and maintenance of pulmonary hypertension.

Oxidative stress has emerged as a central pathophysiological mechanism involved in pulmonary vascular dysfunction. Excessive generation of reactive oxygen species and insufficient antioxidant defense disrupt endothelial homeostasis, promote smooth muscle cell proliferation and impair vasodilatory signaling pathways. In the developing pulmonary circulation, these processes may be particularly detrimental, as immature antioxidant systems and ongoing vascular growth increase susceptibility to redox imbalance.

In children with congenital heart disease, chronic hypoxia, systemic inflammation and altered pulmonary blood flow create conditions that favor sustained oxidative stress. Reduced activity of key antioxidant enzymes, including superoxide dismutase, and depletion of total antioxidant capacity may facilitate endothelial dysfunction and contribute to pulmonary vasoconstriction and remodeling. Importantly, oxidative stress may not only trigger the development of pulmonary hypertension but also participate in its maintenance even after surgical correction of the underlying cardiac defect.

Despite growing experimental and clinical evidence linking oxidative stress to pulmonary hypertension, data focusing specifically on pediatric congenital heart disease remain limited. Most available studies address adult pulmonary hypertension or postoperative outcomes, while the role of oxidative stress in the pathogenesis and persistence of pulmonary hypertension during childhood has not been sufficiently characterized.

The aim of the present study was to investigate the role of oxidative stress in the development and maintenance of pulmonary hypertension in children with congenital heart disease by evaluating key antioxidant markers and their association with pulmonary hemodynamic parameters.

2. Methods

This observational study included children with congenital heart disease who underwent clinical, laboratory and instrumental evaluation in a pediatric cardiac surgery setting. Patients were stratified into groups according to the presence or absence of pulmonary hypertension based on echocardiographic criteria, including elevated pulmonary artery pressure and indirect signs of increased pulmonary vascular resistance.

All participants underwent standardized echocardiographic assessment to evaluate cardiac anatomy and pulmonary hemodynamic parameters.

Routine laboratory investigations were performed in the preoperative period. Oxidative stress status was assessed by measuring superoxide dismutase activity and total antioxidant status in peripheral blood serum using spectrophotometric methods under standardized laboratory conditions.

The analysis focused on the association between oxidative stress markers and pulmonary hypertension. Superoxide dismutase activity and total antioxidant status were compared between groups and analyzed in relation to echocardiographic indicators of pulmonary vascular involvement. Statistical analysis was performed using Microsoft Excel and Jamovi software. Quantitative data were expressed as mean ± standard deviation or median with range, depending on distribution. Intergroup comparisons were conducted using appropriate parametric or non-parametric tests, and correlations were evaluated as indicated. A p-value of less than 0.05 was considered statistically significant.

The study was conducted in accordance with institutional ethical standards, and informed consent was obtained from the parents or legal guardians of all participants.

3. Results

Children with congenital heart disease and pulmonary hypertension demonstrated pronounced differences in pulmonary hemodynamics and oxidative stress parameters compared with patients without pulmonary hypertension. Echocardiographic assessment revealed significantly higher pulmonary vascular load and altered ventricular volume characteristics in children with pulmonary hypertension, indicating persistent pulmonary hemodynamic involvement associated with pulmonary vascular remodeling (Table 1).

Table 1. Echocardiographic characteristics of children with congenital heart disease with and without pulmonary hypertension

Parameter	CHD with pulmonary hypertension	CHD without pulmonary hypertension	p-value
Ventricular septal defect diameter, mm	7.25 ± 3.80	5.11 ± 4.20	<0.05
Atrial septal defect diameter, mm	3.16 ± 4.43	2.53 ± 4.98	>0.05
Patent ductus arteriosus diameter, mm	0.44 ± 1.32	0.50 ± 1.55	>0.05
Pulmonary artery pressure, mmHg	elevated	within normal range	<0.05
LV end-diastolic volume, mL/m²	21.6 ± 17.9	29.0 ± 31.9	<0.05
Left ventricular ejection fraction, %	65.1 ± 3.06	64.1 ± 3.86	>0.05

Note: Data are presented as mean ± standard deviation. Pulmonary hypertension was defined by echocardiographic criteria.

Analysis of oxidative stress markers showed marked impairment of antioxidant defense in the pulmonary hypertension group. As presented in Table 2, superoxide dismutase activity was significantly lower in children with pulmonary hypertension than in those without pulmonary hypertension (91.6 ± 19.3 U/mL versus 119.0 ± 24.36 U/mL; $p < 0.05$). Total antioxidant status followed a similar trend, with reduced TAS values in children with pulmonary hypertension compared with the non-pulmonary hypertension group (0.15 ± 0.08 mmol/L versus 0.19 ± 0.08 mmol/L), reflecting depletion of overall antioxidant reserve. These differences indicate a stable redox imbalance associated with pulmonary vascular pathology rather than isolated perioperative fluctuations.

Table 2. Oxidative stress markers in children with congenital heart disease with and without pulmonary hypertension

Marker	Time point	CHD with pulmonary hypertension	CHD without pulmonary hypertension	p-value
Superoxide dismutase (U/mL)	Preoperative	91.6 ± 19.3	119.0 ± 24.36	<0.05
	Postoperative	95.4 ± 16.8	137.0 ± 24.6	<0.05
Total antioxidant status (mmol/L)	Preoperative	0.15 ± 0.08	0.19 ± 0.08	>0.05
	Postoperative	0.21 ± 0.04	0.22 ± 0.10	>0.05

Note: Data are presented as mean ± standard deviation. Postoperative values refer to the early postoperative period.

Perioperative dynamics of oxidative stress markers further supported these findings. Superoxide dismutase activity increased modestly after surgical intervention in both groups; however, values remained consistently lower in children with pulmonary hypertension throughout the observation period. The dynamics of SOD activity are illustrated in Figure 1. Total antioxidant status also demonstrated partial postoperative recovery, although antioxidant capacity remained reduced in the pulmonary hypertension group compared with patients without pulmonary hypertension, as shown in Figure 2.

Figure 1. Superoxide dismutase activity in children with congenital heart disease with and without pulmonary hypertension

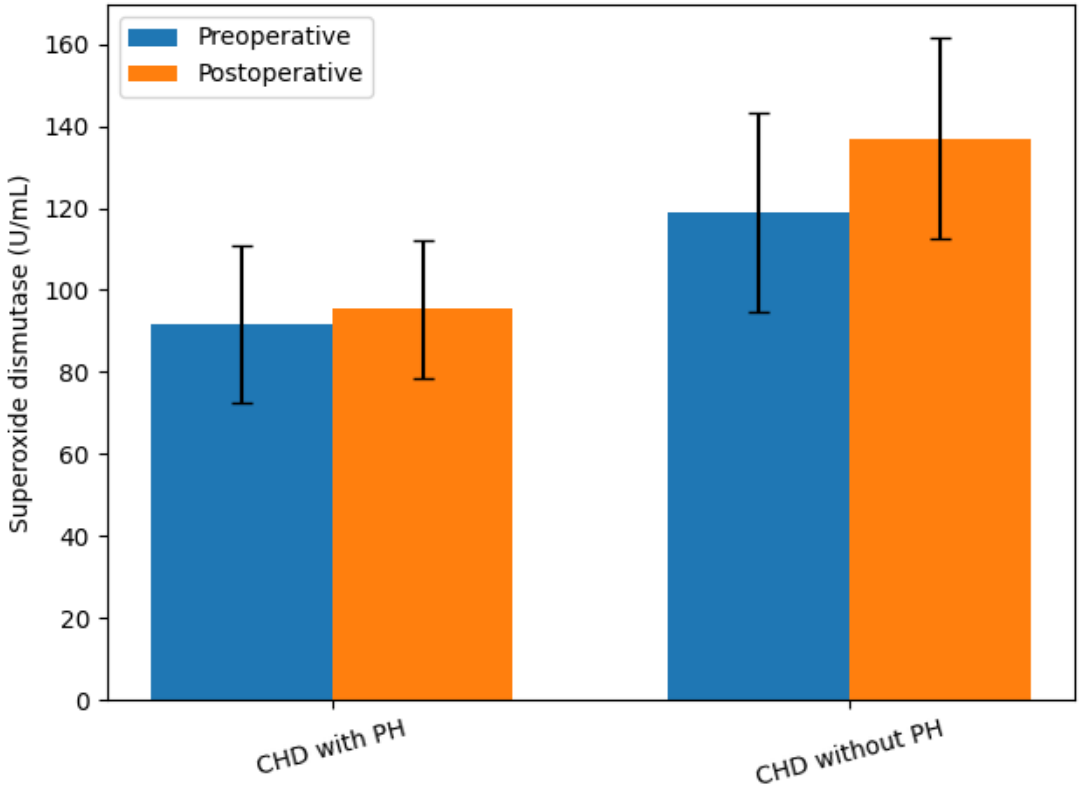
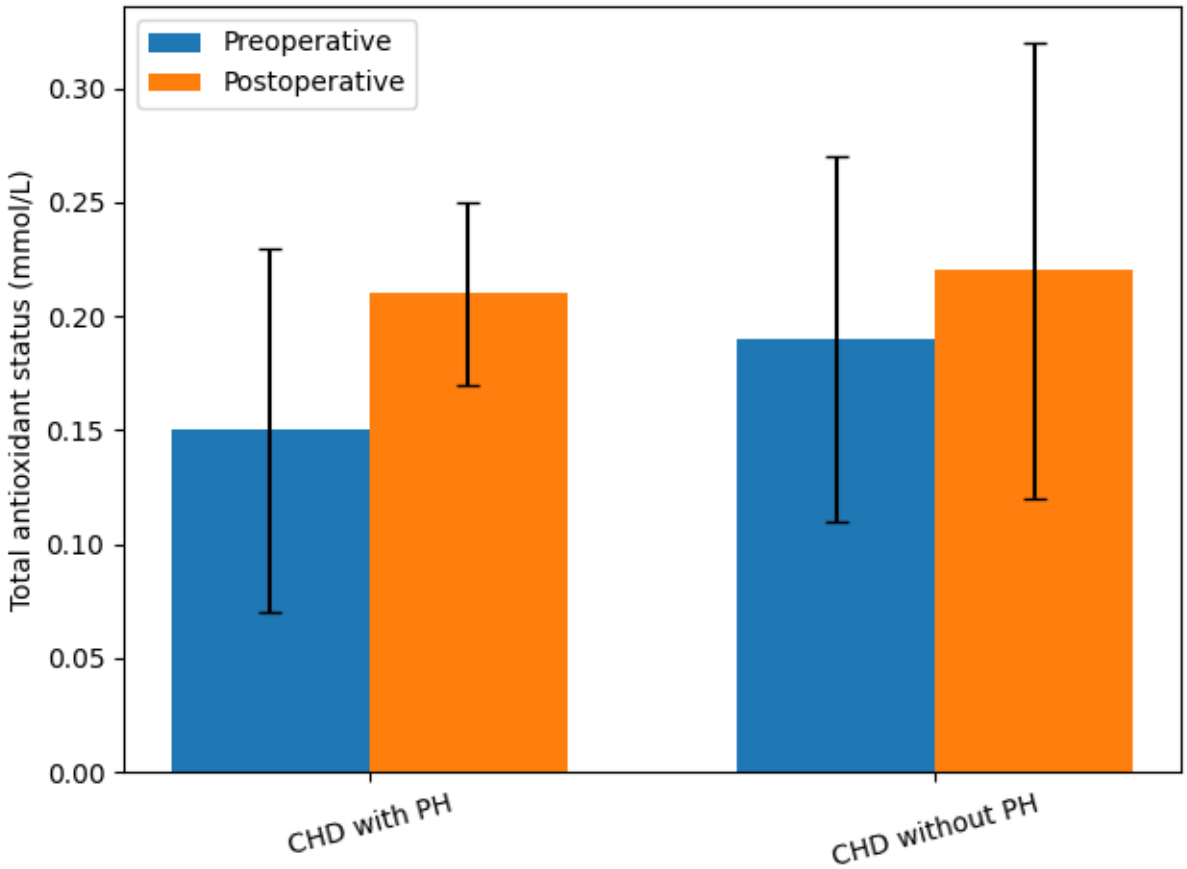


Figure 2. Total antioxidant status in children with congenital heart disease with and without pulmonary hypertension



Correlation analysis demonstrated a significant relationship between oxidative stress and pulmonary hemodynamic severity. Lower superoxide dismutase activity was inversely associated with pulmonary artery pressure, indicating that diminished antioxidant defense corresponded to increased pulmonary vascular resistance. Total antioxidant status showed similar but less pronounced associations with pulmonary hemodynamic parameters. These relationships are summarized in Table 3.

Table 3. Correlation between oxidative stress markers and pulmonary artery pressure

Parameter	Pulmonary artery pressure	Correlation coefficient (r)	p-value
Superoxide dismutase (U/mL)	inverse association	−0.62	<0.05
Total antioxidant status (mmol/L)	inverse association	−0.41	<0.05

Note: Correlation analysis was performed using Pearson or Spearman methods as appropriate.

Overall, the results indicate that children with congenital heart disease and pulmonary hypertension are characterized by persistent oxidative stress, manifested by reduced superoxide dismutase activity and diminished total antioxidant status. The association between impaired antioxidant defense and pulmonary hemodynamic severity supports the involvement of oxidative stress in both the development and maintenance of pulmonary hypertension in this patient population.

4. Discussion

The present study demonstrates that oxidative stress plays a significant role in the development and maintenance of pulmonary hypertension in children

with congenital heart disease. The observed reduction in antioxidant defense, reflected by consistently lower superoxide dismutase activity and diminished total antioxidant status, characterizes a stable biological phenotype associated with pulmonary vascular involvement rather than a transient response to surgical stress.

Children with pulmonary hypertension exhibited impaired enzymatic antioxidant capacity prior to and after surgical intervention, suggesting that oxidative stress is an intrinsic component of pulmonary vascular pathology in congenital heart disease. Reduced SOD activity indicates a decreased ability to neutralize superoxide radicals, which may promote endothelial dysfunction, impair nitric oxide bioavailability and contribute to sustained pulmonary vasoconstriction. These mechanisms are particularly relevant in the immature pulmonary circulation, where antioxidant systems are not fully developed and susceptibility to redox imbalance is increased.

The observed association between oxidative stress markers and pulmonary hemodynamic severity further supports a mechanistic link between redox imbalance and pulmonary hypertension. Lower SOD activity and reduced total antioxidant status were associated with higher pulmonary artery pressure, suggesting that oxidative stress may contribute not only to the initiation of pulmonary vascular remodeling but also to its persistence. Chronic oxidative stress may stimulate smooth muscle cell proliferation, extracellular matrix deposition and inflammatory signaling within the pulmonary vasculature, thereby reinforcing pulmonary vascular resistance even after correction of the underlying cardiac defect.

Although partial postoperative recovery of antioxidant markers was observed, antioxidant capacity in children with pulmonary hypertension remained reduced compared with patients without pulmonary hypertension. This incomplete restoration indicates that surgical elimination of hemodynamic shunting alone may be insufficient to normalize redox balance in the presence of established pulmonary vascular disease. The persistence of oxidative stress after surgery may therefore contribute to continued pulmonary hypertension and delayed postoperative adaptation.

These findings align with experimental and clinical studies demonstrating the involvement of oxidative stress in pulmonary hypertension across various etiologies. However, pediatric congenital heart disease represents a unique pathophysiological context in which chronic hypoxia, abnormal pulmonary blood flow and developmental factors converge to amplify redox imbalance. The present study extends previous observations by highlighting the relevance of oxidative stress specifically in the pediatric population and by demonstrating its association with pulmonary hemodynamic parameters.

From a clinical perspective, assessment of antioxidant defense markers may provide valuable information beyond conventional hemodynamic evaluation. Superoxide dismutase activity and total antioxidant status could serve as indicators of pulmonary vascular vulnerability and assist in identifying children at risk for persistent or progressive pulmonary hypertension. These markers may also represent potential targets for adjunctive therapeutic strategies aimed at modulating oxidative stress and improving pulmonary vascular function.

In summary, the results support the concept that oxidative stress is a key contributor to both the development and maintenance of pulmonary hypertension in children with congenital heart disease. Persistent impairment of antioxidant defense mechanisms is closely associated with pulmonary vascular involvement and may limit postoperative recovery despite surgical correction of the underlying cardiac anomaly.

5. Conclusion

Children with congenital heart disease complicated by pulmonary hypertension exhibit a persistent imbalance of oxidative stress characterized by reduced superoxide dismutase activity and diminished total antioxidant status. The association between impaired antioxidant defense and increased pulmonary artery pressure indicates that oxidative stress contributes not only to the development but also to the maintenance of pulmonary hypertension. Partial postoperative recovery of antioxidant markers does not fully restore redox balance, suggesting that pulmonary vascular pathology remains active despite surgical correction. These findings support the concept of oxidative stress as a stable pathogenic component of pulmonary hypertension in congenital heart disease. Assessment of antioxidant defense markers may enhance risk stratification and provide a pathophysiological basis for adjunctive strategies targeting oxidative stress in this vulnerable pediatric population.

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