Diagnostic Value of Soluble CD40 Ligand in Predicting Pulmonary Arterial Hypertension among Children with Congenital Heart Defects

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Abstract
Background: Pulmonary arterial hypertension (PAH) is a severe complication of congenital heart defects (CHD) with left-to-right shunt, such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Persistent shunting induces pulmonary vascular remodeling, endothelial dysfunction, and in situ thrombosis, predisposing to Eisenmenger physiology if unrepaired. Platelets contribute to PAH pathogenesis through the release of inflammatory mediators, growth factors, and soluble CD40 ligand (sCD40L), a prothrombotic and pro-inflammatory molecule mainly derived from activated platelets. Elevated sCD40L has been reported in cardiovascular disease, systemic lupus erythematosus, and idiopathic PAH, reflecting endothelial activation, leukocyte recruitment, and vascular remodeling. This research aimed to assess the value of sCD40L as a biomarker of PAH in kids with CHD and left-to-right shunt. Understanding the interplay between platelet activation, sCD40L, and pulmonary vascular pathology may provide a useful noninvasive tool for early detection, risk stratification, and therapeutic guidance in pediatric PAH-CHD, where conventional markers such as BNP and hemodynamic parameters remain limited..

Keywords: *congenital heart defects, pulmonary arterial hypertension, soluble CD40 ligand, children*

Introduction

In Egypt, congenital heart defects are frequently described in 8 of 1000 live births. Certain research estimates that ten percent of all cases with CHD develop Eisenmenger syndrome; nevertheless, these growths are as high as thirty percent in cases with unrepaired congenital defects. Pulmonary arterial hypertension is usually 2^{ry} to left-to-right shunt defects causing arterial hypertension. Common defects comprise ventricular septal defects, atrial septal defects, and persistent ductus arteriosus, with several studies finding that the size of the defects is influential in whether patients develop pulmonary arterial hypertension. More complex lesions like truncus arteriosus or atrioventricular septal defects frequently develop pulmonary arterial hypertension early in life **[1].**

Congenital Heart Defects

CHD is the most common congenital anomaly at birth, occurring in ~8/1000 live births. It includes a wide range of malformations, which may be isolated (non-syndromic) or associated with extra-cardiac abnormalities (syndromic). Advances in early interventions have reduced mortality, with >90% surviving into adulthood, though extracardiac defects may contribute to neurodevelopmental delay **[2].**

CHD is classified by structural defects, flow patterns, recurrence risks, and shared susceptibility genes.

[3]

The cause is unknown in ~85% of cases. Chromosomal aneuploidies (Down, trisomy 13/18, Turner, and DiGeorge) cause 8–10% of CHD. Single-gene defects contribute 3–5%, often syndromic (e.g., Alagille, Holt–Oram, Noonan). Environmental factors account for ~2%. Risk factors include maternal diabetes, phenylketonuria, obesity, alcohol, rubella, fever, certain drugs, and solvent exposure. Sex differences exist: ASDs and AVSDs are more common in women, while outflow tract defects are more frequent in men. **[4]**

In fetal circulation, oxygenated blood bypasses the lungs via the foramen ovale (FO) and ductus arteriosus (DA). After birth, FO and DA closure unmasks CCHD. Cyanosis results from persistent fetal circulation, right-to-left shunting, or pulmonary hypertension.
Shunt lesions: Intracardiac shunts are abnormal blood flow pathways, classified as cyanotic (reduced oxygenation) or Acyanotic (intact oxygenation) **[5].**

ASD results from abnormal atrial septum development **[6]. Types include:**
Secundum: excessive septum primum resorption; **Primum:** endocardial cushion deficiency; and **Sinus venosus:** abnormal sinus venosus incorporation. ASD prevalence is ~1.64/1000 live births; 25–30% are diagnosed in adulthood.
Pathophysiology: Left-to-right shunt predominates due to left ventricular pressure and compliance. Conditions reducing right ventricular compliance may cause bidirectional or right-to-left shunting. Shunt size also influences flow **[7].**
PAH affects ~10% of CHD patients, impairing survival and quality of life. In ASD, a chronic left-to-right shunt overloads the right heart and pulmonary artery, raising PA pressure. Hyperkinetic PAH is usually reversible after ASD closure, but ~1% progress to Eisenmenger's syndrome **[*8*].**
Premature infants with ASD have higher odds of developing PH, independent of gestational age and birth weight. PH is linked to morbidity, mortality, and right heart failure, reinforcing the need for early closure when right-sided volume overload is present. **[*9*]**

The ventricular septum forms from muscular walls, endocardial cushions, and the conus cordis, fusing at the membranous septum. Failure of fusion or persistence of fetal channels causes VSD, the most common CHD in children, accounting for >20% of malformations **[1*0*].**
Perimembranous VSDs: most common (~80%).
Muscular VSDs: the 2nd most often, may be single or multiple.
Other types: outlet (common in Asians), inlet (associated with Down syndrome), malalignment defects (e.g., TOF) **[1*1*]**
Moderate/large VSDs cause early heart failure in infants, often requiring closure. Small VSDs frequently close spontaneously but may persist into adulthood if not indicated for closure. Isolated VSDs are less common in adults.

Flow across a VSD happens in systole, determined by systemic vs. pulmonary vascular resistance and defect size. Large VSDs typically cause left-to-right shunting due to low pulmonary resistance, while small VSDs restrict flow. With suprasystemic pulmonary resistance, shunting may reverse to right-to-left regardless of defect size. Left-to-right shunting increases LV end-diastolic volume, leading to LV overload, left atrial hypertension, pulmonary congestion, and left heart failure. Pressure transmission to pulmonary vasculature accelerates pulmonary vascular disease and Eisenmenger physiology **[1*2*].**
Hemodynamically significant VSDs usually present in infancy as pulmonary resistance falls, causing worsening shunt flow. Infants develop heart failure symptoms—tachypnea, feeding intolerance, and failure to thrive **[1*3*].**

Hemodynamics depend on PDA size and resistance differences. Significant left-to-right PDA shunts cause pulmonary overcirculation, LV overload, and left heart failure. Pressure and volume load may induce pulmonary vascular disease and PAH. Eisenmenger physiology develops with suprasystemic pulmonary resistance, reversing shunt flow. Unlike VSD, PDA flow is continuous, which may lower diastolic BP, impair coronary/mesenteric perfusion, and rarely cause endarteritis or aneurysm **[14].**
Presentation varies by shunt size. Silent or small PDAs are often incidental; small PDAs may be detected by continuous murmur but rarely cause overload or PH. Larger PDAs cause LV dilation and pulmonary hypertension and may progress to Eisenmenger physiology. Right-to-left ductal shunting produces **differential cyanosis** (desaturation and clubbing in lower extremities). **[6]**
In isolated PDA, PH is influenced by ductus size and PVR. Larger PDAs cause higher left-to-right shunts and greater PH risk. PDA may produce more severe pulmonary vascular effects than VSD due to high-pressure pulsatile aortic flow into the pulmonary artery, with irreversible changes possible before age two **[15].**

Pulmonary arterial hypertension
Pulmonary hypertension (PH) in CHD often results from left-to-right shunts or left heart obstructive disease. Defects comprise VSD, ASD, and PDA. Defect size influences PAH risk; e.g., only 3% of small/moderate VSDs (≤1.5 cm) develop Eisenmenger syndrome. In children, PH differs from adults, with higher rates of IPAH, PAH-CHD, and developmental lung disease. Management is challenging due to reliance on adult-based evidence. **[16]**
Definitions
Historically, PH = mPAP ≥ 25 mmHg. In children, ≥25 millimeters of mercury following three months of age is used, with PVRI ≥3 WU·m² defining pulmonary vascular disease. The 6th WSPH redefined PH as mPAP >20 millimeters of mercury plus PVR ≥3 WU. The Pediatric Task Force endorsed this definition to harmonize pediatric and adult care [**16].**
Epidemiology
In the UK, PH prevalence = 97/million, female: male = 1.8. The US death rate ranges from 4.5 to 12.3/100,000. VSD is the most frequent underlying defect (42%), with a 3% risk of persistent PH after surgery [**17**].
Classification
WHO groups **[*18*]:** PAH, PH because of left heart disease, PH because of lung disease/hypoxia, CTEPH, and multifactorial/unclear causes (hematologic, systemic, metabolic, renal, etc.). A pediatric-specific classification also exists.
Pulmonary arterial hypertension in CHD
Estimated prevalence 4.2–28% **[*19*].**
Definition
PAH = mPAP ≥25 millimeters of mercury, PCWP ≤15 millimeters of mercury, PVR ≥3 WU [**20**]
Pathophysiology
CHD-APAH severity varies with cardiac lesion, environment, and genetics. BMPR2 and ALK-1 mutations contribute. Large unrepaired defects (>1.5 cm) inevitably develop PAH; early repair reduces risk. Post-Fontan patients may develop PH due to elevated PVR without high PAP. Pretricuspid shunts (ASD) cause low-pressure overload; only ~2% develop Eisenmenger. Post-tricuspid shunts (VSD, PDA) lead to early PAH if untreated. Eisenmenger physiology involves endothelial dysfunction, vascular remodeling, inflammation, thrombosis, and imbalance of vasodilators/vasoconstrictors **[21].**
Classification
CHD-PAH classification follows WHO PH revisions and pediatric-specific categories **[21].**
Pathogenesis
PAH involves endothelial injury, vascular remodeling, occlusion of small arteries, increased PVR/mPAP, and right ventricular failure. Systemic vascular effects are also observed. Autoimmunity, inflammation, and thrombosis further drive progression **[22].**

Etiology

Subgroups: Idiopathic PAH**,** heritable PAH (BMPR2, ALK2, ACVRL1, SMAD9, KCNK3, and CAV1 mutations)**,** drug/toxin-induced PAH, **and** PAH with small arteriole lesions (collagen vascular disease, shunts, HIV, schistosomiasis, and portopulmonary PH). PVOD and pulmonary capillary hemangiomatosis are distinct entities. Persistent pulmonary hypertension of the newborn and hemolytic anemia is reclassified **[*19*].**

Management

PAH requires multidisciplinary, individualized care **[2*3*]**.

PAH-specific therapy

First drug: IV epoprostenol (1995), targeting the prostacyclin pathway. Other therapies target NO and endothelin pathways. High-dose calcium channel blockers are effective in selected long-term responders **[*23*].**

Supportive measures

Oxygen, diuretics, vaccinations, psychological/nutritional support, and supervised exercise improve outcomes **[2*4*].**

Soluble CD40 Ligand

CD40L, a 261-amino acid type II membrane glycoprotein of the TNF family, is primarily expressed on activated CD4+ T cells and serves as an early T-cell activation marker. Its receptor, CD40, is constitutively expressed on B cells, macrophages, and dendritic cells. The CD40–CD40L pathway plays critical roles in immune regulation by enhancing antigen-specific T-cell responses, activating dendritic cells to produce IL-12, sustaining immune responses, and inducing effector functions in target cells. Engagement of CD40 on endothelial cells upregulates ICAM-1, VCAM-1, and E-selectin, promoting leukocyte adhesion. In antigen-presenting cells, CD40–CD40L signaling induces cytokines, chemokines, nitric oxide, and MMPs. Interaction with B cells promotes proliferation, isotype switching, and memory formation; absence of CD40L results in X-linked hyper-IgM syndrome with defective class switching **[2*5*].**

Regulation of CD40L expression

CD40L expression is tightly controlled. TCR ligation induces rapid upregulation, peaking at 1–2 h, with surface protein expression within 4–6 h, and decline by 16 h. This transient window allows activated T cells to provide helper signals. Co-stimulatory molecules (CD28, LFA-3, ICOS) and cytokines (IL-12, IL-2, IL-15) improve expression. Regulation occurs at transcriptional, post-transcriptional (MAP kinase–mediated mRNA stability), and post-translational levels via endocytosis or metalloproteinase cleavage, producing soluble CD40L (sCD40L). CD40L cleavage releases sCD40L (18–20 kDa homotrimers), which retains functional activity. sCD40L can activate and differentiate B cells, indicating an important role in immune regulation **[*26*].**

Value of CD40L in medical practice

Soluble CD40 Ligand in PAH

sCD40L, largely (>95%) derived from activated platelets, drives vascular inflammation, platelet–endothelial interactions, and remodeling. Elevated levels are linked with atherosclerosis, heart failure, and idiopathic PAH. In PAH, raised sCD40L correlates with IL-8, MCP-1, platelet activation markers, and prothrombin fragment F1+2, implicating it in chemokine-mediated inflammation and thrombosis. Platelet-derived CD40L promotes vasoconstriction, tissue factor expression, and thrombus stabilization, contributing to vascular remodeling. Preoperative sCD40L may serve as a biomarker for poor outcomes in CTEPH patients undergoing pulmonary endarterectomy, guiding risk stratification and management **[27].**

However, whether CD40L gives rise to not only systemic, but also pulmonary, vascular inflammation has not been determined, it was found that CD40L induced pulmonary microvascular endothelial cells to secrete inflammatory cytokines and growth factors in vitro. Furthermore, sCD40L levels are significantly higher in patients with idiopathic pulmonary arterial hypertension compared with control **[28].**

Advances in transplantation have been supported by effective immunosuppressive agents. Anti-CD40L monoclonal antibody (MAb) therapy has shown efficacy in animal models. Switching from cyclosporin A to anti-CD40L MAb was effective in monkey renal allografts, despite cyclosporin A's downregulation of CD40L. CD40L gene expression increases fourfold during acute rejection, suggesting potential use as a noninvasive biomarker for monitoring graft function and response to immunosuppressants like cyclosporin A and tacrolimus **[29].**

Active SLE patients show markedly increased CD40L expression on CD4+, CD8+ T cells, and B cells compared to controls. Plasma sCD40L is significantly elevated in active disease, correlating with SLEDAI scores and anti-dsDNA titers. Elevated sCD40L may contribute to vasculitis and nephritis and could serve as a predictive biomarker for disease flares. While CD40/CD40L is an attractive therapeutic target, systemic blockade may carry risks in long-term cardiovascular disease **[30].**

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