Role of dysregulated phospholipid metabolism in development of congenital heart diseases

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ABSTRACT
Phospholipids are major components of cell membranes with complex structures, high heterogeneity and critical biological functions and have been used since ancient times to treat cardiovascular disease.many research literatures said that dysregulated phospholipid results in congenital heart diseases . Their importance and role were shadowed by the difficulty or incomplete available research methodology to study their biological presence and functionality. This review focuses on the current knowledge about the roles of phospholipids in the pathophysiology of congenital heart diseases, which have been increasingly recognized. So screening the phospholipid levels in pregnant females becomes important to prevent and early diagnose congenital heart diseases by following special treatment strategies including nutritional support.

Prevalence of congenital heart diseases:

Congenital heart defects are the most common birth defect (**Mendis S et al.,2011**).In 2015, they were present in 48.9 million people globally **(Vos T et al.,2015)** They affect between 4 and 75 per 1,000 live births, depending upon how they are diagnosed(**Milunsky A et al.,2011**) In about 6 to 19 per 1,000 they cause a moderate to severe degree of problems. Congenital heart defects are the leading cause of birth defect-related deaths in 2015(**Mendis S et al.,2011**), they resulted in 303,300 deaths, down from 366,000 deaths in 1990**(Wang Het al.,2015)**The cause of a congenital heart defect is often unknown.**(2011)** Risk factors include certain infections during pregnancy such as rubella, use of certain medications or drugs such as alcohol or tobacco, parents being closely related, or poor nutritional status or obesity in the mother**(Dean SV et al.,2014)** Having a parent with a congenital heart defect is also a risk factor (**MilunskyA et al.,2011**).

Types of congenital heart diseases:

There are different types of CHDs the most common are Atrial Septal Defect Asymptomatic (ASD) are possibly closed when the kids have got the age of 3–5 years. A significant ASD causes a left to right by-pass causing capacity overload, expansion of the right atrium and ventricle and changed myocardial structure and function. Preterm kids may be three times as common between kids with percutaneous method closure than in the overall population**(Tanghöj G. et al.,2017)**

The myocardium of the preterm kid has permanent morphological and total structural changes. Even long after the neonatal period and into later life, the morphology of both the ventricles as well as the role is decreased or changed. Improvements in perinatal care over the previous 30 years have led to important improvements in survival rates as in **(fig.1) (Mohlkert LA.et al.,2018 and Khaled A.et al.,2024).**
Ventricular septal defect (VSD) is the most public congenital heart deformity, which occuring in 20%-42.86% of all congenital heart deformities (CHD). The occurrence of VSD is around 1.35 to 17.3 per 1000 live births. Some of these deformities can close naturally, or reduce without surgical involvement **(Zhao QM.et al.,2013)** However, some patients will suffer from difficulties such as growth delay, frequent infections, congestive heart failure, and even unexpected death. **(fig.1)**
Atrioventricular Septal Defect it is a congenital cardiac malformation that is characterized by a variable degree of the atrial and ventricular septal defect along with a common or partially separate atrioventricular orifice **(Jacobs JP et al.,2000)** A partial atrioventricular septal defect is characterized by an ostium primum atrial septal defect, separate atrioventricular valves with a common junction, an inlet ventricular septal defect, and a cleft mitral valve. Whereas the complete form of the atrioventricular septal defect (AVSD) is characterized by a common atrioventricular valve with ostium primum atrial septal defect and an unrestricted ventricular septal defect of inlet type.**(Calabrò R, Limongelli G. .,2006)**.

Patent ductus arteriosus it is a fetal vessel that allows the oxygenated blood from the placenta to bypass the lungs in utero. At birth, the lungs fill with air with the first breaths, pulmonary vascular resistance drops, and blood flows from the right ventricle to the lungs for oxygenation. The increased arterial oxygen tension and the decreased flow through the ductus arteriosus allow the ductus to constrict. The ductus arteriosus is functionally closed by 12 to 24 hours of age in healthy, full-term newborns. Permanent (anatomic) closure is complete within 2 to 3 weeks. In the premature infant, the ductus arteriosus does not close rapidly and may require pharmacologic or surgical closure to treat side effects **(Fink D et al.,2018)**
Classic **tetralogy of Fallot (TOF)** is a congenital heart defect (CHD) that is comprised of 4 anatomical alterations **(as in fig. 1)**: a large, anteriorly malaligned ventricular septal defect (VSD), an overriding aorta which results in infundibular (ie, sub-pulmonary) right ventricular outflow tract obstruction (RVOTO), and consequent right ventricular hypertrophy secondary to chronic systemic pressures. The pulmonary valve annulus is often hypoplastic, with a pulmonary valve that is dysplastic and stenotic. The VSD is most frequently located in the perimembranous septum; however, the defect can extend to the muscular septum, and infrequently, there might be additional muscular VSDs. **(Barron DJ. ., 2013)**.

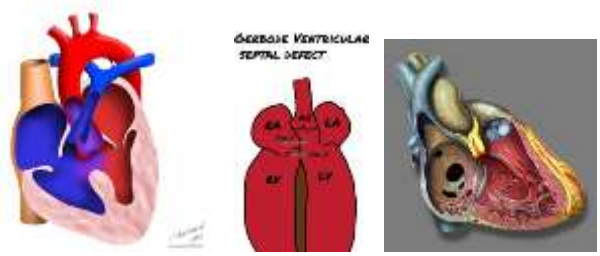

Figure1:TOF(Frank G.,2005),VSD(Wael D.et al.,2024),ASD(Dinsmore R.et al.,1985)

Coarctation of the Aorta it is a congenital cardiovascular anomaly characterized by a narrowing of the aortic lumen, typically located just distal to the origin of the left subclavian artery at the site of the ductus arteriosus. This condition results in a significant obstruction in blood flow, leading to increased pressure proximal to the constriction and reduced distal perfusion. Coarctation of the aorta presents with a broad spectrum of clinical manifestations, ranging from asymptomatic hypertension to life-threatening heart failure in infancy **(Beckmann E, Jassar AS.,. 2018)**.
Less common types are : Double-outlet Right Ventricle, d-Transposition of the Great Arteries,Ebstein Anomaly ,Hypoplastic Left Heart Syndrome, Interrupted Aortic Arch ,Pulmonary Atresia, Single Ventricle, Total Anomalous Pulmonary Venous Return ,Tricuspid Atresia, Truncus Arteriosus , (**Patel SS et al., 2018 and Sandy A.et al .,2024).**

Phospholipid metabolism:

Phospholipids are a class of lipids that form major component of all cell membranes. The phospholipid molecule comprises of a glycerol backbone with two fatty acids i.e. a saturated fatty acid at the sn1 position and an unsaturated fatty acid at the sn2 position. Further, a phosphate group is attached to the organic functional group **(Bartel J et al.,2001)** Phospholipids are divided into two broad categories based on the alcohol present in their backbone **(Mashaghi S.et al.,2013)**. These are:Glycerophospholipids and Sphingophospholipids.Both of them are present in the cellular membranes and perform important functions, essential for the maintenance of life **(Campbell et al.,2006)**.

Glycerophospholipids

Glycerophospholipids are derived from glycerol-3-phosphate in a de novo pathway **Hishikawa et al.,2014)** The term glycerophospholipid signifies any derivative of glycerophosphoric acid that contains at least one *O*-acyl, or *O*-alkyl, or *O*-alk-1'-enyl residue attached to the glycerol moiety **(IUPAC,.1997)** The phosphate group forms an ester linkage to the glycerol

Phosphatidic acid (PA)

The chemical structure of PA consists of a glycerol backbone, two hydrophobic fatty acid side chains, and a negatively charged phosphoric acid head.itcan be synthesized de novo via two different acylation pathways named after their respective precursor, namely the glycerol 3-phosphate (G3P) pathway and the dihydroxyacetone phosphate (DHAP) pathway. In the G3P pathway, G3P is first acylated by G3P acyltransferase to form 1-acyl-G3P (also known as lysoPA; LPA) **(Maraschin F. et al.,2019)** In the DHAP pathway, after the synthesis of 1-acyl-DHAP from DHAP by DHAP acyltransferase, this product is converted to LPA via an NADPH-dependent reduction reaction **(Kim SC & Wang X .,2020)**. Once LPA is formed through either of the two pathways, it is eventually acylated to PA by LPA acyltransferase (LPAAT). The G3P pathway is the universal route of the formation of PA in prokaryotes, plants, yeast, and mammals, whereas the DHAP pathway is only present in yeast and mammals **(Kim SC & Wang X .,2020)**. Having understood the structure of phosphatidic acid, it will easier for us now to have a look at the structure of various glycerophospholipids.

Phosphatidyl alcohol

Many glycerophospholipids simply contain an alcohol esterified to the phosphate group attached to the 3rd carbon of glycerol. These phospholipids are given names by simply adding the name of alcohol after the prefix ‘phosphatidyl’. This prefix represents the presence of phosphatidic acid in the structure of the compound.

Examples of such lipids are as follows:Phosphatidylserine**(Prinz et al.,2017)** which contains serine alcohol attached to phosphatidic acid,Phosphatidylethanolamine which has ethanolamine attached to phosphatidic acid,Phosphatidylcholine which this phospholipid, the alcohol is choline,Phosphatidylinositol: in which inositol is the alcohol in this phospholipid and Phosphatidylglycerol which has a second molecule of glycerol attached to the phosphate group **(M. Narváez et al.,2016)**

Cardiolipin

Cardiolipin is a non-bilayer-forming phospholipid with a specific structure consisting of two diacylated phosphatidyl groups linked by a glycerol bridge **(Iyer SS et al., 2013).**

Synthesis of Cardiolipin:

the first step in the CL biosynthetic pathway is the conversion of phosphatidic acid (PA) to CDP-diacylglycerol (CDP-DAG), which is catalyzed in the inner membrane by CDP-DAG synthase encoded by *TAM41* **(Tamura Y et al.,2013)**in yeast. *PGS1* encoded phosphatidylglycerolphosphate synthase catalyzes transfer of the phosphatidyl group from CDP-DAG to a glycerol-3-phosphate molecule to generate phosphatidylglycerolphosphate (PGP) **(Chang S et al.,1998)** PGP is subsequently dephosphorylated to phosphatidylglycerol (PG) by PGP phosphatase **(van den et al.,1972)**encoded by *PTPMT1* in mammals **(Zhang J et al .,2011)**and *GEP4* in yeast **(Osman C. et al.,2010)**The final step in the biosynthetic pathway is carried out by CL synthase, encoded by *hCLS1* in human cells **(Chen D et al.,2006)**and by *CRD1* in yeast **(Tuller G.et al.,1998)** In this step, a second phosphatidyl group is added to PG from another CDP-DAG molecule, generating unremodeled CL **(Hostetler K et al.,1972)**,**as in fig.2.**

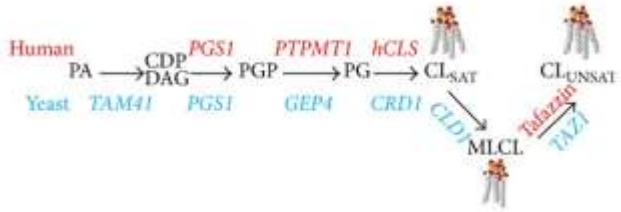

Figure 2: synthesis of cardiolipin(Zheni Shen,et al., August 2015)

Plasmalogens

Plasmalogens are plasmenyls (alkenyl moiety with vinyl ether linkage at sn-1)with an ester (acyl group) linked lipid at the sn-2 position of the glycerol backbone, **(Wallner S, Schmitz G .,2011).** Plasmalogens are classified according to their head group, mainly as PC plasmalogens (plasmenylcholines) and PE plasmalogens (plasmenylethalomines) **(Maeba R. et al.,2015).**

Sphingophospholipids

Sphingolipids are a class of amphipathic lipids which share a sphingoid base backbone that is N-acylated with various fatty acid chains. This group includes lipids such as sphingosine, ceramide, S1P, ceramide-1-phosphate (C1P), and sphingomyelin (SM). Sphingolipids can be divided into three structural classes—sphingoid bases and derivatives, ceramides, and complex sphingolipids—in which sphingoid bases act as the structural foundation for all sphingolipid derivatives (**Schnaar R.** et al.,2015). Sphingomyelin consists generally of a sphingosine base with an 18-carbon chain and a double bond at position 4, attached to a phosphorylcholine fatty acid. The fatty acid chains are generally long and saturated or monounsaturated. In bovine brain SM the most abundant fatty acid chains are 18:0 (42%) and 24:0 (27%), whereas in egg SM the dominant fatty acid is 16:0 (66%) followed by 18:0 (10%)**(Ramstedt et al.,1999)**.

phospholipid arrangement in cell membranes:

In biological membranes, the phospholipids often occur with other molecules (e.g., proteins, glycolipids, sterols) in a bilayer such as a cell membrane **(Campbell et al.,2006)**.Lipid bilayers occur when hydrophobic tails line up against one another, forming a membrane of hydrophilic heads on both sides facing the water as seen in **fig3. (Alberts et al ., 2002)**

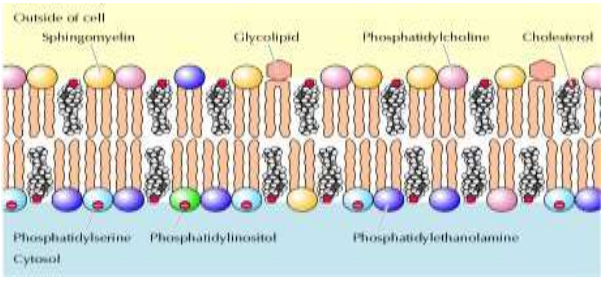

Figure 3: phospholipid arrangement in cell membranes (Geoffrey M. Cooper.S. ., 2000)

Role of phospholipid in cardiovascular diseases:

studies have informed that the phospholipids have a valued and significant role in the pathogenesis and prognosis of congenital heart illness with right or left ventricular capacity or pressure overload as in ASD, VSD or PDA. Cell-specific targeting of phospholipid biosynthetic pathways could work for a significant approach for helping in treatment of congenital heart illnesses **(Ferrari R.et al.,2004)**.It was observed that there is an obvious reduction in the plasma lecithin, cephalin, sphingomyelin and other phospholipids levels in CHD cases in contrast to normal kids and it was established that the findings of this study show that the phospholipids and the Lcarnitine levels have a valued and significant role in the pathogenesis and prognosis of congenital heart illness with right or left ventricular size or pressure overload as in ASD or VSD. Cellspecific targeting of phospholipid biosynthetic paths could help as a potential strategy for helping in treatment of congenital heart illnesses **(Farouk A et al.,2018)** so we can mention examples of different types of phospholipids and their role in congenital heart diseases:

Lecithin, a vital component derived from both plant and animal sources **(Tanno H ,2012**), is a natural amalgamation of diglycerides comprising palmitic, stearic, with oleic acids joined with the choline ester of phosphoric acid **(Wendel A ,1995)**. It is a compound found naturally in various tissues of animals and plants, including egg yolks, soybeans and peanuts. Simple oil from soybeans contains 2 to 3 percent lecithin, and significant quantities can also be found in whey and corn oil **(2015).** It is a complex mixture of phospholipids, triglycerides and glycolipids. Phospholipids are the primary component of lecithin and are responsible for its unique properties. Notably, it is ubiquitous on the outermost layer of plasma membranes **(Nichols BJ et al.,2001)** and has been identified as a substantial phospholipid in amniotic fluid and lung surfactant (**William Taeusch H et al.,1999**).

Lecithin offers potential health benefits, including cognitive enhancement through its choline content **(Canty D,1994)**,and potential cardiovascular improvements by lowering cholesterol levels **(Mourad AM et al.,2010).**

Cardiovascular diseases (CVD) encompass a variety of disarrangements acting on the blood vessels and the heart. Prominent types of CVD consist of atherosclerosis, coronary artery disease, arrhythmias and heart failure

(World Health Organization ,2022). These conditions contribute to the global burden of CVD-related morbidity and mortality(**American Heart Association, 2023)**.

Lecithin has the ability to reduce excess low-density lipoproteins (LDL) while specifically promoting the synthesis of high-density lipoprotein (HDL) particles, thus contributing to clearer understanding of its role in cardiovascular well-being. Emphasizing the importance of lecithin cholesterol acyltransferase (LCAT) in the reverse cholesterol transport (RCT) process, and contribute to remove surplus cholesterol from cells.

Phosphatidic acid (PA) and its lysoform lysophosphatidic acid (LPA) are bioactive phospholipids, involved in the regulation of various cellular responses, by acting on its specific G-protein coupled transmembrane receptors. PA is mainly formed by hydrolysis of phosphatidylcholine after the activation of phospholipase D (PLD). LPA is secreted by several cell types, such as platelets, fibroblasts, adipocytes and cancer cells and can be found in several biological fluids, such as serum, plasma and aqueous humor **(Cao, Y. et al.,2019).** LPA is involved in many chronic inflammatory diseases **(Magkrioti C.et al., 2019)**and cancers **(Tabuchi S., 2015).** In mice, LPA is increased in peripheral blood in the early stages after MI, while its receptor LPA2 expression increases in the heart, promoting angiogenesis **(Pei J.et al.,2022)**, and also in in vitro stimulation of myocardial cell proliferation through LPAR3 **(Wang F.et al.,2020).**

Sphingomyelin (SM) is one of the main sphingolipids located in the membrane that is involved in cell apoptosis and cell migration. SM supports brain myelination and helps regulate chromatin function; therefore, alteration of SM can cause severe neurological diseases **(Signorelli P. et al.,2021)**. In the heart, SM was linked to an increased probability of developing coronary heart disease **(Pongrac et al.,2020)**and heart failure **(Stenemo M. et al.,2019).** Sphingomyelin phosphodiesterase 1 (SMPD1) is the key enzyme that produces about 70% of total cellular ceramides in the heart, converting sphingomyelins to the pro-inflammatory and pro-apoptotic second messenger ceramides **(Opreanu M.et al.,2011)**.

Ceramides (Cer) are another group of sphingolipids, which have a lesser structural role, but interfere with numerous basic physiological functions of the cells, such as cell growth, differentiation, senescence and apoptosis **(Hannun Y.A.et al.,2008**). Similar to other sphingolipids, Cer are important in numerous pathologies, such as cancer **(Huang W.C.**et **al.,2011)**neurodegeneration **(Zhao L.,et al.,2011)**, inflammatory/autoimmune diseases **(Pfeilschifter J et al.,1998**), diabetes **(Holland W.L. et al., 2011)**and atherosclerosis **(Li Z.et al.,2005)** Besides their role in atherosclerosis and valvular diseases **(Zietzer A. et al.,2022)**, Cer levels were found to be significantly increased in patients with left ventricle chronic ischemia **(Shu H.et al.,2022)**, correlating with plaque rupture and the severity of coronary artery stenosis in patients with acute myocardial infarction **(Pan W.et al.,2020).**

Cardiolipin (CL) is a form of diphosphatidylglycerol located exclusively in the inner membrane of mitochondria, where it constitutes about 20% of the total lipid composition, activating numerous enzymes involved in mitochondrial bioenergetic metabolism **(Paradies G.et l.,2019)** Alterations in CL biosynthesis and homeostasis have been linked to numerous inherited disorders, such as Senger syndrome **(Haghighi A. et al.,2019)**. In the heart, ischemia/reperfusion injury and heart failure are associated with significant changes in the cardiolipin mitochondrial content **(Dudek J. et al.,2011).**

Many mitochondrial functions are strongly associated to mitochondrial membranes. The outer membrane (OM) plays a role in connecting the mitochondrion to different organelles in the cell, including the sarco- or endoplasmic reticulum (SR/ER), the lysosome, and the plasma membrane (**D.E. Copeland et al.,1959**). These contacts are important for interorganellar communication and allow for exchanging lipids and small solutes between organelles **(T. Tatsuta, T. Langer.,2016)**. The inner mitochondrial (IM) separates two compartments, the intermembrane space (IMS) from the matrix compartment. Invaginations of the IM form cristae structures, which harbor the respiratory chain and are crucial for the energy conversion by oxidative phosphorylation. The IM also forms the inner boundary membrane where the IM is in close opposition to the OM, which are the sites of protein import from the cytosol. Mitochondrial membranes are characterized by a unique phospholipid pool containing the dimeric phospholipid cardiolipin (CL) as in (**fig.4**), which is specific to mitochondrial membranes as shown in fig.3. CL contains two phosphatidylglyceride backbone molecules and therefore binds four fatty acids. Different fatty acids bound to all four positions give rise to a highly diversified CL pool in most mammalian tissues **(J.J. Maguire et al.,2016)**. In contrast, the mammalian heart has a very defined CL species composition, with linoleic acid (18:2) being the predominant form for all four acyl chains bound to CL**(F. Hoch,1992)**. CL is involved in many essential functions linked to mitochondrial membranes including mitochondrial morphology, mitochondrial metabolism, and respiration. Accordingly, defects in the biosynthesis and remodeling of CL have been linked with different types of congenital heart disease.

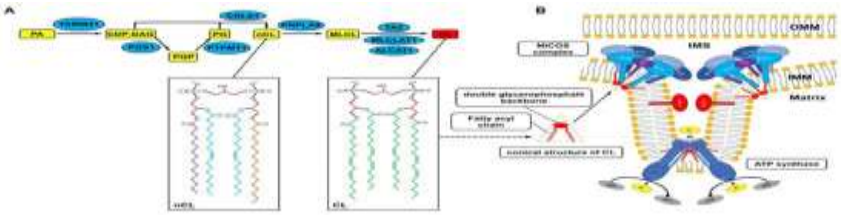

Figure 4: cardiolipin in the inner mitochondrial membrane (Zhitong J et al.,2022)

Role of cardiolipin in genetic diseases

Tangier disease (TD) is a genetic disorder of cholesterol efflux and lipid metabolism characterized by a nearly complete absence of plasma high-density lipoproteins (HDLs), atherosclerosis, peripheral neuropathy, and an increased risk for developing CVD **(Fredrickson D. S., 1964).**. The genetic cause of TD is the mutation of the ABCA1 gene, which is located on chromosome 9 **(Rust S. et al.,1999)**. ABCA1 encodes a highly conserved ATP-binding cassette transporter. The ABCA

subfamily of ABC transporters is involved in lipoprotein metabolism and lipid transport across the plasma membrane **(Knight B. L. .,2004) ..** Researchers propose that a physical interaction between apoA-I and ABCA1 results in the formation of a phospholipid-apoA-I complex that promotes cholesterol efflux **(Wang N. et al.,2001)**. Three phospholipids, including CL, lysoCL 1, and 2 (LC_1 and LC_2), which together contribute only a small fraction of the total cellular phospholipid content, were found to be enriched up to fivefold in TD fibroblasts compared to wild type cells **(Fobker M. et al.,2001)**This finding suggests that phospholipid and cholesterol efflux may be coregulated and, therefore, dually impaired in TD cells. Additionally, it is possible

Heart failure (HF) results from inability of the heart to pump blood with normal efficiency, resulting in edema, shortness of breath, and lack of energy. HF is usually the end stage of CVD, including cardiomyopathy, heart attack, cardiac valvular disease, atrial fibrillation, and high blood pressure **(McMurray J. et al.,2005)**. In both the spontaneously hypertensive HF rat model (SHHF) and human HF patients, decreased tafazzin mRNA levels were observed, concomitant with compensatory increases in the activity of phosphatidylglycerolphosphate synthase and MLCL acyltransferase **(Saini-Chohan H. et al.,2009)**However, studies of the CL profile in HF are controversial. While most studies report a significant reduction of total CL and L4-CL in human HF and in the rat HF model **(Sparagna G et al.,2007)**one study reported an unchanged CL profile in a rat model with intracoronary microembolization-induced HF **(Rosca M. et al.,2011)**. It is likely that different HF pathogenesis mechanisms lead to varying degrees of CL profile change and mitochondrial damage.that increased CL may play an as yet uncharacterized regulatory role in cholesterol trafficking and efflux.

Myocardial composition of phospholipids:

Phospholipid content and fatty acid composition of human heart were determined on 36 biopsy specimens collected during open heart surgery. The main phospholipid classes, phosphatidylcholine (PC), phosphatidylethanolamine (PE), diphosphatidylglycerol (DPG), and sphingomyelin (SPH) were separated by HPLC, quantified, and converted to fatty acid methyl esters which were chromatographed on capillary GLC columns. Sex and age (mainly 40–70) of patients had no significant influence on the relative distribution of phospholipid classes and only a slight effect on fatty acid composition. Incorporation of trans 18:1 in phospholipid classes was low.cis and trans octadecenoic isomers seemed to be selectively incorporated, the Δ9 and Δ11cis or trans isomers being predominant(**McMurchieet al.,1988)**.

Samples of myocardial tissue were obtained during cardiac surgery from children operated for different types of normoxemic and hypoxemic congenital heart diseases. The phospholipid composition was analyzed by thin layer chromatography. The concentration of total phospholipids (PL), phosphatidylcholine and phosphatidylethanolamine (PE) was found lower in atrial tissue of both normoxemic and hypoxemic groups in comparison with the ventricles. When comparing the difference between hypoxemic and normoxemic defects, hypoxemia was found to increase the concentration of total PL, PE and phosphatidylserine in ventricles and total PL and PE in the atria. The increased level of particular phospholipid species may represent adaptive mechanisms to hypoxemia in children with congenital heart diseases.

Studies demonstrated that the concentration of total PL is significantly higher in ventricles as compared with atria. This is due to the higher concentration of major phospholipids PC and PE, which reflects the higher content of intracellular

membranes in ventricles. As the ratio of major phospholipids to mitochondrial DPG is similar in ventricles and atria, the higher total phospholipid concentration observed in ventricles is supposed to reflect the higher content of mitochondrial membranes. Moreover, higher activities of aerobic enzymes were found in ventricles in comparison with atria **(Bass A. et al., 1988)**. The concentration of PL that we found in children heart was higher in comparison with values reported in adult human heart **(Skuladottir et al., 1988).**

Role of different metabolites in CHD:

On metabolomic analysis, CHD patients showed significant differences in the concentrations of a significant number of metabolites. Differences between CHD and controls were greater in number and degree than those between different CHD aetiologies. A specific group of metabolites containing amino acids and their metabolites (those of the arginine metabolic pathway including betaine, dehydroepiandrosterone, cystine, 1-methylhistidine, serotonin and bile acids) were associated with negative clinical outcomes across all anatomic CHD subgroups. **(Cedars, A.et al.,2021)**

A similar metabolomics study showed that the blood amino acid and choline metabolite levels in CHD patients were significantly different in comparison with healthy control children. In particular, four metabolites, betaine, taurine, glutamine, and phenylalanine, could be used as potential biomarkers in the screening and diagnosis of CHD**(Yu, M et al.,2018 and Ahmed M. et al.,2021).**

In VSD ,blood samples and thymus tissue collected from patients with ventricular septal defect underwent liquid chromatography-mass spectrometry-based metabolomics. This showed that two metabolites, uric acid and sphingomyelin, were increased in the serum of these patients **(Pages C. et al.,2001)**

TOF, Metabolomic analysis performed using right atrial biopsy samples in patients with TOF discovered that carbohydrate and heme metabolism were upregulated, whereas bile acid metabolism, lipid droplet, and lipid binding were downregulated**(Liu, J. et al.,2022).**

Barth syndrome typically includes cardiomyopathy, skeletal myopathy, neutropenia, growth retardation, and 3-methylglutaconic aciduria, and it is commonly associated with mutations in the tafazzin *(*TAZ*)* gene, whose products are homologous to phospholipid acyltransferases. However, clinical features of BTHS have also been found in patients with normal TAZgene **(R.I. Kelley et al).**

Cardiolipin, the specific lipid found only in mitochondria, was decreased in all tissues from BTHS patients, whereas concentrations of other phospholipids were normal. The molecular composition of cardiolipin was altered in all tissues from BTHS patients. The molecular compositions of phosphatidylcholine and phosphatidylethanolamine were altered in the heart **(P.G. Barth et al).**

Conclusion: Dysregulation of phospholipids levels especially cardiolipin results in congenital heart diseases.

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