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Original Article

High Sensitivity C-Reactive Protein Level in Children with Congenital Heart Disease: A Single Center Study

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Abstract:
Background: The high sensitivity C-reactive protein (Hs-CRP) is a sensitive acute phase reactant. Hypoxia and asphyxia are known to increase Hs-CRP level. The impact of cyanosis in children with congenital heart disease (CHD) on Hs-CRP values is not known.
Aim of the work: to study the effect of cyanosis in children with cyanotic CHD on level of Hs-CRP compared to apparently healthy children.
Subjects and Methods: This cross-sectional case-control study included 30 children with CHD as a study group (13 cyanotic and 17 acyanotic) and 30 healthy age and sex matched children as a control group. The study was conducted at the Pediatric Cardiology Clinic, Cairo University Children Hospital, Cairo University Hospitals. All underwent measurement of Hs-CRP using immunoassay technique on COBAS 6000.
Results: The mean ± SD age of the included children with CHD and control group was 29.37±37.52 months and 32.60±29.98 months (p=0.097). Females and males comprised 14 (46.7%) and 16(53.3%) of the CHD group and 16 (53.3%) %) and 14 (46.7%) of the control group (p=0.870). The mean ± SD age of acyanotic CHD and oxygen saturation (SpO2) were 55.82 ± 37.51 months and 98.76 ± 0.83% compared to 66.38 ±42.55 months and 87.92 ± 3.76% of the cyanotic CHD (p=0.09), (p=0.51) and (p=0.02) respectively. The mean ± SD Hs-CRP among those with cyanotic, acyanotic and control group was 1.72±3.2, 1.38±2.03 and 0.73±0.41 respectively (p=0.225). The level of Hs-CRP did not correlate with age, birth weight, heart rate, respiratory rate, SpO_2, weight percentile, height percentile, hemoglobin level, total leucocytic level, pulmonary artery pressure, ejection fraction (EF), or fractional shortening (FS).
Conclusion: Hs-CRP level is not influenced by the underlying CHD whether cyanotic or acyanotic. Hs-CRP diagnostic value is not confounded by cyanosis or SpO_2 in children with CHD. The Hs-CRP normal values for healthy children applies to those with CHD whether cyanotic or acyanotic.

Keywords: Acute phase reactant; children; congenital heart disease; cyanotic; cyanosis; Hs-CRP; high sensitivity C-reactive protein
Abbreviations: AHA: American Heart Association; ASD: atrial septal defect; CHD: congenital heart disease; CRP: C-reactive protein; EF: ejection fraction; FS: fractional shortening; Hs-CRP: high sensitivity C- reactive protein; SpO_2: oxygen saturation; TLC: Total leucocytic count.

Introduction

Congenital heart disease (CHD) is an important contributor to morbidity and mortality in children. CHD global burden has raised unique challenges to the healthcare system. The prevalence of CHD is estimated to be 9.4 per 1000 worldwide (*1*). The most common CHDs diagnosed in infancy are muscular and peri-membranous ventricular septal defects followed by secundum atrial septal defects, with a total prevalence of 48.4 in 10,000 live births. The most common cyanotic CHD is tetralogy of Fallot, which is twice as prevalent as transposition of the great arteries. Overall, bicuspid aortic valves are the most common congenital defects, with a reported prevalence as high as 0.5% to 2.0% (*2*). Children with CHD are prone to complications and infections.

High sensitivity C-reactive protein (Hs-CRP) is an acute-phase reactant protein produced in the liver as part of the body's natural inflammatory response. High Hs-CRP concentrations

indicate more serious inflammation. Traditional plasma CRP measurement is a useful non-specific indicator of inflammation and detects infections as it has high detection limits. Hs-CRP has been shown to be more sensitive than the standard CRP tests as it detects very low concentrations of CRP (*3*)**.** The Hs-CRP is not specific for infection, it is elevated in other conditions, such as asthma, migraine, diabetes, and metabolic syndrome. All are thought to influence the levels of systemic inflammation identified by Hs-CRP tests. Therapeutic hypothermia, asphyxia and hypoxia were also reported to be associated with elevation of Hs-CRP (*4*). Therefore, other tests and visible symptoms indicative of each of these conditions should be considered in cases of elevated Hs-CRP results (*5*). Among adults the Hs-CRP is used for cardiac risk stratification according to the CDC and American Heart Association (AHA) classification of coronary heart disease. Hs-CRP levels less than 1 mg/dL are considered low risk. Levels between 1 mg/dL and 3 mg/dL are considered a moderate risk, and a level greater than 3 mg/dL is considered high risk for the development of cardiovascular disease (*6*, *7*). It was reported that higher Hs-CRP was associated with higher risk of cardiovascular events and mortality in adults with congenital heart diseases. These findings suggest that chronic inflammation may contribute to the pathophysiology of deterioration in adult CHD, as Hs-CRP is a sensitive marker of systemic inflammation, but no similar studies were done in children (*8*). The Hs-CRP carries prognostic increment of risk of death or heart failure. The increase in Hs-CRP prior to the occurrence of heart failure or death, support the role of inflammation in the clinical deterioration of patients with adult CHD (*9*). As no previous studies assessed the effect of cyanosis in cyanotic CHD on level of Hs-CRP in children compared to apparently healthy children, we aimed to fill the gap of knowledge.

Subjects and Methods

This current cross-sectional case control study was conducted between November 2023 and May 2024 at the Pediatric Cardiology Unit, Department of Pediatrics, Cairo University Pediatric Hospitals and at the of Department of Clinical and Chemical Pathology, Cairo University Hospitals Kasr Alainy. The parents of all enrolled children gave informed consent prior to the study entry and the study was conducted after approval of Ethical Committee of the Faculty of Medicine, Cairo University, Egypt MS-239-2023).

Participants

Thirty children with confirmed CHD both cyanotic and acyanotic aged one month to 14 years were included in this study and 30 apparently healthy age and sex matched children. Patients with chronic diseases that may affect level of Hs-CRP e.g. bronchial asthma, diabetic nephropathy, acute/ chronic infection and acute heart failure were excluded. Those with CHD were divided into two sub-groups, cyanotic (number= 13) and acyanotic (numbe*r*= 17), based on clinical and echocardiography studies.

Methods

All participants were subjected to full history taking and complete physical examination including anthropometric evaluation and vital signs assessment. CHD diagnosis was confirmed by echocardiography (Sonoscape S6, Sonosite, INDIA). Biochemical analysis of Hs-CRP and complete blood count (CBC) were done for all participants, using 8 cm of venous blood withdrawn from both the cases and the control group. It was divided into 2 tubes, 4 cm of blood was drawn into red topped tube for Hs-CRP, and 4 cm of blood was drawn into an EDTA tube for CBC and immediately sent to the laboratory. CBC was done immediately on Backman Coulter Analyzer (DHX 800 Hematology Analyzer, Backman Coulter, Japan). The blood samples for Hs-CRP were centrifuged to separate serums at 2000 RPM for 5 min. Serums were stored at −20°C in labeled Eppendorf tubes until Hs-CRP analysis. Care was given in choosing samples without hemolysis and that were not lipemic. When the targeted number of samples were obtained, all samples were allowed to come to room temperature (15–18°C) while carefully turned to mix their contents. To avoid possible divergence, all samples were analyzed the same day by nephelometric method on COBAS 6000 (Roche Diagnostics, Hoffmann, Swiss Multinational Holding Healthcare Company, Switzerland) in Chemical and Chemical Pathology laboratory, Kasr Al Aini, Cairo University, Egypt.

Statistical Analysis

Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies and

relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables. Chi square ($\chi 2$) test was performed to compare categorical data. Exact Fischer test was used instead when the expected frequency was less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered statistically significant.

Results

Table 1. Demographic and clinical presentation of the studied children

	CHD (Number=30)		Acyanotic CHD (Number= 17)		Cyanotic CHD (Number= 13)		Control (Number= 30)		P value
	N	%	N	%	N	%	N	%	
Sex									
Females	14	46.7	7	50	7	50	16	53.3	0.870
Males	16	53.3	10	62.5	6	37.55	14	46.7	
Family History									
Consanguinity	7	23.3	3	42.85	4	57.14	0	0	0.788
Similar Condition	3	10.0	2	66.66	1	33.33	0	0	
Sudden death	2	6.7	1	50	1	50	0	0	
Age in months									
Mean ± SD	29.37±37.52		55.82 ± 37.51		66.38 ± 42.55		32.60±29.98		0.09
Range	1-120		1 – 119		8 – 120		3-144		
Weight Z-score									
Mean ± SD	10.87±7.82		15.21 ± 8.54		14.07 ± 8.82		21.53±9.33		0.017
Range	3.30-30		3.3 - 29.24		4.06 – 30		5.50-40		
Height Z-score									
Mean ± SD	81.20±29.04		83.53 ± 23.13		77 ± 32.49		117.67±21.94		<0.001
Range	50-150		52 – 132		50 – 150		65-152		
Oxygen Saturation									
Mean ± SD	98.83 ± 0.79		98.76 ± 0.83		87.92 ± 3.76		98.7 ± 0.65		0.02
Range	98 - 100		98 – 100		78-90		98 - 100		
Diagnosis									
VSD	10	33.3	5	50	5	50	0	0	0.685
TA	1	3.3	1	100	0	0	0	0	
PS	2	6.7	2	100	0	0	0	0	
Fallot	5	16.7	2	40	3	60	0	0	
Double Chamber RV	1	3.3	1	100	0	0	0	0	
DORV	1	3.3	1	100	0	0	0	0	
D-TGA	1	3.3	0	0	1	100	0	0	
COA	1	3.3	0	0	1	100	0	0	
CCTGA	1	3.3	0	0	1	100	0	0	
CAVC	1	3.3	1	100	0	0	0	0	
ASD	5	16.7	3	60	2	40	0	0	
AS	1	3.3	1	100	0	0	0	0	
Complications	10	33.33	6	60	4	4	0	0	1
Hospital Admissions									
Yes	1	3.3	1	100	0	0	0	0	1
No	29	96.7	16	55.17	13	44.82	30	100	
Heart Failure	30	100	17	56.66	13	43.33	0	0	---
Pulmonary Hypertension	12	40	6	50	6	50	0	0	0.547
Medications	12	40	7	58.33	5	41.66	0	0	1

ASD: Atrial septal defect; AS: aortic stenosis; CCTGA: Congenitally corrected transposition of great arteries; COA: Coarctation of aorta; DORV: doble outlet right ventricle; D-TGA :D-transposition of great arteries; PS: pulmonary stenosis; RV: right ventricle :TA: tricuspid atresia; VSD: ventricular septal defect.

The mean ± SD age of the 30 children with CHD and control group were 29.37±37.52 months and 32.60±29.98 months (p=0.097). Females and males comprised 14 (46.7%) and 16 (53.3%) of the CHD group and 16 (53.3%) %) and 14 (46.7%) of the control group (p=0.870). The mean ± SD age, disease duration and oxygen saturation (SpO2) of acyanotic CHD were 55.82 ± 37.51 months, 29.5±37.7 months and 87.92 ± 3.76 and compared to 66.38 ± 42.55months, 27.5±35.7

months and 98.92 ± 0.76% of the cyanotic CHD (p=0.09), (p=0.51) and (p=0.02) respectively. (Table 1).

The mean ± SD age of the 17 children with acyanotic CHD and 13 children with cyanotic CHD was 55.82 ± 37.51 months and 66.38 ± 42.55 months (p=0.09). 14 (46.7%) and 16(53.3%) of the CHD group and 16 (53.3%) %) and 14 (46.7%) of the control group (p=0.870). The history, clinical picture, anthropometric measurements, and diagnosis are presented in Table 1. The laboratory data including the Hs-CRP of both groups are summarized in Table 2. There was no significant correlation between Hs-CRP and the studied parameters (age, birth weight, heart rate, RR, SPO_2, weight z-score, height z-score, HB level, TLC level, pulmonary artery pressure, EF and FS. (Table 3).

Table 2. Laboratory findings in the studied groups

	CHD (Number= 60)	Acyanotic CHD (Number= 17)	Cyanotic CHD (Number= 13)	Control (Number= 60)	P value
Hemoglobin gm/dL					
Mean ± SD	11.79±1.47	11.97±2.02	11.57±1.77	12.24±0.84	0.391
Range	9.20-15.30	9.2-15.3	9.4-15.3	11-13.5	
TLC (x1000)					
Mean ± SD	7.84±2.28	7.26±2.13	8.59±2.34	5.9±0.87	0.001
Range	4.50-13	4.6-12.4	4.5-13	4.3-7	
Hs-CRP mg/dL					
Mean ± SD	1.53±2.56	1.38±2.03	1.72±3.2	0.73±0.41	0.225
Range	0.1-12	0.1-7	0.1-12	0.1-1.3	

Hs-CRP: high sensitivity C-reactive protein; TLC: total leucocytic count

Table 3. Correlation of level of Hs-CRP with the studied parameters

	Number	HSCRP (mg/l)	
		Correlation Coefficient	P value
Age (months)	30	0.175	0.355
HR (B/min) awake	30	-0.004	0.982
RR	30	-0.100	0.598
SPO_2 (%)	30	-0.229	0.410
Weight (Z-score)	30	0.209	0.267
Height (Z-score)	30	0.181	0.338
HB (gm/dL)	30	0.264	0.159
TLC (x1000)	30	0.047	0.806
PAP	30	-0.159	0.403
EF (%)	30	0.322	0.082
FS (%)	30	-0.244	0.194
Pulmonary Hypertension	30	-0.088	0.64

EF: ejection fraction; FS: fractional shortening; Hs-CRP: High sensitivity C- reactive protein; SpO_2: oxygen saturation.

Discussion

The main finding in our study is that congenital heart disease -whether cyanotic or acyanotic- does not incur raise of Hs-CRP. Hence, a raise of Hs-CRP among these children would not be attributed to the underlying CHD. It seems that the structural defect in CHD is not inherently associated with ongoing inflammation. The cyanosis in our studied cohort did not influence the Hs-CRP level. The lack of influence of cyanosis on Hs-CRP provides evidence that the reported higher baseline Hs-CRP values of those with asphyxia (*10*) seems to be related to the undergoing pathology, breakdown and repair and not to the lower oxygen saturation.

We excluded those with active acute or chronic infection, to assure that any raise in Hs-CRP is related to underlying CHD and not to infection. We did not compare Hs-CRP to procalcitonin in those with CHD and ongoing infection as it was beyond the scope of the study. Hs-CRP is reported to valuable in early detection of sepsis, and inflammation. Children with CHD are prone to pneumonia, endocarditis, brain abscesses and other infections (*11*). Based upon our work elevations of Hs-CRP among children with CHD dictates searching for infection. This is especially valuable as Hs-CRP is reported to be as prompt, sensitive and specific as procalcitonin in detection of infection among older adults (*12*), and that both are more sensitive and specific than the contemporary CRP levels. Prompt diagnosis and management of infection among those with CHD is necessary to reduce morbidity and mortality. Hs-CRP may be used to detect infection among those with CHD, as CHD does not cause confounding rise in Hs-CRP.

The lack of influence of CHD on Hs-CRP irrespective of the underlying structural defect as ventricular septal defect or others, may allow Hs-CRP to be part of work up after teeth extraction or any intervention that may be complicated by infective endocarditis, or other infections (*13*). Future studies are needed to verify the role Hs-CRP in the work up for infective endocarditis.

Hs-CRP was not influenced by pulmonary hypertension, weight at birth, or weight percentile or height percentile during the study. Hence, it seems that the structural or functional changes among children with CHD do not include ongoing inflammatory pathogenesis. Our work supports that the increments of Hs-CRP remain valuable in diagnosis of inflammation and infection among children with CHD whether cyanotic or acyanotic.

We did not include children with rheumatic heart disease; hence we are not aware of the influence of rheumatic heart disease and rheumatic activity on Hs-CRP. More studies are needed to validate the Hs-CRP role in rheumatic heart disease (*14*).

Among adults Hs-CRP is included in the work-up for risk stratification for coronary heart disease (*5*). We did not include children with hypercholesterolemia or coronary heart disease to study their effect on Hs-CRP. Our study was a cross-sectional one and not a prospective one, hence we cannot study the prognostic value of Hs-CRP among our studied cohort.

Conclusion

Hs-CRP is not influenced by the underlying CHD whether cyanotic or acyanotic. Hs-CRP diagnostic value is not confounded by cyanosis or SpO_2 in children with CHD. The Hs-CRP normal values for healthy children applies to those with CHD.

Author Contributions

R.M. conceptualized the work, shared in the patient collection. F.A.A. and N.N. supervised the work. H.H.Z. shared in the patient collection did the data analysis, H.A.H., and R.M. wrote and revised the manuscript and supervised in all steps. H.A.H. did the laboratory work and is the submitting and corresponding author. R.M. shared in the patient collection. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study.

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