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Short Communication

Relationship between G protein level with left ventricular systolic function in children with acyanotic heart disease

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Abstract

Heart failure is a pediatric emergency caused by the heart's inability to adequately meet the body metabolic needs and the most common cause is congenital heart disease (CHD). The G protein is the most prominent family of membrane-bound protein known to act in major regulatory events of the cardiovascular system, one of which is heart failure. The aim of this study was to determine the level of G protein and its relationship with left ventricular systolic function in children with acyanotic CHD. A cross-sectional study was conducted in Dr. Zaionel Abidin Hospital, Banda Aceh, Indonesia. The patients aged 0 to 18 years and had acyanotic CHD diagnosis by echocardiography were included. Anthropometry measurement was performed according to standard WHO procedures and G protein level was measured using the ELISA method. The Chi-squared test was used to measure the relationship between G protein level and left ventricular systolic function. Out of a total of 38 children with acyanotic CHD, the mean level of G protein was 36.25 ng/mL and the mean of left ventricular systolic function was 73.1%. There was no relationship between G protein and left ventricular systolic function in children with acyanotic CHD. However, further study with a larger sample size and considering other variables are needed to confirm this finding.

Keywords: Heart failure, congenital heart disease, acyanotic, G protein, left ventricular systolic function

Introduction

Pediatric heart failure constitutes a critical emergency, marked by the heart's inability to meet the body's metabolic demands [1,2]. It manifests through progressive left ventricular dysfunction, dilatation of the heart chambers, and decreased myocardium contractility. In contrast to adults, heart failure in children is caused by various etiologies with diverse clinical manifestations; congenital heart disease (CHD) and cardiomyopathy are among the leading causes. Unfortunately, heart failure in children leads to high morbidity and mortality [1,3]. Early diagnosis and proper management are crucial to for mitigating these risks [4,5].

CHD is a disease with abnormalities in the heart structure or circulatory function of the heart carried from birth caused by disruption or failure of the development of the heart

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structure in the early phases of fetal development [6,7]. There are two large groups of CHDs: the acyanotic and cyanotic types, the acyanotic type makes up the biggest part of all congenital heart diseases, such as patent ductus arteriosus (PDA), ventricular septal defect (VSD), and atrial septal defect (ASD) [8,9]. Clinical manifestations of CHD in children vary widely, from asymptomatic to severe symptoms such as shortness of breath, difficulty sucking milk, frequent pulmonary infections, and growth disorders to congestive heart failure [1,10]. The mechanism of heart failure in CHD children is heart pump disorders, hemodynamic abnormalities from the left to the right shunt, pulmonary overcirculation, and excessive volume load [1,11].

In recent years, biochemistry and molecular methods have revealed that the initial cellular response occurs at membrane receptors [12,13]. The G protein paired receptor, or the G protein-coupled receptor (GPCR), is the most prominent family of proteins bound to membrane receptors and is the focus of numerous drug targets [14]. These G proteins are essential in translating extracellular stimuli into intracellular signals [15]. Various GPCRs are involved in key regulatory processes within the cardiovascular system, including myocardial contractions, arterial resistance, kidney function, cardiac hypertrophy, and heart failure [12,16].

The G protein comprises three distinct polypeptide chains—α, β, and γ subunits. When the β and γ chains come together, they form a potent βγ complex, anchoring the G protein firmly to the cytoplasmic surface of the plasma membrane [16,17]. Most cardiac activity is managed by adrenoreceptors, consisting of two central receptors, α and β. Adrenoreceptors β are the main regulatory macro-proteins, predominantly found in the heart and are responsible for lowering cardiac signals [18,19]. Heart failure patients often exhibit elevated levels of circulated adenylate cyclase, resulting in hyperstimulation of adrenergic receptors and increased presence of G-protein-coupled receptor kinase (GRK) in the heart [16,19]. Research on G proteins in children with heart failure remains limited, with scarce attention directed towards this demographic. The aim of this study was to assess the relationship between G protein levels and left ventricular systolic function in children with acyanotic type of CHD.

Methods

Study design, setting and sampling

A cross-sectional study was conducted at the pediatric cardiology polyclinic and the pediatric ward of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from February to August 2022. Consecutive sampling was employed in this study. The Lemeshow formula was calculated to determine the minimum sample size, resulting in 34 patients.

Patients' criteria

This study included children aged 0–18 years with acyanotic CHD, including PDA, VSD, and ASD. All diagnosis of CHD was confirmed by echocardiography using the GE vivid E95 Ultrasonic Pulsed Doppler Imaging System (General Electronics, New York, USA) by assessing cardiac structure defects for PDA, ASD, and VSD. All echocardiography examinations were conducted by a pediatric cardiology consultant. Children with respiratory tract infections, central nervous tract infections, urinary tract infections, kidney disorders, gastrointestinal disorders, liver diseases and multiple congenital anomalies were excluded from the study.

Study variables and data collection

The independent variable of the study was left ventricular systolic function and the dependent variable was G protein levels. In addition, further co-variates were also assessed such as gender, age, nutritional status and albumin level. An echocardiography assessment was conducted to measure cardiac systolic function of which normal left ventricular ejection fraction: 56–78%, mild dysfunction (EF 41–55%), moderate dysfunction (EF 31–40%), and severe dysfunction (EF ≤30%). The level of G protein was measured using enzyme-linked

immunosorbent assay (ELISA) method following the manufacturer protocol (MyBioSource, Inc. San Diego, CA, USA), with a normal value 67.8–199.3 ng/mL. To measure the nutritional status, anthropometry measurement was performed according to the standard WHO guideline for each patient (classified as good nutrition and underweight) [20]. The level of albumin was measured using an automatic Cobas 8000 analyzer.

Statistical analysis

The Chi-squared test was used to identify the relationship between G protein level and left ventricular systolic function. Statistically significant was considered at $p<0.05$. All data was processed using the Statistical Package for the Social Science (SPSS) program version 26 (IBM Inc., Chicago, USA).

Results

Characteristics of the patients

A total of 38 children with acyanotic CHD were included in the study and their characteristics are presented in **Table 1**. The majority of children were girls (65.79%) and aged between 0–47 months (52.63%). Among them, 33 (86.8%) had a single congenital heart defect. PDA and VSD were the most frequently observed CHD, 36.8% and 31.6%, respectively. More than half of the children were underweight (55.3%) and the mean albumin level was 3.38 g/dL.

Table 1. Characteristics of the children with acyanotic congenital heart disease (CHD) included in the study (n=38)

Characteristics	Frequency	Percentage (%)
Gender		
Boy	13	34.2
Girl	25	65.8
Age, month		
0–47	20	52.6
48–95	10	26.3
96–155	6	15.8
>155	2	5.2
Congenital heart defect (CHD)		
Single	33	86.8
Multiple	5	13.2
Type of CHD		
Patent ductus arteriosus (PDA)	14	36.8
Ventricular septal defect (VSD)	12	31.6
Atrial septal defect (ASD)	7	18.4
PDA+ASD	2	5.3
ASD+VSD	3	7.9
Nutritional status		
Good nutrition	17	44.7
Underweight	21	55.3
Albumin level, mean (min-max), g/dL	3.38 (3.05–3.8)	

G protein level and left ventricular systolic function in children with acyanotic congenital heart disease (CHD)

Abnormal G protein levels were observed frequently among the children with acyanotic CHD. Only four children had normal levels of G protein. The median showed a value of 36.25 ng/mL, suggesting that it was below the normal (**Table 2**). The normal systolic function of the left ventricular was found in 36 children with acyanotic CHD and only two had abnormal systolic function (**Table 2**). In addition, the mean of left ventricular systolic function of the total patients was 73.1%.

Relationship between G protein and left ventricular systolic function

Our data indicated that a large portion (84.2%) of children with abnormal levels of G protein had normal left ventricular systolic function. The analysis showed no relationship between G protein levels and left ventricular systolic function in children with acyanotic CHD, $p=0.248$ (**Table 3**).

Table 2. The level of G protein and left ventricular systolic function in children with acyanotic congenital heart disease (CHD) (n=38)

Variable	Frequency	Mean
G protein level, ng/mL		36.25
Normal (67.8–199.3 ng/mL)	4	35.46
Abnormal	34	102.05
Left ventricular systolic function, %		73.10
Normal (56–78%)	36	51.15
Abnormal	2	74.36

Table 3. Relationship between G protein levels and left ventricular systolic function in children with acyanotic congenital heart disease (CHD) (n=38)

Variable		Left ventricular systolic function, n (%)		Total	*p*-value*
		Normal	Abnormal		
G protein level	Normal	4 (10.5)	0 (0.0)	4 (10.5)	0.248
	Abnormal	32 (84.2)	2 (5.3)	34 (89.5)	
	Total	36 (94.7)	2 (5.3)	38 (100)	

*Analyzed with Chi-squared test

Discussion

This study sought to assess the relationship between G protein levels and left ventricular systolic function in children with acyanotic CHD, and data suggested that there was no significant relationship between G protein and left ventricular ejection fraction. These results are similar to a previous study, which was unable to confirm the association of the G protein 3-subunit C825T polymorphism with left ventricle structure and diastolic function [21]. However, the present study is different from another study among adult patients with heart failure that obtained low myocardial protein kinase G activity in heart failure with preserved ejection fraction was associated with raised cardiomyocyte F (passive) and was related to increased myocardial oxidative stress [22].

Our study revealed that, although the G protein levels were abnormal, the left ventricle demonstrated normal function in some patients. This normal left ventricle function might be affected by factors such as medication (including length and type), nutrition, and physical activity. Additionally, we suggested that the patients had a high level of adherence to the medication that was administered (with regular visits to the hospital). Although this study yielded statistically insignificant, this could be as basic for further research in children, especially in children with congenital or acquired heart defects, to prevent heart failure.

It is known that cardiovascular homeostasis is regulated by a series of hormones and neurotransmitters, and many of them activate G protein receptors expressed in the heart [23]. G protein plays an important role in the physiological regulation of cardiac function as well as in biomolecular disease processes that are required at the level of cellular mediate processes and physiological responses [24]. Over the last years, GPCRs emerged as important players in recognizing these mediators, because of their diverse functions not only in steady state but also during chronic inflammatory processes [25]. GPCRs are a fundamental signal transduction component associated with cardiovascular remodeling and disease progression [26].

GPCR receptors found in the heart are related to blood pressure, heart rate, myocardial contractility, apoptosis, remodeling, vasculature [12,27,28]. There have been many previous studies assessing the role of G protein in the regulation of cardiovascular function both physiologically and pathologically [12,16,29]. G protein is currently widely used in drug research to prevent cardiovascular disease progression [12,30]. The ß-adrenergic receptors and angiotensin II type 1 receptors are important GPCRs in cardiovascular function. In addition, there are many other GPCRs, such as apelin receptor, lysophosphatidic acid receptor and endothelin receptors, that play important roles in cardiovascular diseases [14,31,32].

There are some limitations of the study that need to be discussed. This study did not assess factors that might affect either G protein levels and left ventricular systolic function,

such as duration of CHD, the magnitude of heart defects, and comorbidities (such as recurrent infections). In addition, the number of samples included in this study is relatively small. Therefore, a study with a higher sample size assessing more factors affecting the G protein and systolic function of the left ventricle is required.

Conclusion

Our data revealed that the mean G protein level was 36.25 ng/mL among children with acyanotic CHD included in the study, and the majority of them had normal left ventricular systolic function. The statistical analysis suggested that there was no significant relationship was observed between G protein levels and left ventricular systolic function.

Ethics approval

This study was approved by the Health Research Ethics Committee of Dr. Zainoel Abidin Hospital and the Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia (020/EA/FK-RSUDZA/2022).

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Competing interests

All the authors declare that there were no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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References

1. Hinton BR, Ware MR. Heart failure in pediatric patients with congenital heart disease. Circ Res 2017;120:978-994.
2. Sapna F, Raveena F, Chandio M, *et al.* Advancements in heart failure management: A comprehensive narrative review of emerging therapies. Cureus 2023;15:e46486.
3. Jayaprasad N. Heart failure in children. Heart Views 2016;17:92-99.
4. Masarone D, Valente F, Rubino M. Pediatric heart failure: A practical guide to diagnosis and management. Pediatr Neonatol 2017;58;303-312.
5. Nugroho S, Arafuri N. Gagal jantung pada penyakit jantung bawaan: Perubahan hemodinamik dan tatalaksana. Pediatric Cardiology Update 7th Palembang 2019:15-26.
6. Saiki H, Senzaki H. Basic concepts of circulatory physiology in congenital heart disease: A view from pressure-volume relationship. Japanese Soc Pediatr Cardiol Card Surg 2011;27:76-87.
7. Wichman CL, Moore KM, Lang TR, *et al.* Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. Mayo Clin Proc 2009;84:23-27.
8. Sachdeva S, Ramakrishnan S, Choubey M, *et al.* Outcome of COVID-19-positive children with heart disease and grown-ups with congenital heart disease: A multicentric study from India. Ann Pediatr Cardiol 2021;14:269-277
9. Moss AJ. Moss and Adams' heart disease in infants, children, and adolescents: Including the fetus and young adult. Ed VI. Philadelphia: Lippincott Williams & Wilkins Co; 2001.

10. Kishore S, Kumar M, Kumar A, *et al.* Clinical and echocardiographic profile of congenital heart diseases in the 0-12-year age group in a tertiary care medical institute in Eastern India: A retrospective, cross-sectional study. Cureus 2022;14:e26114.
11. Sun RR, Liu M, Lu L, *et al.* Congenital heart disease: Cause, diagnosis, symptoms, and treatments. Cell Biochem Biophys 2015;72:857-860.
12. Wang J, Gareri C, A Howard, *et al.* G-protein–coupled receptors in heart disease. Circ Res 2018;123(6):716-735.
13. Severin ES, Savvateeva MV. Molecular and physiological mechanisms of membrane receptor systems functioning. Acta Naturae 2018;3(1):20-28.
14. Li Y, Li B, Cheng WD, *et al.* Role of G-protein coupled receptors in cardiovascular disease. Front Cardiovasc Med. 2023;10:1130312.
15. Wettschureck N, Offermanns, S. Mammalian G proteins and their cell type specific functions. Physiol Rev 2005;85:1159-1204.
16. Syrovatkina V, Alegre KO, Dey R, *et al.* Regulation, signaling, and physiological functions of G-proteins review. J Mol Biol 2016;428(19):3850-3868.
17. Smrcka AV. G protein βγ subunits: Central mediators of G protein-coupled receptor signaling. Cell Mol Life Sci 2008;65:2191-2214.
18. Mahmood A, Ahmed K, Zhang Y. β-adrenergic receptor desensitization/down-regulation in heart failure: A friend or foe?. Front Cardiovasc Med 2022;9:925692.
19. Altamish M, Samuel PV, Dahiya R, *et al.* Molecular signaling of G-protein-coupled receptor in chronic heart failure and associated complications. Drug Dev Res 2020;81(1):23-31.
20. Fryar CD, Gu Q, Ogden CL, *et al.* Anthropometric reference data for children and adults: United States, 2011–2014. Vital Health Stat 3 Anal Stud 2016;(39):1-46.
21. Rengo G. The adrenergic system in cardiovascular pathophysiology: A translational science point of view. Front Physiol 2014;5:356.
22. Sedlácek K, Fischer M, Erdmann J, *et al.* Relation of the G Protein β3-Subunit Polymorphism with left ventricle structure and function. Hypertension 2002;40(2):162-167.
23. Foster SR, Roura E, Moleenar P, *et al.* G protein-coupled receptors in cardiac biology: Old and new receptors. Biophys Rev 2015;7(1):77-89.
24. Heerebeek LV, Hamdani N, Falca o Pires I, *et al.* Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation 2012;126:830-839.
25. Patel KP, Schultz HD. Angiotensin peptides and nitric oxide in cardiovascular disease. Antioxid Redox Signal 2013;19(10):1121-1132.
26. Van der Vorst EPC, Peter LJF, Muller M, *et al.* G-Protein coupled receptor targeting on myeloid cell in atherosclerosis. Front Pharmacol. 2019;10:531.
27. Tadevosyan A, Vaniotis G, Allen BG, *et al.* G protein-coupled receptor signalling in the cardiac nuclear membrane: Evidence and possible roles in physiological and pathophysiological function. J Physiol 2012;590:1313-1330.
28. Goswami SK. G protein-coupled receptor signaling in cardiovascular system: Specificity versus diversity. J Pract Cardiovasc Sci 2019;5:68-75.
29. Tang CM, Insel PA. GPCR expression in the heart: "New" receptors in myocytes and fibroblasts. Trends Cardiovasc Med 2004;14:94-99.
30. Trzaskowski B, Latek D, Yuan S, *et al.* Action of molecular switches in GPCRs--theoretical and experimental studies. Curr Med Chem 2012;19:1090-1109.
31. Ali DC, Naveed M, Gordon A, *et al.* β-adrenergic receptor, an essential target in cardiovascular disease. Hearth Fail Rev 2020;25:343-354.
32. Manthieu NM, Nakagawa P, Grobe JL, *et al.* Insights into the role of angiotensin-II AT1 receptor-dependent β-arrestin signaling in cardiovascular disease. Hypertension 2024;81:6-16.