Original Article

ERA'S JOURNAL OF MEDICAL RESEARCH VOL.8 NO.1

DOI:10.24041/ejmr2021.7

TO STUDY THE EFFECT OF IRON DEFICIENCY ANEMIA ON CARDIOVASCULAR FUNCTIONS IN CHILDREN

Mohammad Kashif*, ZeebaZaka-Ur-Rab,**

Department of Pediatrics, Department of Pathology***

Mayo Institute of Medical Sciences, Gadia, Barabanki, U.P., India-225003*

Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, U.P., India-202002**

Sadaf Mirza*, Asif Hasan**

*Department of Pathology**

Mayo Institute of Medical Sciences, Gadia, Barabanki, U.P., India-225003*

Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, U.P., India-202002**

Received on : 11-06-2021
Accepted on : 20-06-2021

Address for correspondence
Dr. Sadaf Mirza
Department of Pathology
Mayo Institute of Medical Sciences,
Gadia, Barabanki UP
Email: sadafazmi2@gmail.com
Contact no: +91-7619979399

ABSTRACT

The objective of this study is to know the changes in cardiovascular functions on echocardiography in children of iron deficiency anemia in terms of stroke volume, stroke index, cardiac output, cardiac index, end systolic wall stress and end systolic volume index. This study included 68 children aged 1–12year having iron deficiency anemia (Group A). 32 non anemic healthy controls in the age group 1-12 years without anemia were included in control group for comparing the baseline cardiac parameters on echocardiography (Group B). Iron deficiency anemia was confirmed by doing serum iron, serum ferritin and total iron binding capacity. Echocardiography and pulsed Doppler echocardiography were done in all children with Iron deficiency anemia and control group without anemia to evaluate cardiovascular functions. Result of all 68 patients Iron deficiency anemia (IDA) was confirmed in all patients and 32 control patients were non iron deficient. Left ventricular early diastolic filling was significantly higher in the patientswith anemia.The ratio of left ventricular end-systolic wall stress to left ventricular volume, an index of systolic function that is independent of preload and afterload, was significantly lower in the patients with anemia. The cardiac index, stroke volume, stroke index were also significantly higher in anemia patients because of theincreases in preload, heart rate and early diastolic filling, as well as the decrease of afterload. Children with iron deficiency anemia has significant changes in cardiovascular parameters on echocardiography as compared to control group without iron deficiency anemia. Iron deficiency anemia has significant deleterious effect on cardiovascular parameters in children.

KEYWORDS: Iron Deficiency Anemia. Cardiovascular functions. Echocardiography. Hematological parameters. Hemoglobin. Iron.

INTRODUCTION

Iron deficiency continues to be the most prevalent nutritional disorder in the world1. Iron deficiency anemia (IDA) is the most common form of nutritional anemia in both developed and developing countries.It is well known that anemia is having deleterious effects on the heart. In 1830, Marshall Hall commented that if a person is subjected to repeated blood lettings instead of one full blood letting , the changes on the heart and arteries is morbidly increased, leading to palpitation and variations in the pulse from 100 to 120 or 130. There has been an increasing concern of the high prevalence and important role that different comorbidities play in defining the syndrome of heart failure2. Among these comorbidities, anemia plays an important role considering the similarities in symptoms and the importance of oxygen carrying capacity in the manifestations of heart failure 3.In order to maintain adequate oxygen delivery cardiac output increases as a compensatory physiological mechanism in anemia.There is increases in blood volume, heart rate, preloadand stroke volume, along with a decrease in afterloadas a compensatory mechanism to increase the cardiac output 4.Severe iron deficiency can lead to left ventricular (LV) dysfunction and overt heart failure5. Anemia has also been linked with the development of LV hypertrophy6. Echocardiography is an important tool to demonstrate

many hemodynamic changes that accompany iron-deficiency anemia.7-8

With all this background, this study is being taken by authors to assess the change in cardiovascular functions on echocardiography with iron deficiency anemia.

MATERIAL AND METHODS

This hospital based study was conducted from February 2011 to November 2012 in the Department of Pediatrics in collaboration with the Centre for Cardiology, Department of Medicine of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh.The study involved children with iron deficiency anemia (microcytic hypochromic) with hemoglobin levels between 4-9 gm/dl in the age group of 1-12 years attending the Pediatric O.P.D. and Pediatric Hematology Clinic of J.N. Medical College. These were screened for eligibility for inclusion in the study9 Group A). A group of apparently healthy children in the age group 1-12 years without anemia were included in control group (Group B) for comparing the cardiovascular parameters on echocardiography.. This study included 68 children in study group A and 32 children in control group B. An informed written consent was taken from the patients and their parents after fully explaining the nature of study.

An approval from the IRB (Institutional Review Board) was obtained to conduct the study. Inclusion criteria was apparently healthy children with iron deficiency anemia between 1-12 years of age and hemoglobin between 4-9 gm%. Children with hemoglobin ≤ 4 gm/dl or > 9gm/dl, acute or chronic medical disorders, fever within last 4 weeks, haemolytic anemia, iron/vitamin/mineral supplements (including herbal drugs) within 8 wks, blood transfusion within 3 months, malignancy, congestive heart failure, congenital heart disease/ rheumatic heart disease/ cardiomyopathy and having frank features of rickets were excluded.

All children underwent a detailed clinical history and complete physical examination.All available medical records were reviewed carefully. Details of treatment taken within 6 month were noted including history of receiving hematinics, multivitamins and .minerals, preparations containing zinc, herbal medicines, and blood transfusions.

Children were assessed for nutritional status, anthropometry, presence and severity of anemia, signs of malnutrition, icterus, hemolytic facies, facial dysmorphism, hemorrhages,skin rash, lymphadenopathy, edema, frontal bossing hepatosplenomegaly and signs of rickets and other vitamin deficiencies. Heart rate in children less than 2 years and pulse rate in children more than or equal to 2 years were taken after 5 minutes rest. At the time of measurement of heart rate or pulse rate children were calm, resting and were not crying or irritable.

ALL THE SUBJECTS UNDERWENT THE FOLLOWING INVESTIGATIONS

- Hemoglobin by Sahli's method
- Red cell indices: mean corpuscular volume(MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and red cell distribution width (RDW) by Lab Life 3D hematological autoanalyzer
- Seum ferrritin, by ELISA based kitsfrom CALBIOTECH, INC.
- Serum iron and total iron binding capacity by spectrophotometry or colorimeter using kits from GIESSE DIAGNOSTICS SNC, ROMA- ITALY
- **M 2D mode Echocardiography** to determine the cardiac output, cardiac index, diastolic and systolic LV cavity size and wall thickness, LV fractional shortening/ LV ejection fraction, LV end-diastolic and end-systolic dimensions, ratio of end-systolic wall stress to end-systolic volume index (ESS/ESVI), and cardiac pressures.

The following cardiac parameters were seen on echocardiography.

- Heart rate
- Cardiac output
- Left ventricular early diastolic filling
- Left ventricular preload and afterload
- Cardiac index
- LV fractional shortening/ LV ejection fraction
- LV end-diastolic and end-systolic dimensions and wall thickness
- Ratio of end-systolic wall stress to end-systolic volume index (ESS/ESVI)

ECHOCARDIOGRAPHY

The following indices were calculated:

1. Left ventricular end-diastolic volume (LVEDV) = LVDd3
2. LVEDV index (LVEDVI) = LVEDV/BSA, where BSA is the body surface area
3. LV end-systolic volume (LVESV) = LVDs3
4. LVESV index (LVESVI) = LVESV/BSA;
5. LV ejection fraction (EF) = (LVEDV–LVESV)/ LVEDV and left ventricular fractional shortening,
6. End-systolic wall stress (ESS) = P*LVDs*1.35/4*LVPWTs (1+LVPWTs/LVDs), where P is the LV end-systolic pressure calculated from the measured upper limb systolic blood

pressure (P=0.66*systolic blood pressure+13.5).

LVDs is left ventricular diameter in systole

LVPWTs is left ventricular posterior wall thickness in systole

7. End systolic volume index(ESVI) = LVESV/BSA
8. ESS/ESVI ratio
9. Stroke volume (SV) = LVDd3– LVDs3
10. Stroke index (SI)=SV/BSA
11. Cardiac output (CO) = SV`*heart rate
12. Cardiac index = Cardiac output / BSA
13. Left ventricular early diastolic filling = ventricular early filling velocity (E)
14. Left ventricular preload = End diastolic volume index, EDVI (LVEDV Index) which reflects LV preload.
15. Left ventricular afterload = End-systolic wall stress (ESS) indices of afterload
16. Rate-corrected atrial contraction peak velocity (corrected A) = A/ √R–R interval
17. Corrected A/E ratio.

Statistical analysis was done, using the statistical package for social science (SPSS 17) for Windows Software. Continuous variables were expressed as means, standard deviation (SD), confidence intervals (95% CI), frequency and range. P value < 0.05 was taken as significant. The Pearson Chi-square test was used to compute the difference for a set of variables in two categories.

RESULTS

A total of 114 patients with suspected iron deficiency anemia were evaluated initially, of which 90 patients fulfilled the criteria for inclusion in the study. Out of these, 68 patients whose parents consented for the study were recruited. These were assigned to groups A(68).

The following observations were made during the course of the present study:

Characteristic	IDA Group (A) N= 68 Mean±SD (95% CI)	Control Group (B) N=32 Mean±SD (95% CI)	P value
Age (months)	33.43 ± 22.82 (27.68,39.18)	39.81±28.68 (29.47,50.16)	.241
Male : Female	2.7:1	2.2:1	-
Hemoglobin (g/dl)	6.86±1.33 (6.52,7.19)	11.03±1.17 (10.60,11.45)	.000
Serum iron (µg/dl)	40.68±16.8 (36.45,44.92)	88.14±29.91 (77.35,98.92)	.000
TIBC (µg/dl)	499.67±148.02 (496.72,664.19)	291.43±120.69 (247.92,334.95)	.000
Serum ferritin (ng/ml)	6.02±9.39 (3.68,8.37)	34.29±69.75 (9.14,59.44)	.002
Heart rate (beats/ min)	123±14.09 (120.07,127.17)	106.19±8.5 (10.09,109.28)	.000
E (cm/s)	124.49±18.64 (119.80,129.19)	110.63±16.64 (104.62,116.63)	.001
Corrected A/E ratio	0.127±0.017 (0.122,0.131)	0.14±0.01 (0.14,0.15)	.000
LVEDV Index (ml/m2)	42.71±19.50 (37.80,47.62)	33.78±11.38 (29.68,37.89	.019
LVESV Index(ml/m2)	8.71±4.60 (7.55,9.87)	7.77±2.69 (6.79,8.74)	.291
ESS/ESVI (gm/cm^2 per ml per m^2)	6.37±2.01 (5.86,6.88)	8.13±2.79 (7.13,9.14)	.001
FS (%)	36.88±2.41 (36.28,37.49)	37.15±3.71 (35.81,38.49)	.673
LVEF(%)	78.29±8.77 (76.08,80.50)	76.39±5.67 (74.34,78.43)	.268
SV(ml/min)	17.23±10.40 (14.60,19.85)	17.35±8.65 (14.23,20.47)	.954
SI(ml/min per m^2	34.00±16.00 (29.97,38.03)	26.01±9.64 (22.53,29.49)	.011
CO (l/min)	2.09±1.13 (1.80,2.37)	1.79±0.78 (1.51,2.07)	.191
CI(l/min/per m^2	4.17±1.92 (3.69,4.66)	2.74±1.01 (2.37,3.11)	.000

Tab. 1Baseline Characteristics of Patients with Iron Deficiency Anemia (IDA) and Controls

Ages of subjects ranged between 13 – 132 months (mean 33.43 ± 22.82 (27.68,39.18) and 12 -110 months (mean, 39.81±28.68; 95% CI: 29.47,50.16) in groups A & B respectively. Maximum number of anemic patients belonged to 12 -36 months age group (73.02%), followed by 36.1-72 months age group (19.04%). Similarly, maximum number(65.62%) of subjects in the control group were between 12-36 months of age.There was an obvious male preponderance with males accounting for 77.40%, and 68.75% of subjects in group A & B, respectively. A similar trend was noted across all age groups.

At the end of the study, heart rate (p=0.00), Ventricular early filling velocity (E) (p=0.001), Left ventricular end-diastolic volume (LVEDV) (p=0.019), Stroke index (SI) (p=0.011), Cardiac output (p=0.191), Cardiac index (p=0.000) was significantly higher in group A. Left ventricular diameter in systole (p=0.003), left ventricular end systolic volume (p=0.010), fractional shortening (p=0.007), and left ventricular end systolic wall stress (p=0.002) were observed to be significantly lower in group A as compared to baseline values of controls group B. On the other hand, left ventricular ejection fraction was observed to be significantly higher in group A as compared to controls Group B.

DISCUSSION

Iron deficiency anemia (IDA) is the most common nutritional disorder. It affects individuals and communities not only in developing nations but also in a highly developed ones 9-10. Mild form of anemia are asymptomatic but dyspnea and fatigue may occur when severity of anemia increases. Left ventricular (LV) dysfunction and overt heart failure can occur in severe form of iron deficiency anemia. Chronic tissue hypoxemia, which may lead to myocyte dysfunction develop in severe anemia due to compromised oxygen delivery capacity.5 It was observed that resting cardiac output increases only when hemoglobin concentration decreases to 10g/dl or less11. It is complex and several mechanisms are responsible (i) decrease in afterload due to decrease in systemic vascular resistance, (ii) increase in preload due to increased venous return, (iii) increased left ventricular (LV) functions due to increased sympathetic activity and ionotropic factors12-14. Increase in preload results from an increase in venous return due to a decrease in hematocrit and blood viscosity and increased sympathetic activity causing vasoconstriction favouring cardiac filling. Increase in LV functions is caused by an increase in preload (Frank-starling mechanism) and changes in ionotropic state in relation to increased sympathetic activity and ionotropic factors 12-14.

Echocardiography can demonstrate most of the hemodynamic changes that occur iron-deficiency anemia. In the present study, mean cardiac output was observed to be more in patients with iron deficiency anemia in comparison to healthy control groups, the difference, however, not being statistically significant. Increase in cardiac output in anemia has also been reported by several other authors 4,11,15-16 . When the hemoglobin concentration goes below < 7 g/dl, Varat et al (1972) observed a significant increase in cardiac output of patients with iron deficiency anemia11.

Mean heart rate (p=0.000) and mean stroke index (p = 0.011) were observed to be significantly higher in anemia patients as compared to healthy controls in the present study. These findings are in agreement with those of other studies4,8,11,16-17. Hayashi et al (1999) and Val-Meijas et al (1979) were of the view that the increase in heart rate and stroke index resulted in an increase in cardiac output. Similar to a study done by Hayashi et al (1999), cardiac index (CI) was also observed to be significantly increased in patients with anemia as compared to healthy controls (p value = 0.000) in the present study.This increase has been attributed to increase in heart rate and preload, and a decrease in afterload (Hayashi et al, 1999).In the present study, a statistically insignificant (p= 0.268) increase in mean ejection fraction was observed in anemia patients as compared to healthy controls. This finding is similar to those reported by Hayashi et al (1999) where the increase in mean ejection fraction and mean fractional shortening in anemic patients was not found to be significant.

LV preload which was reflected by left ventricular end diastolic volume index (LVEDV Index) is significantly higher in patients with anemia as compared with healthy controls in the present study. This finding is similar to that observed in other studies 7-8,18-20. It is well known that end-diastolic and end-systolic volume indices, which reflect left ventricular preload, increase in anemia7-8,18.

To evaluate cardiac contractility ratio of end-systolic wall stress to end-systolic volume index (ESS/ESVI) is used. This ratio is reduced which imply functional compromise in patients with hemoglobin levels of less than 6 g/dl 8. The ESS/ESVI ratio was superior to the EF for assessment of cardiac contractility was also suggested by Barry et al 21 as these indices are mostly independent of preload, afterload, and heart rate and are believed to accurately reflect LV contractility. In our study the ratio of mean ESS/ESVI was observed to be significantly reduced in anemic

patients as compared to healthy controls (p value = .001). Similar results were observed in some other studies8,21. The ventricular early filling velocity (E) was significantly higher in patients with anemia as compared with the healthy controls (p= 0.001). Therefore, the corrected A/E ratio was significantly lower in patients with anemia as compared with the healthy controls (p value = 0.000). Similarly, Hayashi et al (1999) reported that corrected A/E ratio was lower in patients with anemia as compared with the healthy controls8.

Takahashi et al (1990) observed that Doppler parameters of early diastolic filling (E) were increased in patients with iron deficiency anemia20. It was observed by Takahashi et al (1990) that LV stroke index was significantly increased in the patients with anemia. It was due to increased in preload and decrease in afterload which compensate the significant decrease in LV contractility. However, no significant difference was observed in the rate-corrected peak atrial contraction velocity (A) of anemic and healthy controls. Left ventricular early diastolic function was found to be significantly higher in the patients with anemia as compared with the healthy controls in the present study which is similar to that reported by other authors (7-8,22).

CONCLUSION

Iron deficiency anemia affects cardiovascular functions in children. Cardiac index, stroke index, heart rate, left ventricular preload and left ventricular diastolic function increase in patients of iron deficiency anemia as compared to healthy controls. On the other hand left ventricular afterload (ESS) and cardiac contractility (ESS/ESVI) decrease in iron deficiency anemia patients as compared to healthy controls. Children with iron deficiency anemia has significant changes in cardiovascular parameters on echocardiography as compared to control group without iron deficiency anemia. Iron deficiency anemia has significant deleterious effect on cardiovascular parameters in children.

REFRENCES

1. Seshadri S. Nutritional anaemia in south Asia. In: Gillespie S, editor. Malnutrition in South Asia. A Regional Profile. Publication No.5. Kathmandu: UNICEF RegionalOffice for South Asia, 1997; p.75.
2. Lang CC, Mancini DM. Noncardiac co morbidities in chronic HF. Heart 2007; 93:665–671.
3. GhaliJK. Anemia and heart failure. CurrOpin Cardiol. 2009; 24(2): 172- 178.
4. Pereira AA, Sarnak MJ. Anemia as a risk factor for cardiovascular disease. Kidney IntSuppl 2003;87:S32–S39.
5. Hegde N, Rich MW, Gayomali C. The Cardiomyopathy of Iron Deficiency. Tex Heart Inst J 2006; 33(3): 340–344.
6. Portoles J, Torralbo A, Martin P, et al. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis 1997; 29:541–548.
7. Georgieva Z, Georgieva M. Compensatory and adaptive changes in microcirculation and left ventricular function of patients with chronic iron-deficiency anaemia. Clin Hemorheol Microcirc 1997; 17: 21–30.
8. Hayashi R, Ogawa S, Watanabe Z, et al. Cardiovascular function before and after iron therapy by echocardiography in patients with iron deficiency anemia. PediatrInt 1999; 41: 13-17.
9. Brunken GS. Avaliação da eficácia de suplementaçãosemanal no controle da anemia empré-escolares. (Thesis). São Paulo: Faculdade de CiênciasFarmacêuticas da Universidade de São Paulo; 1999.
10. Brandalise SR, Matsuda E. Anemiascarenciais. In: Nóbrega F, editor. Desnutrição Intra-uterina e Pós-natal. São Paulo: Panamed 1981; p. 395-405.
11. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 1972;83(3):415-426
12. Rosenthal DS, Braunwald E. Hematological-oncological disorder and heart disease. In: Braunwald E, editor. Heart Disease: A Textbook of Cardiovascular Medicine.4th edition. Philadelphia: Saunders, 1992.
13. Beard JL, Tobin BW, Smith SM. Effects of iron repletion and correction of anemia on norepinephrine turnover and thyroid metabolism in iron deficiency.Proc SocExpBiol Med 1990;193(4):306-312.
14. Müller R, Steffen HM, Brunner R, et al. Changes in the alpha adrenergic system and increase in blood pressure with recombinant human erythropoietin (rHuEpo) therapy for renal anemia. Clin Invest Med. 1991 Dec;14(6):614-622.
15. Glick G, Plauth WH, Braunward E. Role of the autonomic nerve system in the circulatory response to acutely induced anemia in unanesthetized dogs. J Clin Invest 1964; 43: 2112–2124.

16. Val-Meijas, Lee WK, Weisse AB, et al. Left ventricular performance during and after sickle cell crisis. Am. Heart J 1979; 97: 585–591.
17. Roy SB, Bhatia ML, Mathur VS. et al. Hemodynamic effects of chronic severe anemia. Circulation. 1963;28:346-356.
18. Denenberg BS, Criner G, Jones R, et al. Cardiac function in sickle cell anemia. Am J Cardiol. 1983;51:1674-1678.
19. Sonnenblick EH, Braunwald E, Williams JF. et al. Effects of exercise on myocardial force-velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity, and ventricular dimensions. J Clin Invest 1965;44(12):2051-2062.
20. Takahashi M, Kurokawa S, Tsuyusaki T. et al. Studies of hyperkinetic circulatory state in chronic anemia. J Cardiol 1990; 20: 331–339.
21. Barry S, Denenberg BS, Criner G et al. Cardiac function in sickle cell anemia. Am J Cardiol1983; 51: 1674–1678.
22. Spirito P, Maron BJ. Doppler echocardiography for assessing left ventricular diastolic function. Ann InternMed 1988;109:122-126.

How to cite this article : Kashif M., Zaka-Ur-Rab Z., Mirza S., Hasan A. To Study the Effect of Iron Deficiency Anemia on Cardiovascular functions in Children. Era J. Med. Res. 2021; 8(1): 39-44