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Assessment of left ventricular systolic function in children with iron deficiency anemia by two-dimentional echocardiography and tissue Doppler in Beni- Suef university hospital

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Abstract:

Cardiac structure and function in iron deficiency anemia are mainly affected by two competing factors: iron deficiency and increased cardiac output (CO). Anaemia and iron deficiency (ID) are common causes of heart failure, both separately and in combination.The goal of this study is to assess the systolic function of left ventricle in (IDA)using tissue doppler in pediatrics . Sixty (60) children grouped into two groups,one with IDA and another control group. All candidates were suspected to history taking, full clinical examination ,complete blood count ,iron profile and echocardiographic examination. There was significant difference between cases and controls regarding peak systolic velocity across mitral annulus (SM) using tissue doppler imaging . There was no significant difference in left ventricle (LV) dimentions between cases and controls, The mean value of LVESV in case group was 2.0 ± .28 cm while it was 2.1 ± .3 cm in control P value was (.64) . There was no correlation between HB level or ferritin level and SM or EFThe study revealed preserved LV systolic functions as detected by conventional echocardiography however tissue Doppler imaging technique had shown latent LV systolic dysfunction Further follow up is needed for cases to assess reversability of finding .

Keywords: Iron deficiency –left ventricle – contractility -tissue doppler .

1. Introduction

Among diseases that is prevalent in the world , anemia is the most common . According to the prevalence done at 2010, it affects 32.9% of the population .[1] There are many causes of anemia , but iron deficiency is the main cause .People inflicted by IDA suffer from multisystem

affection and consequences such as (central nervous system CNS , CVS circulatory system , immunity) . Regarding the outcome of cardiac patients, anemia is considered as an independent risk factor considered as an independent risk factor for prognosis of cardiac disease , anemia is also associated with high percentage of morbidity and mortality among HF patients ..[1]

Etiology of IDA (iron deficiency anemia) may be due to any of the following , inadequate supply of iron ,impaired iron absorption, mismatching between intake and requirements of iron ,increased iron requirements during rapid growth rates ,and severe or chronic iron losses[2].

Lopez A et al [3],reported that Patients inflicted by IDA may suffer from manifestations that are associated with all anemias. That manifestation include pale (skin, conjunctivae, nail beds),Other presentations and clinical manifestations are due to the fact that these patients suffer from relative hypoxia at the tissue level . These include fatigue, exertional dyspnea proceeds to breathlessness at rest, vertigo, syncope, headache, tachycardia at rest , and a cardiac systolic flow murmur (hemic mumur).

As stated by Hegde et al [4], depending on the physiological importance of O2 carried by hemglobin(HB) to cardiomyocytes , severe consequences of anemia may affect CVS and anemia itself may be the clinical manifestation of other severe diseases in the body . The mechanism by which the body try to compensate anemia is by increasing the cardiac output (CO) The physiological response to anemia is a compensatory increase in CO in order to keep sufficient O2 delivery at the tissue level.

Persistant not treated cases of severe IDA , may manifest clinicaly by heart failure (HF) and LV dysfunction[4].

As per Martijn F et al [5], In addition to the significant role of iron as a component of hemoglobin (HB) molecule in uptake of O2 and carrying it to the tissues , iron has an important role in O2 storage and metabolism in the cells , redox cycling and as an enzymatic cofactor in many processes . SO, Keeping a normal iron level is critical for cells that require a high energy demand such as cardiomyocytes .

2. Subjects and Methods

This study was conducted on 30 patients proved to have IDA by clinical examination, haemoglobin level and iron profile (Group 1) and 30 age and sex-matched healthy controls (Group 2). Both patients and controls were recruited from Pediatric hematology outpatient clinic or inpatient ward of paediatric department, Beni- suef university hospital.

2.1 Inclusion criteria:

1) Patients with anemia proved to have iron deficiency by clinical examination, haemoglobin level and iron profile.

The subjects included in the study were symptomatic patients with IDA who had normal cardiac structure .

2) Age between 6 monthes -13 years.

3) Both gender included.

- Anemic patients were defined as , children with HB level two standard deviations below the mean for age[6].

Age	*Mean hemoglobin level (g/dL)*	*–2 standard deviations (g/DL)*
Birth (term infant)	**16.5**	**13.5**
1 month	13.9	10.7
2 months	11.2	9.4
3 to 6 months	11.5	9.5
6 months to 2 years	12	10.5
2 to 6 years	12.5	11.5
6 to 12 years	13.5	11.5
12 to 18 years **Males 14.5 g per dL: 13 g per dL.** **Females 14 g per dL: 12 g per dL.**		

***Table(1) Age based HB level* [24,25]**

Exclusion criteria:

1) Other types of anaemia. (chronic haemolytic anemias)

2) Patients with congenital heart disease.

3) Patients with rheumatic heart disease.

4) Patients known e cardiomyopathy .

5)Patients with chronic renal or hepatic disease

6) Patient with history of Blood transfusion

All patients were subjected to:

1) Full history taking including :

a) Age.

b) Sex.

c) Family history of cardiac conditions and positive consanguinity.

D) Nutritional history.

E) History of fatigue, poor activity, exertional dyspnea, breathlessness at rest.

F) Iron supplementation therapy, dose and compliance.

G) History of blood transfusion.

2) Full clinical examination including:

a) General examination.

b) Abdominal examination.

c) Cardiac examination.

3) Investigations:

A) Laboratory:

a. Complete blood picture.

b. Reticulocytic count

c. Serum ferritin.

d. Serum iron.

e. TIBC.

f. Transferrin saturation

B) Imaging:

Transthoracic Echocardiographic Techniques:

All echocardiographic measurements were obtained using the same ultrasound equipment ***(GE Health care , Vivid S5)*** with a 6 MHz transducer. Echocardiographic measures were obtained according to American society of echocardiography guidelines for cardiac chamber quantification by echocardiography in adults [8] including:

Patients were examined in a resting state with prior sedation for non-cooperative infants .They breathe freely during the investigation, whereas older children were investigated for their **Sm** values at end-expiration.

(1) Conventional Transthoracic echocardiography that involved:

A) Two dimensional echocardiography

It was used to measure the followings:

Left ventricular (LV) dimensions:

measurements using M‑mode is from the leading edge to leading edge . **The 2015 ASE/ESCI guidelines** states that "the same range of normal values for LV and RV chamber dimensions and volumes apply for both TEE and TTE.

The measurement of LV diameter taken just below or at the tip of the mitral valve leaflets in the parasternal short axis view.

In M‑mode echocardiography, the M‑mode cursor was aligned just at the tip of mitral leaflets or exactly perpendicular to the inferior wall and passing through the center of the LV cavity will give us a M‑mode trace.

BIPLANE SIMPSON'S METHOD OF MULTIPLE DISCS

This method is the only method currently recommended

for the calculation of LV volumes and EF using 2D echocardiography. This employs the principle of summation of twenty cylindrical discs of equal height. Diameter of the cylinder varies depending on the shape of the LV cavity. This requires the LV cavity to imaged in LAX including the base and apex in two orthogonal planes. The endocardial border has to be drawn and connected at the mitral valve level by a straight line. Inbuilt software in all the echocardiography machines automatically divide this LV area into twenty equal divisions once the LV LAX has been marked from the apex to the middle of the line joining the mitral annulus.

Volume of each of these twenty discs is summated separately in the two orthogonal planes which are the ME 4C and ME 2C with TTE and averaged to give the LV volume.

(PW)-TDI of the lateral mitral annulus was

performed using transducer frequencies of 3–6 MHz with spectral Doppler filters adjusted until a Nyquist limit of 5–20 cm/sec. The minimal optimal gain setting was used. Guided by the four-chamber view, a 2- to 5-mm sample volume was placed at the lateral corner of the mitral annulus at the attachment of the anterior leaflet of the mitral valve.

Care was taken to obtain an ultrasound as parallel as possible to the direction of the mitral annular motion. Peak annular velocities *during systole were recorded and analyzed offline. The resulting* velocities were recorded for three to five cardiac cycles and were averaged.

Statistical Methods

All statistical calculations were done using computer programs Microsoft Excel (Microsoft Corporation, NY, and USA) & SPSS (Statistical package for the social science version 20) statistical programs (SPSS Inc., Chicago, IL, USA). Data were statistically described in terms of mean ± SD, frequency and percentages. Descriptive statistics were done for quantitative data as mean ± SD for quantitative parametric data, while it was done for qualitative data as number and percentage.

- When appropriate,the qualitative variables will be described in the form of frequency and percentages.
- Pearson correlation will be used to correlate quantitive variables fulfilling normal distribution.
- P value(which is either non-significant(NS) if>0.05,significant(S)

If<0.05,or highly significant (HS) if<0.01 will be calculated.

3. Results:

Demographic, clinical, lab and finally echocardiographic results were analysed, summarized, and presented as follow:

1) Demographic and clinical results :

(The two groups were not significantly different with respect to baseline characteristics.)

Both groups were matched regarding age and sex distribution

	Cases	**Controls**	**p**
Age (mean±2sd)	**5.8227± 3.45639**	**6.5074± 2.96608**	**.45**
Weight	**16.2091± 5.93696**	**19.2593± 5.31755**	**.06**
Heart rate	**108.2727± 21.50345**	**107.5556± 15.01367**	**.98**

Data are expressed as mean ± SD

Table (2): base line demographic data

	Cases	**Controls**	**p**
HB	9.6318 ± 1.27443	12.7481 ± .68521	.000
MCV	67.7864 ± 7.60353	83.1852 ± 3.58444	.000
MCH	22.7182 ± 2.60926	25.6000 ± 2.03394	.000
RDW	*16.0727 ± 2.57796*	*13.7963 ± 2.10119*	*.001*
Retics	*1.2727 ± .57170*	*1.1296 ± .49210*	*.35*
PLT	*387.4091 ± 153.63149*	*292.3333 ± 98.84565*	*.012*

Data are expressed as mean ± SD

Table (3) : comparison between cases and controls as regard complete blood picture parameters.

The mean **weight** of cases was 16.2 ± 5.9 kg while that of controls 19.2 ± 5.3 kg with no statistical significant difference between both groups (p value was .06). The mean **heart rate** of cases was 108. ± 21. BPM while that of controls 107. ± 15 BPM with

out statistical significant difference between both groups (p value=.98).

2)Laboratory results :

The mean **hemoglobin** level in cases was 9.6 ± 1.27g/L while the mean

level in controls 12.7 ± .68 g/L (p value=0.00) with highly statistical significant difference .

Serum ferritin level was significantly lower in the IDA patients compared to control group where the mean level was 7.26 ± 7.32 ng/ml in cases and was 199.4 ± 89.4 ng/ml in controls (p-

value=0.00).The **transferrin saturation** showed significant difference in both groups where the mean level was in 11.9 ± 3.7 in cases and was 30.6 ± 5.7 in controls (p-value=0.00).

	Cases	**Controls**	p
Iron	46.3864± 17.82450	92.3704 ± 12.41323	.000
Ferritin	7.26291± 73.20283	199.4444 ± 89.47038	.000
TIBC	390.4545 ± 80.11880	311.4444 ± 37.27067	.000
Tsat	11.9114 ± 3.76341	30.6070 ± 5.76043	.000

Data are expressed as mean ± SD

Table(4) : comparison between cases and controls as regard iron indices

4) Echocardiographic results :

Two dimensional echocardiography with measurement of the followings:

Left ventricular end systolic volume :

The mean value of **LVESV** in case group was 2.0 ± .28 cm while it was 2.1 ± .3 cm in control group without statisticaliy significant difference between both groups, P value was (.64).

The mean value of **LVESV** in male cases was 2.2 ± .2 cm while in female cases was 1.9 ± .2 cm ,P value (.01) with statisticaly significant difference .

Left ventricular end diastolic volume :

The mean value of **LVEDV** in case group was 3.2 ± .4 cm while it was 3.3 ± .4 cm in control

group and P value was (0.27) without significant difference between both groups.

The mean value of LVEDV in male cases group was 3.4 ± .5 cm while it was 3.0 ± .27 cm in female cases , P value was (.05)

Left ventricular ejection fraction :

There was no statistical significant The mean value of **LVEF** among cases was 66. ± 7.%

While it was 67.2 ± 5.5% among controls without statistical significant difference **P value was (.48)** .

The mean value of **LVEF** among male cases was 63.6± 7.4%,while it was 67.6 ± 6.5% in female cases without statistical significant difference (p value >0.05) .

A) Tissue Doppler imaging (TDI) :

peak systolic velocity of mitral annulus (SM)

The mean value of **SM** was .07 ± .04 m/sec in

case group while it was .09± .01 m/sec in control group with statistical significant difference between two groups , P value was (.005) .

SM mean value in male cases was .04 ± .04 m/sec while it was .09 ± .017 m/sec in female cases , P value .002

	Cases	**Controls**	**p**
LVEF	66.0000 ± 7.03732	67.2593 ± 5.57186	.48
LVEDV	3.2227 ± .41165	3.3519 ± .40608	.27
LVESV	2.0864 ± .28502	2.1259 ± .31329	.64
SM	.0718 ± .04205	.0970± .01203	.005

Data are expressed as mean ± SD

Table (5) : comparison between cases and controls as regard echo findings.

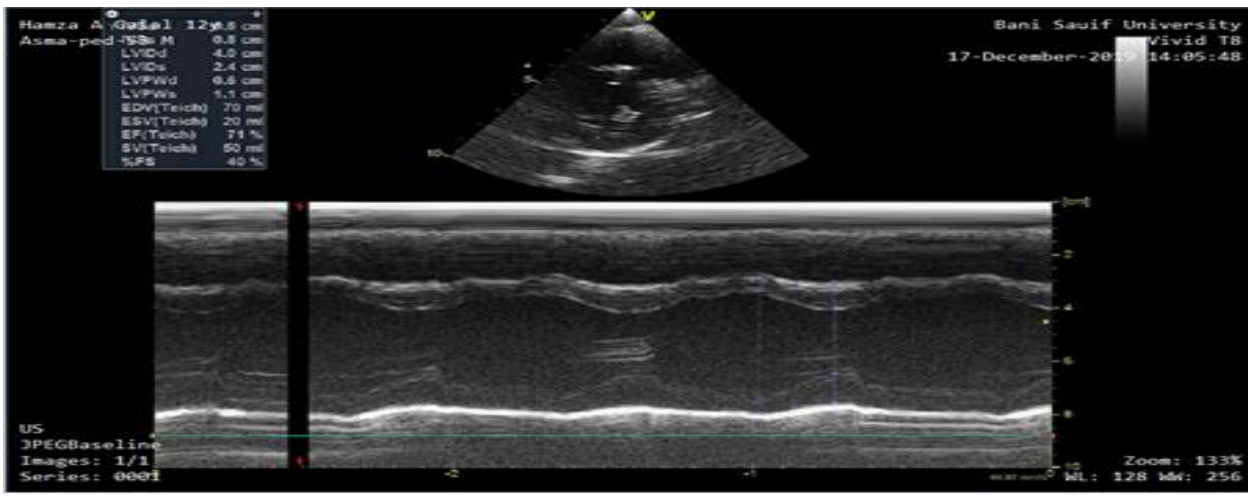

Figure 1: Transthoracic echocardiography (TTE) demonstrating LV systolic function using M-Mode.

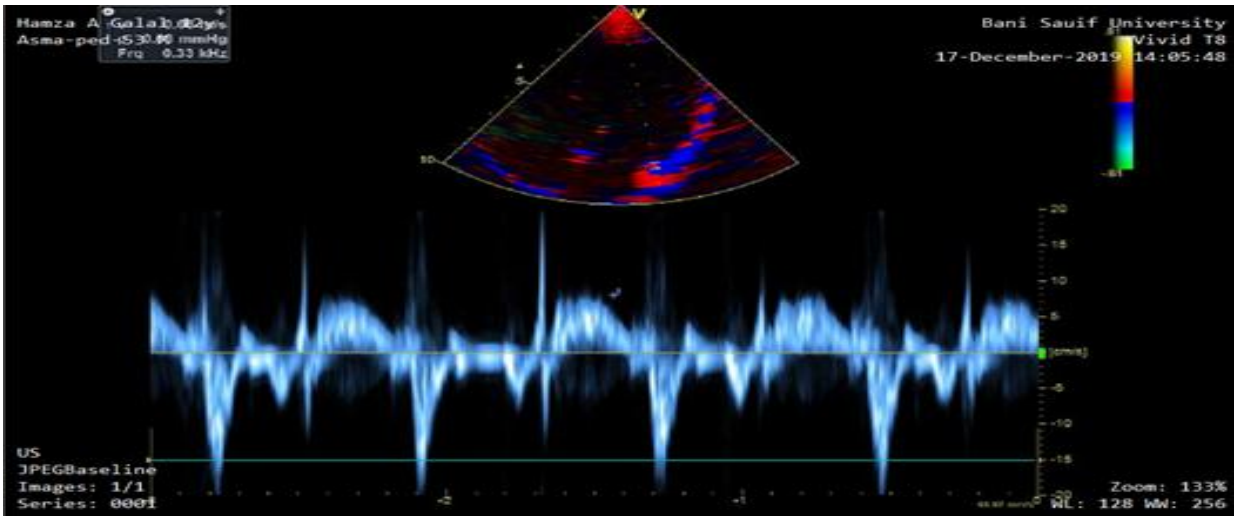

Figure 2: **peak systolic velocity of mitral annulus (SM)** using tissue doppler imaging

		LVEF	LVEDV	LVESV	SM
BSA	Pearson Correlation	.256	**.746****	**.543****	-.213-
	Sig. (2-tailed)	.251	**.000**	**.009**	.341
Weight	Pearson Correlation	.255	**.740****	**.537****	-.198-
	Sig. (2-tailed)	.252	**.000**	**.010**	.376
Height	Pearson Correlation	-.098-	**-.716-****	**-.570-****	.361
	Sig. (2-tailed)	.663	**.000**	**.006**	.099
HB	Pearson Correlation	.349	.316	.062	-.280-
	Sig. (2-tailed)	.111	.152	.786	.207
Iron	Pearson Correlation	.298	.244	-.009-	-.055-
	Sig. (2-tailed)	.178	.273	.968	.807

Ferritin	Pearson Correlation	.175	.093	-.018-	.184
	Sig. (2-tailed)	.437	.680	.937	.413
TIBC	Pearson Correlation	-.007-	.256	.189	-.042-
	Sig. (2-tailed)	.977	.250	.399	.854
Tsat	Pearson Correlation	.347	.162	-.095-	-.047-
	Sig. (2-tailed)	.113	.471	.673	.836
LVEF	Pearson Correlation	1	.120	**-.496-***	.171
	Sig. (2-tailed)		.595	**.019**	.448
LVEDV	Pearson Correlation	.120	1	**.790****	**-.520-***
	Sig. (2-tailed)	.595		**.000**	**.013**
LVESV	Pearson Correlation	**-.496-***	**.790****	1	**-.514-***
	Sig. (2-tailed)	**.019**	**.000**		**.014**
SM	Pearson Correlation	.171	**-.520-***	**-.514-***	1
	Sig. (2-tailed)	.448	**.013**	**.014**	

Table (6): Correlations between echo findings and other study parameters in the patient group.

Sm was negatively correlated with LVEDD , LVESD (R=**--.520-**, P=**.014)**

There was no correleation statisticaly significant between iron and SM .

4. Discussion:

Anemia has been shown to be an important factor in increasing cardiac output to maintain adequate oxygen supply to the tissues [4]The transition from a high output (compensated) state to a state of LV dysfunction (decompensated) and LV remodling is manifested by echocardiography finding in patients with hemoglobin level ranging from 6-9 g/dL in iron-deficient patients [9]. The reduction of hemoglobin level is related to future increased morbidity and mortality [10]. So early diagnosis and treatment of iron deficiency can

greatly improve quality of life and can promptly reduce hospitalization rate, and ultimately, reduce medical consumption [11].

Tissue Doppler Imaging is a relatively new Doppler ultra- sound modality that records regional systolic and diastolic velocities within the myocardium. It allows quantitative measurement of both systolic and diastolic velocities directly from the ventricular myocardium during the systole and diastole [12]. This technique can show additional information compared with other echocardiography techniques, detecting even minor changes before the occurrence of abnormal indices of global ventricular dysfunction .[13].

The aim of this study was to assess the systolic left ventricular functions of children with IDA using conventional trans-thorathic echocardiography measures in addition to pulsed tissue Doppler imaging and to determine whether this latter echocardiographic technique is an adequate diagnostic tool for the screening and detection of subclinical cardiac dysfunction compared with conventional transthorathic echocardiography.

Regarding the demographic results both groups were matched for age and sex distribution. The weight and BSA were matched in cases and controls group.

Regarding the laboratory results the platelet count in patients with IDA was increased reflecting an accelerated rate of hematopoiesis, (reactive thrombocytosis), this was in agreement with Xavier-Ferrucio et al [14] that recognized the association between IDA and the thrombocytosis and its underlying physiology .

Transferrin saturation was significantly lower among cases reflecting affinity for iron .

Regarding the echocardiographic results, by two dimentional Echocardiography Left Ventricular end diastolic volume (LVEDV), Left Ventricular end systolic volume (LVESV),Left Ventricular ejection fraction (LVEF), as calculated by simpson's rule show no statistical significant differences between both groups(p value >0.05), this result was in agreement with [15] where they found no statistical significant difference between LV dimentions of cases of IDA and controls as measured by conventional 2D echocardiography M- mode,but they recorded a statistical significant difference between IDA cases and controls using speckle tracking echocardiography . However several studies reported a significantly lower LVEF % and significant difference between LVED, LVES dimentions between IDA cases and controls where a low HB level cause heart enlargement , LV mass and LV filling pressure increase in patients with IDA [16].This may be explained by the fact that it require a long standing non treated anemia and iron deficiency to change from a high output (compensated) state to a state of LV dysfunction and heart failure (decompensated),and due to the lack of data regarding duration of IDA among our case group, affection of LV dimentions is not significant .

By TDI derived peak systolic velocity of mitral annulus (SM) was significantly lower in patients group in comparison with control group with P value (0.005). A decreased SM has been showen as a marker of reduced LV long axis systolic function according to [17]who suggested the SM to be more sensitive index of global LV contractility than the LVEF. So The impaired SM as detected by TDI in patients with normal conventional echocardiographic measurements, supported the idea that TDI can be an early sensitive indicator of cardiac dysfunction in asymptomatic IDA patients. It has been reported that SM better reflects LV contraction than LV end-systolic echocardiographic indices in healthy adults according to [18] **.**

This finding was in agreement with the report of [19], [20] authors who found that , Measurement of myocardial velocities by tissue Doppler imaging (TDI) is a promising approach for quantitative assessment of longitudinal systolic ventricular performance in adults.

TDI enables measurements of atrio-ventricular and regional myocardial velocities, and may be more sensitive than conventional echocardiography in detecting abnormal left ventricular (LV) systolic function [21],[22].

SM may be an attractive technique because of its simplicity and ease of application to screen subclinical affection of contractility in IDA patients**.**

There was a negative correlation between SM and LV dimensions and this may be explained by the [16] who found that dilatation of cardiac chambers occur in response to anemia and this is reflected as low SM value which indicates contractility impairment **.**

There was no correlation between HB level or ferritin level and SM or LVESD, LVEDD. This is against what was reported by Jiaqi et al [23], who reported a significant correlation between HB level and LV dimensions . this could be explained that we did not have the duration of the anemia before the diagnosis and the study , although it might affect the contraction of the myocardium.

A potential limitation of our study is that we did not have enough patients with severe IDA , because patients with hemoglobin level below 7 mg/dl were immediately cured . thus there duration at severe anemia stage did not last long .

The study revealed preserved LV systolic functions as detected by conventional echocardiography however tissue Doppler imaging technique had shown latent LV systolic dysfunction.

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