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Original Research Article

A study of left ventricular diastolic dysfunction in patients of sickle cell disease

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ABSTRACT

Background: Left ventricular diastolic filling patterns are altered in patients with sickle cell anaemia and these diastolic abnormalities may be present in the absence of heart failure. These abnormal patterns suggest an intrinsic myocardial abnormality in patients with sickle cell anaemia and may prove to be early markers of cardiac disease. The ventricles do not properly relax and become stiff meaning they cannot fill with blood properly.
Methods: This study was carried out in tertiary health care hospital in western India, where homozygous sickle cell disease patients and age and haemoglobin matched controls were taken into cross sectional observational study design.
Results: The mean values of E, A, E/A, IVRT, DT, AT, were in normal range in controls. In cases although the mean values of E, A, E/A, IVRT, DT, AT were in normal range, there were 19 cases of sickle cell anaemia who had significant alteration in indices of diastolic LV function from normal range. Out of these 20 cases with diastolic dysfunction, 11 cases had significant increase in (E) velocity from normal range with E/A ratio more than 2 suggestive of restrictive filling pattern of diastolic dysfunction while in 8 cases E value was less than normal with increase in (A) velocity and E/A ratio was less than 1 suggestive of impaired relaxation pattern of diastolic dysfunction. When indices of diastolic LV function were compared in cases and controls, mean early peak filling velocity (E) was significantly higher in cases.
Conclusions: In present study, out of 37 cases 19 (51%) cases had LV diastolic dysfunction. Of these 19 cases with diastolic dysfunction, 11 cases had restrictive filling pattern and 8 cases had impaired relaxation pattern of diastolic dysfunction.

Keywords: Sickle cell disease, LV diastolic dysfunction, Systolic dysfunction

INTRODUCTION

Sickle cell disease, a haemoglobinopathy, affects all systems of the body. The sickle cell trait (AS) in which the sickle cell gene is inherited from one parent and a normal BA chain gene from other, results in a benign condition.

The homozygous Sickle cell disease (SS) in which the sickle cell genes are inherited from both parents results in variety of pathological conditions cardiovascular abnormalities are observed in majority of patients of sickle cell anaemia. Cardiovascular abnormalities are more severe and more common in SS than in other forms of anaemia which is attributed to chronicity and severity of anaemia.

The cardiovascular system of patients with sickle cell disease is subjected to a series of long-term stresses. Among these, a raised cardiac output, consequent to reduced oxygen carrying capacity of blood is probably of paramount significance. Arterial oxygen unsaturation and thrombotic occlusion of vascular bed is a contributing factor.[1]

Left ventricular diastolic filling patterns are altered in patients with sickle cell anaemia and these diastolic

abnormalities may be present in the absence of heart failure. These abnormal patterns suggest an intrinsic myocardial abnormality in patients with sickle cell anaemia and may prove to be early markers of cardiac disease.

Diastolic dysfunction refers to when the diastole part of this action is abnormal. The ventricles do not properly relax and become stiff meaning they cannot fill with blood properly. Diastolic dysfunction is an independent risk factor for death in patients of sickle cell disease.

The precise role of sickling in the pathogenesis of cardiomyopathy is not clear. It is possible that clumping of sickled RBCs within smaller vessels of myocardium interferes with cellular metabolism and thereby results in avascular necrosis of myofibrils and their subsequent replacement with fibrous tissue.[2]

One of the major problems in making a diagnosis of cardiomyopathy is the lack of a sensitive tool to detect ultra-structural changes in myocardium. The gold standard for detection of cardiomyopathy is endomyocardial biopsy, which is not a feasible procedure to be applied to the community. Echocardiography is a useful non-invasive technique to study changes in cardiac structure and function.[3]

Objectives

The objectives of this study were (a) to study left ventricular diastolic functions in patients of sickle cell anemia by echocardiography; and (b) to compare echocardiographic parameters of patients of sickle cell anemia with that of patients who are anemic without sickle haemoglobinopathy.

METHODS

The study type was cross sectional observational study. The study was carried out at SMIMER Hospital, Surat, Gujarat, India**.** The study period was from November 2019 to December 2021.

The homozygous sickle cell disease patients and age and haemoglobin matched controls were taken. All patients were subjected to 2D echocardiography and sickling slide test by sodium metabisulfite, peripheral smear and Hb electrophoresis to confirm homozygous nature of disease.[4] The study was carried out for 15 months, after ethical approval and all patients were made to sign informed consent in native language.

Sample size

The sample size was calculated using following formula:

$$N = \frac{(Z_{\frac{\alpha}{2}})^2 * p * (1-p)}{MOE^2}$$

Where $Z_{\alpha/2}$ is the critical value of the normal distribution at α/2 (level of significance), MOE is the margin of error (10%), p is the sample proportion (35), (1-p) is the q value, and N is the population size.

Sample size was calculated on the basis on the prevalence of homozygous sickle cell disease in Asia based on the study Hockham et al. The spatial epidemiology of sickle-cell anaemia in India.[5]

Sample size was 35±2.

Inclusion criteria for case group

This study included patients of sickle cell disease (SS), (HB<7 g) age between 18-45 years; (b) patients of sickle cell disease (SS), (HB<7 g) free of crisis for 2 weeks prior to study; (c) no history of blood transfusion in preceding 3 months; and (d) attending outpatient department and those admitted in wards and willing to participate in the study were enrolled in the present study.

Inclusion criteria for control group

Age, gender and hemoglobin matched subjects of anemia without any haemoglobinopathy attending OPD and those admitted in wards and willing to participate in study were included.

Exclusion criteria for case and control group

Exclusion criteria for patients was (a) age<18 years and above 45 years; (b) structural heart disease (valvular/congenital); (c) IHD (history suggestive of IHD or documented on ECG); (d) hypertension (systolic BP≥140 or diastolic BP≤90,according to JNC 7 criteria); (e) diabetes mellitus (BSL fasting>126 mg/dl, post meal/casual BSL>200 mg/dl; (f) heavy smoker (more than 15 cigarettes per day for more than 20 years) and excessive smoker (more than 20 cigarettes per day for more than 20 years); (g) chronic alcoholic [habitual use of alcoholic beverages in poisonous amounts for a long period of time; more than 60 g (male), more than 20 g (female) per day for more than 10 years]; and (h) chronic obstructive airway disease.

The following variables of diastolic function were studied and the normal range of (a) peak velocity E wave (cm/sec): 85±16cm/sec; (b) peak velocity A wave (cm/sec): 58±13 cm/sec; (c) E/A ratio: 1-2; (d) Isovolumetric relaxation time (IVRT)- it is the time taken from aortic valve closure to mitral valve opening. Normal value is 74±26 msec; (e) Acceleration time (AT): measured from onset of diastolic filling to peak of E wave. Normal 90-110 msec; and (f) deceleration time: peak of E wave to the end of E wave. Normally less than 220 msec.

Ethical approval was obtained from committee in November 2019.

Statistical analysis

Statistical analysis was done by student 't' test in Microsoft excel, probability value of $p<0.05$ was significant and $p<0.01$ highly significant.

RESULTS

The following results were obtained in 2D ECHO findings of cases and controls. In present study, all the indices of diastolic LV dysfunction such as E, A, E/A, IVRT, DT, AT were in normal range in all controls. Also, the mean values of E, A, E/A, IVRT, DT, AT, were in normal range in controls. In cases although the mean values of E, A, E/A, IVRT, DT, AT were in normal range, there were 19 cases of sickle cell anaemia who had significant alteration in indices of diastolic LV function from normal range. Out of these 20 cases with diastolic dysfunction, 11 cases had significant increase in (E) velocity from normal range with E/A ratio more than 2 suggestive of restrictive filling pattern of diastolic dysfunction while in 8 cases E value was less than normal with increase in (A) velocity and E/A ratio was less than 1 suggestive of impaired relaxation pattern of diastolic dysfunction. When indices of diastolic LV function were compared in cases and controls, mean early peak filling velocity (E) was significantly higher in cases 0.93±0.23 m/s than in controls 0.78±0.07 m/s with p=0.0002.

Late active filling velocity (A) was also significantly increased in cases 0.63±0.08 m/s than in controls 0.60±0.07 m/s. Mean E/A ratio was significantly higher in cases than in controls. Mean IVRT was increased in cases 77.291±18.12 msec than in controls 62.71±5.521 msec with p value<0.0001. Mean AT was decreased in cases as compared to controls.

Table 1: Gender wise distribution of cases and controls.

Subjects	Cases (N=37)	Controls (N=38)
Male	14 (38%)	19 (50%)
Female	23 (62%)	19 (50%)

Table 2: Haemoglobin range in cases and controls.

Hb (g/dl)	Cases (N=37)	Controls (N=38)
Below 4	0 (0%)	0 (0%)
4-5.5	12 (32%)	12 (31%)
5.6-6.5	12 (32%)	14 (37%)
6.6-7	13 (35%)	12 (31%)
Above 7	0 (0%)	0 (0%)

Table 3: Comparison of LV diastolic function indices in the study.

Diastolic indices	Normal range	Cases (N=37)	Controls (N=38)	P value
E (m/s)	0.85±16	Mean±SD	Mean±SD	0.0002
A (m/s)	0.58±13	0.93±0.23	0.78±0.07	0.088
E/A	1-2	0.63±0.08	0.60±0.07	0.011
IVRT (msec)	74±26	1.53±0.511	1.31±0.116	<0.0001
DT (msec)	<220	77.29±18.12	62.71±5.521	0.004
AT (msec)	90-110	168.62±42.87	142.47±9.385	0.0033

DISCUSSION

In present study LV diastolic dysfunction was observed in significant number of cases of sickle cell anaemia. Kingue et al reported that peak early mitral filling velocity (E) and late active filling velocity (A) are significantly increased in cases of sickle cell anaemia than in controls indicating diastolic dysfunction.[10] In the study of Taksande et al (E) and (A) wave amplitudes were increased in cases of sickle cell anaemia than in controls although the difference was not statistically significant in their study.[12] In their study, early peak mitral filing velocity (E) was significantly higher in cases (0.93±0.23 m/s) than in controls (0.78±0.07 m/s; p=0.0002). Late active filing velocity (A) was also significantly more in cases (0.63±0.08 m/s) than in controls (0.60±0.07 m/s; p=0.088).

Andrade et al reported decreased E/A ratio in cases (1.902+ 0.453) than in controls (2.266±0.780) with P value 0.052 indicating diastolic dysfunction in cases of sickle cell anaemia.[11] Taksande et al also reported increased DT in cases (126.96±5.88 msec) than in controls (120.83±32.66; p=0.393) however the difference was not statistically significant in their study.[12] In present study, DT was significantly more in cases (168.62±42.87 msec) than in controls (142.47±9.385 msec; p=0.004). AT was less in cases of sickle cell anaemia (67.90±14.50 msec)

than in controls (72.80±13.50 msec) in the study of Taksande et al.

In present study also AT was less in cases of sickle cell anaemia (90.46±8.93 msec) than in controls (95.55±5.166 msec; p=0.0033).

LV diastolic dysfunction prevalence

In present study, out of 37 cases of sickle cell anaemia, 19 (54%) cases had echocardiographic parameters suggestive of diastolic dysfunction, while no dysfunction was present in controls.

Of the 19 cases with diastolic dysfunction, 11 cases had restrictive filling pattern of diastolic dysfunction i.e. increased E velocity with an increased E/A ratio; DT less than 160 msec and isovolumetric relaxation time <70 msec.

In these patients, the compliance is decreased in early diastole, causing a considerable increase in pressure for small changes in volume. These patients have high left atrial pressures which accelerate mitral valve flow during early diastole and cause rapid early filling i.e.; increased (E) velocity. Since the LV pressure rises rapidly prior to atrial contraction, atrial contribution reduced and there is a corresponding decrease in (A) velocity i.e.; increased E/A ratio. A decrease in DT is seen as the LV pressure increases rapidly, leading to rapid equalization of LA and LV pressure. 8 cases had abnormal relaxation pattern of diastolic dysfunction i.e.; decreased (E) velocity with decreased E/A ratio; DT more than 240 msec and IVRT more than 90 msec. In these patients, due to delay in active relaxation of LV which maintains a higher LV pressure gradient, the time from aortic valve closure to mitral valve opening (IVRT) is increased. With a prolonged relaxation time and a higher LV pressure, the pressure gradient existing at the time of mitral valve opening is low with a subsequent increase in (E) velocity. The prolonged pressure drop of LV tends to increase the time for LA and LV pressure to equalize resulting in a prolonged DT. As a consequence of less filling in early filling phase, the late filling from atrial contraction (A) is increased leading to prominent (A) wave and decreased E/A ratio. However, none of these 19 cases patients of sickle cell anaemia with diastolic dysfunction had signs or symptoms of congestive cardiac failure.

Limitations

In present study, the study population was small. For confirmation of results of present study, a large study sample of patients of sickle cell anaemia is required. It was a cross sectional analytical study and there was no follow up of cases of sickle cell anaemia. As the diastolic dysfunction precedes systolic dysfunction in most cardiovascular disorders, the cases of sickle cell anaemia with diastolic dysfunction in present may eventually develop systolic dysfunction as well, but repeat Echocardiographic follow up and evaluation of systolic function was beyond the scope of this study.

CONCLUSION

In present study, out of 37 cases 19 (51%) cases had LV diastolic dysfunction. Of these 19 cases with diastolic dysfunction, 11 cases had restrictive filling pattern and 8 cases had impaired relaxation pattern of diastolic dysfunction. Systolic dysfunction was not observed in any subject in present study. All controls were having normal LV systolic and diastolic function.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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