Cardiology in the Young (2015), **25**, 1319–1325
doi:10.1017/S1047951114002455

Original Article

Left ventricular function by echocardiogram in children with sickle cell anaemia in Mumbai, Western India

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Abstract *Introduction:* Cardiovascular events and complications are the leading cause of mortality and morbidity in patients with sickle cell disease. Cardiac abnormalities occur frequently and at an early stage in sickle cell anaemia patients, despite being more evident in adulthood. Sickle cell anaemia patients are increasingly able to reach adulthood owing to improved healthcare, and may, therefore, suffer the consequences of chronic cardiac injury. Thus, the study of cardiac abnormalities is essential in children *Objective:* The aim of this study was to determine the echocardiographic changes in left ventricular function in children suffering from sickle cell disease in Mumbai, Western India. *Methods:* The study comprised of 48 cases of sickle cell anaemia and 30 non-anaemic controls with normal haemoglobin and electrophoresis pattern. M-mode, two-dimensional, and Doppler echocardiographic measurements of patients and controls were performed according to the criteria of the American Echocardiography Society. *Results:* On Doppler study, the A wave height was increased and the E/A ratio was decreased, whereas the deceleration and isovolumetric relaxation times were prolonged, which is typically seen in slowed or impaired myocardial relaxation ($p < 0.001$). Although chamber dilatations were present, echocardiographic parameters showed no statistically significant correlation with severity of anaemia and age among the sickle cell patients. *Conclusions:* We conclude that the increased left ventricular stiffness, compared with controls, might be due to fibrosis related to ischaemia caused by SS disease in addition to wall hypertrophy.

Keywords: Sickle cell anaemia; deceleration time; isovolumetric relaxation time

Received: 22 April 2014; Accepted: 18 November 2014; First published online: 18 December 2014

Haemoglobin S occurs when thymine is exchanged for adenine at the sixth codon of the β-globin gene. This exchange encodes valine instead of glutamine in the β-globin molecule. Haemoglobin S accounts for over 50% of all haemoglobin and is as high as 80–90% of the total haemoglobin in sickle cell anaemia.[1]

Herrick[2] first described the characteristic sickle-shaped erythrocytes in 1910. It is prevalent in many parts of India, including Central India, where its prevalence in different communities ranges from 9.4 to 22.2%.[3] Cardiac complications are an important cause of the morbidity and mortality associated with this disease.

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The chronic anaemia associated with sickle cell disease results in an increase in cardiac output with only a minimal increase in heart rate. The left ventricular stroke volume increases with significant dilation of the left ventricle,[4] and the degree of left ventricular dilation is closely linked to the degree of anaemia.[5] The dilated left ventricle adapts to the increased wall stress by developing eccentric hypertrophy in which the wall is thickened and the myofibers are elongated. Eccentric hypertrophy allows the left ventricle to adapt to chronic volume overload by initially preserving diastolic compliance and maintaining normal filling pressures. Over time, progressive dilation leads to increased wall stress and an increase in left ventricular mass.[6]

The study of heart abnormalities associated with sickle cell anaemia has become essential because these

cardiac alterations occur frequently in adulthood, but may also occur at a much earlier stage in sickle cell anaemia patients. This has been observed despite the current context of sickle cell anaemia care, in which improvements to health conditions have decreased mortality, especially in the first 5 years of life, thus leading to delayed disease-related mortality.[7] These children have been increasingly able to reach adulthood, thus suffering the consequences of chronic cardiac damage. Overall, the search for better understanding of this issue has increasingly become more relevant.

The aim of this study was to determine echocardiographic changes in left ventricular function in children suffering from sickle cell disease in Mumbai, Western India.

Materials and methods

Study population

This prospective controlled study was conducted from 1 January, 2013 to 31 January, 2014 at our institute. The study comprised 48 cases of sickle cell anaemia and 30 non-anaemic controls (Hb > 11 gm/dl) with normal haemoglobin and electrophoresis pattern. The control group patients were comparable in age and sex, free from any cardiovascular disorder and not taking any cardioactive drugs. Detailed clinical examination and investigations including haemogram, chest radiogram, and electrocardiogram were obtained in the study cases. Each patient underwent an echocardiographic study including M-Mode, two-dimensional, colour Doppler indices using a GE Vivid i echocardiographic machine (GE Medical Systems, Israel Ltd., Israel). Standard techniques were used to obtain the measurements in a quiet, wakeful, and non-sedated state, and all the measurements were made by only one cardiologist in Lokmanya Tilak Medical and General Hospital, Sion, Mumbai, while in a clinically stable state. The examination was conducted with the patient lying in supine position. Patients were crisis free for at least 2 weeks before the study.

Inclusion criteria

Diagnosed cases of sickle cell anaemia by haemoglobin electrophoresis under 18 years of age.

Exclusion criteria

Those who:

- had received recent – in the preceding 3 months – blood transfusion;
- had haemoglobinopathies other than sickle cell disease;
- had known congenital or acquired cardiac or pulmonary diseases;
- had electrocardiographic abnormalities that might affect the interpretation of the echocardiographic findings; or
- had any medical conditions other than anaemia affecting their myocardial performance. Patients with inadequate acoustic windows were also excluded.

Echocardiographic measurement

The left atrial dimensions, left ventricular end-systolic, and left ventricular end-diastolic dimensions were measured by M-mode according to the recommendation of the American Society of Echocardiography. The left ventricular ejection fraction, fractional shortening, and left ventricular mass were calculated. The left ventricular mass and left ventricular mass index were calculated according to the formula described by Devereux et al.[8]

To record left ventricular inflow velocities, the pulsed-wave Doppler sample volume was placed at the level of the tips of the mitral valve leaflets in the apical four-chamber view where the highest peak velocity was recorded. Peak flow velocities of the left ventricular inflow in early diastole (E) and late diastole with atrial contraction (A) were measured. E/A velocity ratios were calculated for each cardiac cycle. The deceleration time was measured as the interval between the peak of the E wave and the point at which the descending segment of the E wave crosses the zero velocity line. Left ventricular isovolumic relaxation time was measured as the interval between aortic valve closure and the onset of mitral flow. The pulse wave Doppler Tei index was calculated.[9] Tissue Doppler was performed from the four-chamber apical view. The peak mitral annular velocity (e') was measured using the echo machine calibration tool and electronic callipers. The E/e' ratio was used as a measure of global left ventricular diastolic function.

Each measurement was obtained for three cardiac cycles and their arithmetic average was obtained.

With continuous-wave Doppler, the maximum peak tricuspid jet velocity recorded from any view was used to determine the pulmonary artery systolic pressure with the simplified Bernoulli equation, with right atrial pressure assumed to be 10 mmHg. A tricuspid regurgitant jet velocity of 2.5 m/second or more, which corresponds to a systolic pulmonary artery pressure of 30 mm Hg, has been used to define elevated pulmonary artery pressure in patients with sickle cell disease.[10,11]

Statistical analysis. Data were represented as means ± standard deviation for continuous variables and as proportions for categorical variables. Comparisons of continuous variables between groups were created by independent Student's t-test. For discrete variables,

https://doi.org/10.1017/S1047951114002455 Published online by Cambridge University Press

Table 1. Demographic characteristics of sickle cell disease patients versus normal controls.

Variables	Study group ($\bar{X} \pm SD$) (n = 48)	Control group ($\bar{X} \pm SD$) (n = 30)	p value
Age (years)**	11.19 ± 3.63	10.3 ± 3.85	0.189 (NS)
Gender (%)***			
Male	27 (56.2)	19 (63.3)	0.536
Female	21 (43.8)	11 (36.7)	NS
Weight (kg)**	19.94 ± 6.83	28.16 ± 9.71	0.001*
Height (cm)**	114.33 ± 13.60	131.31 ± 17.17	0.001*
HR (bpm)	90 ± 10	88 ± 12	0.473
Systolic BP (mmHg)	92 ± 12	94 ± 11	0.453
Diastolic BP (mmHg)	62 ± 7	70 ± 6	0.001*
Hb	8.40 ± 1.38		
Retic	2.75 ± 1.55		

BP = blood pressure; Hb = haemoglobin; HR (bpm) = heart rate (beats per minute)
*Significant
**By the Student's t-test
***By chi square test

distribution between groups was compared with the χ^2 test. The multivariate Pearson's correlation coefficient was applied to determine the relationships of diastolic dysfunction parameter E/e' with pulmonary artery systolic pressure, age, haemoglobin level, and number of crises. All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS Inc., Chicago, Illinois, United States of America) software version 11.0 and EPi-Info version 3.4. Statistical tests with two-tailed probability values <0.05 were considered statistically significant. A value of $p < 0.05$ was considered statistically significant. The figure was constructed using the application GhaphPad Prism 5 (GraphPad Software, San Diego, California, United States of America).

Informed consent from the patients and/or their guardians was obtained.

Results

In the study cases, the age range was from 5 to 18 years, with the mean age of 11.19 ± 03.63 years. There were 27 boys and 21 girls in the study group. On cardiovascular examination, mean heart rate was 90 ± 11 beats/minute, which was slightly higher compared with controls, mean blood pressure was 92 ± 12/ 62 ± 7 mmHg. Mean haemoglobin level was 8.4 ± 1.38 gm% in study cases (Table 1). Severe anaemia, haemoglobin levels under 7 gm%, was present in 26 (54%) cases. On chest X-ray, cardiomegaly was detected in 22 (46%) cases. The electrocardiographic changes of left ventricular hypertrophy were present in two (5%) cases.

All the patients reported taking vitamin supplements with B complex vitamins. In all, five patients received hydroxyurea, none used deferasirox, and six children used prophylactic antibiotics. Almost all the patients were hospitalised at some point of time and received blood transfusions, exact details of which were not available.

Echocardiographic measurements in patients with sickle cell anaemia were compared with those of non-anaemic controls with a normal haemoglobin electrophoresis pattern (Table 2). Patients with anaemia (study cases) had higher left ventricular internal dimension in diastole, left atrial dimension in systole, and left ventricular mass in comparison with those who were non-anaemic (controls) with a normal haemoglobin electrophoresis pattern ($p < 0.001$) (Table 2). On Doppler study, "E" (100.9 ± 11.95, 89.30 ± 2.73, $p < 0.001$) and "A" (71.85 ± 15.65, 42.33 ± 2.38, $p < 0.001$) wave amplitudes were higher in sickle cell anaemia cases as compared with the controls. The A wave height was increased and the E/A ratio was decreased, whereas the deceleration and isovolumetric relaxation times were prolonged ($p < 0.001$), which is typically seen in slowed or impaired myocardial relaxation. In addition, by tissue Doppler, E/e' ratio was higher ($p < 0.001$) (Table 2). A total of 11 patients (23%) had pulmonary artery systolic pressure >30 mmHg (Fig 1).

Systolic parameters showed no statistically significant difference between sickle cell anaemia patients and healthy controls (Table 2). Pulse wave Doppler left ventricular myocardial performance index – that is, the Tei index was slightly on the higher side.

Left atrial dimension in systole (mean 21.27 ± 4.27 mm) and left ventricular internal dimension in diastole (mean 36.91 ± 3.02 mm) were more in patients with haemoglobin levels under 7 gm% as compared with those with haemoglobin levels over 7 gm% (19.58 ± 5.22, 33.96 ± 5.39 mm). Although cardiac chambers were dilated, no statistically significant correlation was found between echocardiographic

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Table 2. Comparison among variables between the study and control groups (LV structure, volumes, systolic and diastolic function.)

Echo variables	Study group ($\overline{X} \pm SD$) (n = 48)	Control group ($\overline{X} \pm SD$) (n = 30)	p value
A. *LV structure, volumes, and systolic function*			
LA(mm)	20.35 ± 4.84	19.63 ± 2.95	0.416 NS
LVIDd (mm)	35.31 ± 4.66	27.47 ± 5.16	0.001*
LVIDs (mm)	23.27 ± 04.04	17.43 ± 3.90	0.001*
SV (ml)	31.32 ± 9.32	22.40 ± 4.67	0.001*
FS%	31.68 ± 5.80	30.20 ± 3.50	0.302
EF%	67.00 ± 7.50	66.00 ± 4.40	0.452
LV mass index(g/m^2)	65.50 ± 7.92	52.97 ± 6.39	0.001*
B. *LV diastolic function*			
LV E (cm/second)	100.90 ± 11.95	89.30 ± 2.73	0.001*
LV A (cm/second)	71.85 ± 15.65	42.33 ± 2.38	0.001*
E/A	1.46 ± 0.30	2.12 ± 0.14	0.001*
LV DT (ms)	165.08 ± 15.51	157.83 ± 11.44	0.020*
IVRT (ms)	78.04 ± 10.58	72.00 ± 7.36	0.003*
Tei index	0.44 ± 0.12	0.31 ± 0.9	0.3251*
A duration(ms)	107.96 ± 21.48	107.37 ± 06.75	0.860 NS
LA (ml)	24.46 ± 03.86	20.00 ± 02.96	0.001*
E/e' ratio	7.8 ± 0.9	5.8 ± 1.9	0.001*
PASP by TR Jet	28.94 ± 6.75	24.10 ± 1.54	0.004*

E/A = early diastole (E) and late diastole with atrial contraction (A); LA = left atrial dimension in systole; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; LV E = mitral inflow velocity in early diastole; LV A = mitral inflow velocity in late diastole; IVRT = isovolumic relaxation time; DT = deceleration time; SV = stroke volume; FS = fractional shortening; EF = ejection fraction; LV = left ventricular; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation; e' = peak mitral annular velocity

By Student's t-test

*Significant

Figure 1.
Prevalence of pulmonary artery hypertension in sickle cell patients.

parameters, M-mode and Doppler, and severity of anaemia in the sickle cell patients (Tables 3 and 5).

Left atrial dimension in systole (mean 22.31 ± 3.86 mm) and left ventricular internal dimension in diastole (mean 36.69 ± 4.06 mm) were higher in patients above 10 years of age, as compared with those below 10 years of age (mean 17.37 ± 4.73, 33.21 ± 4.83 mm) (Table 4). Again, although cardiac chambers were dilated, echocardiographic parameters, M-mode and Doppler, showed no statistically significant correlation with age in the sickle cell anaemia patients (Table 5).

A significant correlation of left ventricular E/e' ratio with frequency of crisis (Pearson's correlation = 0.3122*, p = 0.03075*) was found but not with pulmonary artery systolic pressure (Table 5).

Discussion

Left ventricular systolic and diastolic function

Patients in the present study had Doppler evidence of a diastolic dysfunction. The systolic and diastolic dimensions and left ventricular muscle mass were increased compared with controls; however, systolic function remained normal. The A wave height was increased and the E/A ratio was decreased, whereas the deceleration and isovolumetric relaxation times were prolonged; this pattern is typically seen with slowed or impaired myocardial relaxation. Taken together, these changes indicate early diastolic dysfunction. Decreasing e', and, therefore, increasing E/e' ratio, values reflect a decrease in relaxation ability – that is, increasing stiffness – of the left ventricle. This was supported by the observed significant increase in the E/e' ratio in the study group.

The cardiovascular system is known to be stressed by chronic anaemia, recurrent small pulmonary artery occlusion, and myocardial haemosiderosis. Autopsy studies have revealed that right and left ventricular dilation is common in both children and adults.[12] Large screening echocardiographic studies have indicated that left ventricular systolic function was preserved in the majority of sickle cell disease patients studied at rest,[13–15] and that the presence of

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Table 3. Echocardiographic and echo-doppler parameters of sickle cell disease patients versus controls among haemoglobin levels.

Variables	Study group ($\overline{X} \pm SD$) <7 Hb (n = 26)	>7 Hb (n = 22)	p value
LA(mm)	21.27 ± 4.27	19.58 ± 5.22	0.223 NS
LVIDd (mm)	36.91 ± 3.02	33.96 ± 5.39	0.021*
LVIDs (mm)	22.54 ± 4.47	24.14 ± 3.37	0.164 NS
LV E (cm/second)	100.73 ± 12.50	101.09 ± 11.54	0.917 NS
LV A (cm/second)	70.46 ± 17.05	73.50 ± 14.03	0.501 NS
E/A	1.49 ± 00.30	1.42 ± 00.31	0.432 NS
LV DT(ms)	161.69 ± 15.77	169.09 ± 14.53	0.097 NS
IVRT (ms)	76.12 ± 07.98	80.32 ± 12.83	0.189 NS
LA (ml)	23.54 ± 3.23	25.55 ± 4.33	0.079 NS
A duration (ms)	108.62 ± 21.14	107.18 ± 22.36	0.820 NS
PASP by TR Jet	28.46 ± 07.00	29.50 ± 06.55	0.597 NS

E/A = early diastole (E) and late diastole with atrial contraction (A); Hb = haemoglobin; LA = left atrial dimension in systole; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; LV E = mitral inflow velocity in early diastole; LV A = mitral inflow velocity in late diastole; IVRT = isovolumic relaxation time; DT = deceleration time; LV = left ventricular; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation
By the Student's t-test
*Significant

Table 4. Echocardiographic and echo-doppler parameters of sickle cell disease patients versus controls among different age groups.

Variables	Study group ($\overline{X} \pm SD$) ⩽10 years (n = 19)	>10 years (n = 29)	p value
LA (mm)	17.37 ± 4.73	22.31 ± 3.86	0.001*
LVIDd (mm)	33.21 ± 4.83	36.69 ± 4.06	0.012*
LVIDs (mm)	22.00 ± 4.22	24.10 ± 3.76	0.085 NS
LV E (cm/second)	100.79 ± 10.80	100.97 ± 12.83	0.958 NS
LV A (cm/second)	67.68 ± 16.95	74.59 ± 14.38	0.149 NS
E/A	1.55 ± 00.30	1.40 ± 0.30	0.097 NS
LV DT (ms)	160.05 ± 13.10	168.38 ± 16.28	0.056 NS
IVRT (ms)	77.00 ± 11.52	78.72 ± 10.06	0.597 NS
LA (ml)	23.32 ± 3.87	25.21 ± 3.74	0.100 NS
LV mass index (g/m^2)	63.74 ± 6.92	66.66 ± 8.42	0.196 NS
A duration (ms)	107.16 ± 24.37	108.48 ± 19.81	0.844 NS
PASP by TR Jet	29.53 ± 7.65	28.55 ± 6.20	0.642 NS

E/A = early diastole (E) and late diastole with atrial contraction (A); LA = left atrial dimension in systole; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; LV E = mitral inflow velocity in early diastole; LV A = mitral inflow velocity in late diastole; IVRT = isovolumic relaxation time; DT: deceleration time; LV = left ventricular; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation
By Student's t-test
*Significant

segmental wall motion abnormalities is uncommon. Left ventricular dysfunction has mainly been seen in older patients and in association with chronic conditions such as hypertension and renal disease.[16]

The almost normal systolic function observed in both the groups was consistent with the literature, independent of the echo parameters used.[4,14,17] Ribera et al[18] also demonstrated that sickle cell anaemia resulted in a volume-overloaded heart and a significant increase in left ventricular cardiac mass, both of which were proportional to the degree of anaemia. Despite these abnormal loading conditions, systolic function tends to be preserved. Lester et al[4] concluded that the major echocardiographic abnormality in sickle cell anaemia children was enlargement of left heart chambers, which they correlated with the severity of anaemia.

Our study showed that, although there were significant chamber dilatations in sickle cell anaemia patients in comparison with controls, there were no significant correlations with other factors within sickle cell anaemia patients, a fact also observed in the study by Kilinc et al.[19]

Table 5. Diastolic dysfunction parameter (E/e'): correlation with number of crises, PASP, age, and haemoglobin.

Parameters	r	p value
Number of crises	0.3122*	0.03075*
Age	–0.0812	0.584178
Haemoglobin	0.1424	0.334293
PASP	–0.1092	0.460837

r = Pearson's correlation coefficient; p = probability value, a Spearman correlation; PASP = pulmonary artery systolic pressure
*Statistically significant

Wali et al[20] showed that dilated cardiac chambers in sickle cell anaemia were neither associated with any abnormality in systolic or diastolic left ventricular function nor with significant pulmonary artery hypertension, which they explained by the less severity of sickle cell disease in Omani children.

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Of note, in the present study, diastolic dysfunction showed a significant difference between the study group and the healthy control group, although there was no correlation with severity of anaemia within the study group. This observation indirectly supports the study by Seliem et al,[17] who found that the main difference between thalassaemia and sickle cell disease patients was in the higher E wave and E/A ratio in thalassaemia patients and shorter diastolic filling period in sickle cell disease patients. Although it is understood that the haemodynamics in both diseases are similar in some aspects – that is, chronic anaemia leading to dilated ventricles with increased muscle mass – they differ in the basic pathophysiological process – that is, iron overload versus sickling – which may explain the difference in the diastolic abnormalities.

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

Myocardial performance index

In our study, pulse wave Doppler Tei index was slightly on the higher side. As systolic function was found to be preserved in these patients, the elevated left ventricular myocardial performance index most likely is explained by decreased diastolic function.[21]

Pulmonary hypertension

Out of 48 sickle cell disease patients, 11 (23%) had pulmonary artery systolic pressure as indicated by tricuspid regurgitant jet velocity of over30 mmHg. A recent review of published studies comprising over 600 children indicated that the prevalence of a jet velocity of 2.5 m/second or more was about 30%.[22] Another study[23] found only 11% prevalence of a jet velocity of over 2.6 m/second. Haemolysis and obliterative thrombosis are likely to be responsible for the development of pulmonary hypertension, as no correlation was found with diastolic dysfunction (Table 5).

Age and sickle cell disease

As diastolic dysfunction is much more prevalent in adults, the incidence of diastolic abnormalities should increase with the increase in the patient's age. Zilberman[24] et al found no correlations between the age and indices of cardiac enlargement, ventricular hypertrophy, or indices of ventricular stiffness. We had statistically significant chamber dilatations, but were not able to demonstrate a significant difference between Doppler indices of patients younger and older than 10 years in our study. This may be due to a number of factors, including the fact that the severity of anaemia, the number of previous transfusions received, and the number of crises differed in these two age groups. In addition, our study made comparisons between two paediatric age groups and not between paediatric and adult patients. In addition, we believe that it is not the degree of anaemia, but the basic pathophysiological process – that is, sickling – which affects cardiac function. Survival in a relatively asymptomatic state indicates less severity of disease in patients older than 10 years of age.

Conclusion

Our patients had Doppler evidence of a diastolic dysfunction, as compared with controls. Systolic and diastolic dimensions and left ventricular muscle mass were increased compared with the controls. As diastolic dysfunction showed no statistically significant correlation with either haemoglobin or age among sickle cell patients, we believe that sickle cell disease leading to microvascular dysfunction and microvasculopathy leading to ischaemia are likely to be responsible for cardiac dysfunction.

The present study and the study by Seliem,[17] as discussed, suggest that an intrinsic myocardial abnormality due to sickle cell disease – sickle cardiomyopathy – plays a major role in diastolic dysfunction.

We conclude that the increased left ventricular stiffness found in our study, when compared with controls, might be due to fibrosis related to ischaemia caused by sickle cell disease in addition to wall hypertrophy.

Cox et al[25] found that the tricuspid regurgitant jet velocity predicted future hospitalisations. Similarly, early detection of diastolic dysfunction, using simple non-invasive echocardiographic parameters, might also predict future hospitalisations and improve the morbidity and mortality statistics in sickle cell disease patients. Further studies with long-term follow-up are required to test this hypothesis.

Study limitations

The sample size of our study was limited and was evaluated for a short period of time (14 months), and these shortcomings should be considered in the interpretation of the results. Other potentially confounding factors such as body mass index, gender, and haemolysis indicators were not assessed. Furthermore, some diastolic indices such as pulmonary venous flow velocities were not part of the Doppler assessment of these young patients for technical reasons.

Further research is required to assess cardiac function in the long term in patients with sickle cell disease.

https://doi.org/10.1017/S1047951114002455 Published online by Cambridge University Press

Acknowledgements

The authors would like to convey their particular thanks to Dr Vijay Babar, associate professor, preventive and social medicine department, Jawaharlal Nehru Medical College, Wardha, for helping them in statistical analysis.

Financial Support

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of Interest

None.

Ethical Standards

An appropriate ethical standard was maintained throughout the study and approved by our institutional committee.

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