Echocardiographic abnormalities in adolescent and adult Saudi patients with sickle cell disease

Aamer Aleem, MRCP(UK), MRCPath(UK), *Ahmed Jehangir,* MD, MRCP(UK), *Mohammad Owais,* MBBS, *Abdulkarim Al-Momen,* MD, FRCP(C), *Abdulrahman Al-Diab,* MD, *Huda Abdulkarim,* MD, *Hatem Alameri,* MD, FRCP(C).

ABSTRACT

Objective: Cardiovascular complications in sickle cell disease (SCD) have been well documented but cardiac involvement in Saudi patients with SCD is not known. We sought to identify cardiac abnormalities by echocardiography in adolescent and adult Saudi patients with stable SCD.

Methods: Sixty-five consecutive patients with SCD followed at King Khalid University Hospital, Riyadh, were prospectively studied from January 2005 to December 2005. All patients underwent echocardiographic examination to determine chamber dimensions, left ventricular function, valvular anomalies and pulmonary artery pressure. Data were compared to normal age and gender-matched controls. Hematological data were also collected from the patients and correlated with the echocardiographic results.

Results: Twenty-eight males and 37 females were evaluated. The mean age of the group was 24.5 ± 9.2 (range 14-44) years. The most common abnormality found was pulmonary hypertension (PH) present in 25 (38%) patients. The majority of these patients had mild PH and only 6 (9%) patients had pulmonary artery systolic pressure (PASP) more than 40 mm Hg. Older age, lower level of fetal hemoglobin and high serum ferritin were associated with increased PASP. Other abnormalities present included dilated left atrium in 17 (26%) patients, dilated right atrium 13 (20%), dilated left ventricle 10 (15%), valvular anomalies 21 (32%) and reduced ejection fraction in 4 (6%) patients.

Conclusion: Cardiac abnormalities are found in a significant proportion of Saudi patients with SCD. Pulmonary hypertension is the most common finding while other abnormalities are less frequent.

Saudi Med J 2007; Vol. 28 (7): 1072-1075

From the Departments of Medicine, Divisions of Hematology/Oncology (Aleem, Owais, Al-Momen, Al-Diab, Abdulkarim), Cardiology (Jehangir) and Pulmonary Medicine (Alameri), College of Medicine and King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Received 31st October 2006. Accepted 14th February 2007.

Address correspondence and reprint request to: Dr. Aamer Aleem, Consultant Hematologist, Division of Hematology/Oncology, Department of Medicine (38), College of Medicine & King Khalid University Hospital, PO Box 7805, Riyadh 11472, Kingdom of Saudi Arabia. Tel. +966 (1) 4671771. Fax. +966 (1) 4679277. E-mail: aameraleem@hotmail.com

Sickle cell disease (SCD) is a debilitating genetic disorder characterized by chronic hemolysis and frequent vaso-occlusive crises due to production of abnormal hemoglobin. Subsequent acute and chronic tissue ischemia usually leads to progressive organ damage with increased morbidity and mortality. As the patients with SCD survive longer because of significant advancement in medical care and new therapeutic options, they tend to develop organ involvement rather late.[1] Several disease sequels that were previously less common because of shorter patient survival, are now frequently seen including cardiovascular complications. Chronic hemolysis, hyperdynamic circulation and sickle cell vasculopathy leading to endothelial dysfunction and increase in vascular resistance are thought to be the main mechanisms leading to cardiac damage.[2-4] The prevalence of cardiac involvement is not known in Saudi patients with SCD. This study was conducted to evaluate the presence of cardiac abnormalities by echocardiography among adolescent and adult Saudi patients with SCD.

Methods. Consecutive patients with documented SCD (homozygous sickle cell anemia [HbSS] or sickle cell-beta thalassemia (HbS/ß^{O}]) aged ≥14 years were recruited from the outpatient hematology clinic at King Khalid University Hospital, Riyadh, Saudi Arabia. All patients were evaluated in steady state defined as no acute illness during the previous 2 weeks. The study was conducted as part of a continuing routine clinical assessment of the patients from 1st January 2005 to 31st December 2005. All patients gave informed consent. Patients with sickle cell trait were not included in the study.

Hemoglobin level and other hematological parameters were measured when patients in stable condition preferably within 2 weeks of the echocardiographic examination. Echocardiographic findings of the patients were compared to 58 age and gender-matched normal control subjects. The 2-dimensional, M mode and color Doppler images were obtained using a 5500 HP ultrasound system. Echocardiograms were reviewed by a single cardiologist to eliminate observer variation. Cardiac dimensions were measured according to the American Society of Echocardiography (ASE) criteria. Heart chamber dimensions, left ventricular posterior wall and interventricular septal thickness, ventricular function, valve structure and abnormal flow across the valves, were recorded. Pulmonary artery systolic pressure (PASP) was estimated by measuring tricuspid valve regurgitant jet velocity by continuous-wave Doppler ultrasound. All the parameters obtained were compared with 58 age and gender-matched normal controls. As pulmonary hypertension (PH) is thought to be common in these patients, particular emphasis was given to this finding.[19,24-26] Patients were categorized to have mild pulmonary hypertension (PASP 31-40 mm Hg), moderate PH (PASP 41-55 mm Hg) or severe PH (PASP >55 mm Hg).

Data were reported as mean ± SD. Comparison of measurements were made using Student's t-test. Spearman's rank correlation coefficient was used to investigate the relation between the various parameters. Regression analysis was made to identify the predictors of pulmonary hypertension in the disease group (SPSS 13.0 for window, Chicago, IL). A p value of ≤ 0.05 was considered significant.

Results. A total of 68 patients with SCA were evaluated by echocardiography. Three patients were excluded because of incomplete data and 65 patients constitute the study population. There were 37 (57%) females and 28 (43%) males. Mean age was 24.5 ± 9.2 years (range 14 to 44 years). Mean hemoglobin level was 9.27 ± 1.86 (range 5.6-13.0) g/dl and mean fetal hemoglobin level was 13.2 ± 7.7 (3.8-32.6) percent. Fifty-nine (91%) patients had hemoglobin SS genotype, 6 (9%) patients had S/β^0 thalassemia, while none of the patients had SC genotype. The clinical characteristics of the studied group are presented in **Table 1**. The echocardiographic findings in both SCA patients and control subjects are shown in **Table 2**. The most common abnormal finding was raised PASP found in 25 (38%) patients. The mean PASP of the group with pulmonary hypertension was 42 mm Hg. Nineteen (76%) of the patients with raised PASP had mild pulmonary hypertension, 4 (16%) patients had moderate PH and only 2 (8%) patients had severe PH. Old age, lower level of fetal hemoglobin and high serum ferritin were associated with increased PASP. In stepwise multiple regression analysis, the lower level of hemoglobin F (p=0.026) and older age (p=0.020) were the only predictors of pulmonary hypertension in patients with SCD. The second common abnormality found was dilated left atrium above the upper limit of normal in 17 (26%) patients. Other abnormalities detected include dilated right atrium in 13 patients (20%), dilated left ventricle in 10 (15%) patients, increased inter-ventricular septal thickness in 8 (12%) and increased posterior wall thickness in 4 patients (**Table 3**). Although the mean values of chamber dimensions and other cardiac parameters of the whole cohort of SCD patients were within the normal range, they were significantly increased as compared to normal control subjects (p values shown in **Table 2**). There was no difference in ejection fraction between the 2 groups. Valvular regurgitation was present in 21 (32%) patients. As trivial regurgitation lesions are a common finding in normal people, patients who were reported to have trivial regurgitant lesions were not considered to have a significant abnormality.[5] Six patients had mild, while 3 patients had moderate to severe mitral regurgitation. Mild aortic regurgitation was found in one patient. Mild pulmonary stenosis along with mild regurgitation was present in one patient. Eight patients had mild and 2 patients had moderate and severe tricuspid regurgitation. Four patients had reduced ejection fraction at 50%, 45%, 40% and 30% each.

Discussion. Sickle cell disease is a chronic hemolytic disorder with frequent complications. The rate of development of these complications is variable

Table 1 - Clinical and hematological characteristics of patients with sickle cell disease.

Characteristics	Patients' values (Mean ±SD)
Age (years)	24.5 ± 9.2
Hemoglobin (g/dL)	9.27 ±1.85
Hematocrit %	28 ± 4.9
MCV	87 ± 12
Platelets (10^9/l)	428 ± 195
Serum ferritin (ng/ml)	685 ± 841
HbS %	70.8 ± 19.6
HbF %	13.9 ± 8.0

MCV - Mean Corpuscular Volume, HbS - hemoglobin S, HbF -hemoglobin F

Table 2 - Echocardiographic findings in sickle cell disease patients and controls.

Characteristics	Patients (Mean ± SD)	Controls (Mean ± SD)	*P* value
PASP (mm Hg)	28.4 ± 9.8	20.3 ±1.8	0.0001
Left atrial size (mm)	34.4 ± 5.0	30.7±3.7	0.0001
Right atrium (mm)	27.0 ±2.9	26.0±3.6	0.14
LVIDd (mm)	49.1 ± 6.2	45.7±4.0	0.001
LVIDs (mm)	30.1 ± 5.7	28.1±4.7	0.038
IVS (mm)	9.7 ±1.3	9.1±1.4	0.02
PWT (mm)	9.4 ±1.2	8.9±1.2	0.027
Ejection fraction (%)	58.7 ± 4.0	58.2±8. 0	0.65

PASP - pulmonary artery systolic pressure LVIDd - left ventricle internal dimension diastolic,
LVIDs - left ventricle internal dimension systolic, IVS - interventricular septum, PWT - posterior wall thickness

Table 3 - Echocardiographic abnormalities in patients with sickle cell disease.

Variable	n	(%)
Pulmonary hypertension	25	(38)
Dilated left atrium	17	(26)
Dilated right atrium	13	(20)
Dilated left ventricle	10	(15)
Left ventricular hypertrophy	4	(6)
Interventricular septal hypertrophy	8	(12)
Increased posterior wall thickness	4	(6)

but many patients develop organ damage. Patients with SCA survive longer with better supportive care. However, they are more likely to develop organ damage although this progression is quite variable.[6, 7] Virtually any organ of the body may be affected including the heart and the lungs.[2] We undertook this study to evaluate cardiac abnormalities by echocardiography in adolescent and adult Saudi patients with SCD. Echocardiography has become the technique of choice for initial workup of cardiac structure and function and several studies have shown good correlation with cardiac catheterization results.[8-12] Numerous studies have been published regarding cardiac sequels among SCD pediatric patients;[13-16] however, there are only a few studies carried out in adult patients. Moreover the results of these studies are variable and conflicting.[3,17-21] No such study has been carried out in Saudi Arabia previously. One study from Eastern province of KSA in children with congenital chronic anemias (thalassemia and sickle cell anemia) under the age of 13 years showed well preserved left ventricular systolic performance but left ventricular volumes were larger in SCD patients as compared to controls.[22] Our results show that cardiac abnormalities, particularly PH, are common in our patient population. Thirty-eight percent of patients had pulmonary hypertension although majority (76%) of them had only mild elevation in PASP (<45 mm Hg) which is similar to some previous reports. Ataga et al[23] found that the prevalence of pulmonary hypertension in 60 adults with SCA was 30%, while other studies have shown higher prevalence of up to 58%.[24] In an earlier study, PH was found in two-third of the patients but this abnormality may have been over estimated.[20] Similarly, studies showing high prevalence of PH in hospitalized patients are not very reliable as these patients tend to be ill with several diagnoses, have lower hemoglobin level and thus, are likely to have increased hemodynamic disturbances.[24-25] In contrast, one prospective multicenter study of 191 patients with SCD found that none of the patients had PH on echocardiography.[18] However, this study was not designed to assess the prevalence of PH. The incidence of PH appears to increase with advancing age.[23-24,26] The finding of PH in a significant number of younger patients was somewhat surprising for us since a study of cardiovascular function in children (including teenagers) with sickle cell anemia in neighboring Oman, none of the children were found to have pulmonary hypertension.[27] Other significant abnormalities found in our study were dilated left atrium, dilated left ventricle, thickened interventricular septum and increased posterior wall thickness. These results are similar to other studies.[21] Valvular abnormalities particularly mitral regurgitation, were present in 32% of our patients. The etiology of this lesion in some of the patients was thought to be rheumatic heart disease and this reflects the presence of this disease in the community.

In summary, cardiac abnormalities particularly pulmonary hypertension and dilated left sided chambers

are common in adolescent and adult patients with SCD. These patients should be actively monitored and those with significant abnormalities should be considered for early intervention.

References

1. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. ***Medicine (Baltimore)*** 2005; 84: 363-376.
2. Bunn HF. Pathogenesis and treatment of sickle cell disease. ***N Engl J Med*** 1997; 337: 762-769.
3. San M, Demirtascedil M, Burgut R, Birand A, Li F. Left ventricular systolic and diastolic function in patients with sickle cell anemia. ***Int J Angiol*** 1998; 7: 185-187.
4. Gladwin MT, Kato GJ. Cardiopulmonary complications of sickle cell disease: role of nitric oxide and sickle cell anemia. ***Hematology (Am Soc Hematol Educ Program)*** 2005; 51-57.
5. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Taliercew CP, Taylor CL, et al. Age related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. ***J Am Soc Echocardiogr*** 1990; 3: 54-63.
6. Powars D. Sickle cell anemia: ßS –gene-cluster haplotypes as prognostic indicators of vital organ failure. ***Semin Hematol*** 1991; 28: 202-208.
7. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. ***N Engl J Med*** 1994; 330: 1639-1644.
8. Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. ***J Am Coll Cardiol*** 1985; 6: 359-365.
9. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. ***J Am Coll Cardiol*** 1985; 6: 359-365.
10. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. ***Circulation*** 1984; 70: 657-662.
11. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. ***N Engl J Med*** 2004; 350: 886-895.
12 Currie PJ, Seward JB, Hagler DJ, Tajik AJ. Two-dimensional/ Doppler echocardiography and its relationship to cardiac catheterization for diagnosis and management of congenital heart disease. ***Cardiovasc Clin*** 1986; 17: 301-322.
13. Batra AS, Acherman RJ, Wong WY, Wood JC, Chan LS, Ramicone E et al. Cardiac abnormalities in children with sickle cell anemia. ***Am J Hematol*** 2002; 70: 306-312.
14. Lester LA, Sodt PC, Hutcheon N, Arcilla RA. Cardiac abnormalities in children with sickle cell anemia. ***Chest*** 1990; 98: 1169-1174.
15. Chung EE, Dianzumba SB, Morais P, Serjeant GR. Cardiac performance in children with homozygous sickle cell disease. ***J Am Coll Cardiol*** 1987; 9: 1038-1042.
16. Balfour IC, Covitz W, Davis H, Rao PS, Strong WB, Alpert BS. Cardiac size and function in children with sickle cell anemia. ***Am Heart J*** 1984; 108: 345-350.
17. Cipolotti R, Costa GB, Lima WH, Franco RP, Mello EV, Dal Fabbro AL et al. Echocardiographic characteristics of patients with sickle cell anaemia in Sergipe, Brazil. ***J Trop Pediatr*** 2001; 47: 73-76.
18. Covitz W, Espeland M, Gallagher D, Hellenbrand W, Leff S, Talner N. The heart in sickle cell anemia. ***Chest*** 1995; 108: 1214-1219.
19. Braden DS, Covitz W, Milner PF. Cardiovascular function during rest and exercise in patients with sickle-cell anemia and coexisting alpha thalassemia-2. ***Am J Hematol*** 1996; 52: 96-102.
20. Simmons BE, Santhanam V, Castaner A, Rao KR, Sachdev N, Cooper R. Sickle cell heart disease. Two-dimensional echo and Doppler ultrasonographic findings in the hearts of adult patients with sickle cell anemia. ***Arch Intern Med*** 1988; 148: 1526-1528.
21. Covarrubias EA, Sheikh MU, Solanki DL, Morjaria M, Fox LM. Left ventricular function in sickle cell anemia: a noninvasive evaluation. ***South Med J*** 1980; 73: 342-344.
22. Seliem MA, Al-Saad HI, Bou-Holaigah IH, Khan MN, Palileo MR. Left ventricular diastolic dysfunction in congenital chronic anaemias during childhood as determined by comprehensive echocardiographic imaging including acoustic quantification. ***Eur J Echocardiogr*** 2002; 3: 103-110.
23. Ataga KI, Sood N, De Gent G, Kelly E, Henderson AG, Jones S et al. Pulmonary hypertension in sickle cell disease. ***Am J Med*** 2004; 117:665-669.
24. Ahmed S, Siddiqui AK, Sadiq A, Shahid RK, Patel DV, Russo LA. Echocardiographic abnormalities in sickle cell disease. ***Am J Hematol*** 2004; 76: 195-198.
25. Suell MN, Bezold LI, Okcu MF, Mahoney DH, Shardonofsky S, Mueller BU. Increased pulmonary artery pressure among adolescents with sickle cell disease. ***J Pediatr Hematol Oncol*** 2005; 27: 654-658.
26. Kokou OI, Agbere AD, Atakoumi DY, Gbadoe AD, Tsolenyanu E, Djossou-Agbodjan O et al. [Heart involvement in children with sickle cell disease in Lome. Apropos of 70 cases]. ***Arch Pediatr*** 1999; 6: 1134.
27. Wali YA, Venugopalan P, Rivera E, al-Lamki Z. Cardiovascular function in Omani children with sickle cell anaemia. ***Ann Trop Paediatr*** 2000; 20: 243-246.