# Dyspnea, pulmonary function and exercise capacity in adult Saudi patients with sickle cell disease

*Hatem F. Alameri,* FRCP(C), FCCP, *Aamer Aleem,* MRCP(UK), MRCPath(UK), *Walid Kardas,* MD, *Ahmed Jehangir,* MD, MRCP(UK), *Mohammad Owais,* MD, *Abdulkarim Al-Momen,* MD.

## ABSTRACT

**الأهداف**: دراسة وظائف الرئة وضيق النفس وقدرة تحمل الجهد في المرضى البالغين المصابين بفقر الدم المنجلي SCD.

**الطريقة**: أجريت الدراسة في الفترة ما بين يناير وحتى ديسمبر 2005م في مستشفى الملك خالد الجامعي بالرياض – المملكة العربية السعودية. ضمت هذه الداسة 39 مريضاً بفقر الدم المنجلي SCD (بحالة مستقرة) (20 امرأة – 19 رجل). متوسط العمر 7.1±22.7 سنة. معدل الخضاب الوسطي 14.6±95.5 g/L، مستوى الخضاب الجنيني 8.6±13.7% خضع المرضى لدراسة وظائف الرئة: حجم الزفير القسري الأقصى في الثانية الأولى (FEV1)، السعة الحيوية القسرية (FVC)، نتشار غاز أول أكسيد الكربون خلال الغشاء التنفسي(DLco). وقد تم عرض المعطيات كنسبة مئوية من القيم الطبيعية. اختبار المشي لمدة ستة دقائق (6MWT)، تصوير القلب بالأمواج فوق الصوتية (ECHOCARDIOGRAPHY)، وقد تم تقييم ضيق التنفس بحسب مقياس بورغ (Borg score). تمت مقارنة نتائج اختبار المشي لمدة ستة دقائق مع القيم الطبيعية للأشخاص السليمين المماثلين للمرضى بنفس مشعر كتلة الجسم (BMI).

**النتائج**: تبين في الدراسة أن 41% من المصابين بفقر الدم المنجلي SCD لديهم ضيق نفس متوسط الشدة عند الراحة وتزداد النسبة إلى 61% بنهاية اختبار المشي لمدة ستة دقائق. كان اختبار وظائف الرئة غير طبيعي في 51% من المرضى، (36% من المرضى لديهم نموذج حاصر و 10% لديهم نقص في انتشار غاز أول أكسيد الكربون فقط و 5% لديهم نموذج مختلط من اضطرابات تنفسي حاصر وساد). كانت مسافة السير لمدة ستة دقائق أقصر عند مرضى فقر الدم المنجلي SCD مقارنة مع الأصحاء (368±67versus 407±47 m, $p$=0.005).

**خاتمة**: رغم أن الاختلاطات الرئوية عند مرضى فقر الدم المنجلي SCD في السعوديين البالغين خفيفة إلا أنها شائعة، وتختلف وظائف الرئة عند هؤلاء المرضى مقارنة مع ما نشر من نتائج عند مرضى فقر الدم المنجلي SCD ذوي الأصول الأفريقية. يعكس هذا الفرق اختلافاً في طبيعة المرضى بين المجموعتين السكانيتين.

**Objectives:** To examine pulmonary function, dyspnea and exercise capacity in adult Saudi sickle cell disease (SCD) patients.

**Methods:** The patients were recruited from the hematology clinic at King Khalid University Hospital in Riyadh from January to December 2005. The study involved 39 patients with stable SCD (20 women and 19 men), with a mean age of 22.7±7.1 years, hemoglobin level of 95.5±14.6 g/L and hemoglobin F level of 13.7±8.6%. Patients underwent pulmonary function tests (PFT) (forced expiratory volume in first second [FEV1], forced vital capacity [FVC], and diffusion capacity of carbon monoxide [DLco] data are presented as a percentage of the normal prediction), a 6-minute walk test (6MWT) and echocardiography. Dyspnea was assessed using the Borg score. The 6MWT data were compared to body mass index-matched healthy controls.

**Results:** Forty-one percent of SCD patients had mild dyspnea at rest, and this increased to 61% at the end of the 6MWT. Pulmonary function tests were abnormal in 51% (36% of patients had a restrictive pattern, 10% had isolated decrease in DLco, and 5% had a mixed restrictive-obstructive pattern). The 6MWD was shorter in SCD patients compared to the controls (368±67 versus 407±47m, $p$=0.005). No hematological variables correlated with outcome variables.

**Conclusion:** Chronic pulmonary complications in adult Saudi SCD patients are relatively mild but common. Pulmonary function in these patients differs from that published for African-origin SCD patients. This difference may reflect a different natural history of SCD in the 2 populations.

***Saudi Med J 2008; Vol. 29 (5): 707-713***

*From the Pulmonary Unit (Alameri), Hematology/Oncology Unit (Aleem, Al-Momen), Internal Medicine (Kardas, Owais), and Cardiology Unit (Jehangir), Department of Medicine, King Khalid University Hospital and King Saud University College of Medicine, Riyadh, Saudi Arabia*

*Received 26th September 2007. Accepted 29th March 2008.*

*Address correspondence and reprint request to: Dr. Hatem F. Alameri, Pulmonary Unit, Department of Medicine, Mafraq Hospital, PO Box 2951, Abu Dhabi, United Arab Emirates. Fax. +971 (2) 5821549. E-mail: hatem.alameri@gmail.com (Formerly affiliated to the Pulmonary Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia)*

Sickle cell disease (SCD) is one of the most common hereditary blood disorder and results from a homozygotic mutation in the ß-globin chain. This mutated gene produces sickle hemoglobin (HbS), which is less soluble than normal hemoglobin. The resulting altered erythrocytes aggregate in the microvascular circulation of many organs and cause vascular damage and organ infarct. The lungs are affected by such vaso-occlusive disease,[1] and chronic pulmonary complications of SCD can be present in up to 77% of adult patients.[2] Chronic sickle cell lung disease is identified by pulmonary function tests indicating restrictive impairment, decreased diffusion capacity of carbon monoxide (DLco), obstructive ventilatory physiology and hypoxia.[3-8] A recent study of SCD patients found that 90% had abnormal pulmonary function and 66% had restrictive ventilatory impairment.[9] Another study of 49 SCD patients found that dyspnea and exercise capacity correlated with DLco but not with biochemical, spirometric, or lung volume variables.[10] The Arab-Indian homozygous sickle cell form is the predominant haplotype variant in the Saudi population, and is characterized by elevated fetal hemoglobin (Hb F) levels. This Saudi SCD from the Eastern province is milder than African-origin SCD, and patients have near normal survival.[11] Patients from the Southern and Western province have more severe disease which resembles the African haplotype.[11-13] Common African-origin SCD complications such as chronic neurological damage, leg ulceration, and priapism are not commonly observed even in Saudi SCD patients from southern provinces who are thought to have more severe disease.[14] Pulmonary complications associated with SCD have not been previously reported in Saudi patients. It is likely such complications will differ from those of other SCD populations due to the milder form of disease in Saudi patients. The present study examined pulmonary function, breathlessness, and exercise capacity in adult Saudi patients with homozygous SCD.

**Methods.** Consecutive referred patients diagnosed with sickle cell anemia (HbSS) were recruited from the hematology clinic at King Khalid University Hospital in Riyadh from January to December 2005. The study was conducted as part of a continuing routine clinical assessment. The protocol was approved by the Departmental Ethical Committee and informed consent was obtained from each patient. Inclusion criteria were >14 years of age and a steady state clinical condition defined as no acute illnesses during the 4 weeks before assessment. Exclusion criteria were a history of cardiac or pulmonary diseases (other than conditions related to SCD) and a history of smoking. Blood was tested for hemoglobin, HbF, sickle hemoglobin (HbS) and other pertinent biochemical markers, and was withdrawn preferably within one week of the physiological testing. The patients were divided in 2 groups according to their drug history; patients on no medication except folic acid and patients on hydroxyurea treatment for at least one year before recruitment. Majority of the patients in our study originated from the Southern province.

***Pulmonary function test (PFT).*** Pulmonary function tests (Jaegar Master Screen PFT, Germany) were performed using the standard protocol recommended by the American Thoracic Society (ATS).[15] All tests were reviewed by a certified pulmonologist to ensure quality. Each subject underwent spirometry, lung volume, and DLco measurements. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC ratio and total lung capacity (TLC) were determined. Diffusion capacity of carbon monoxide was measured using the single breath holding technique, and results were corrected for the level of hemoglobin.[16] Pulmonary function test variables were presented as the percentage of the value predicted according to age, gender and height. Pulmonary function was classified as being one of 5 patterns as previously described:[9] 1. Normal pattern = all parameters within normal ranges (≥80% predicted). 2. Obstructive pattern = the FEV1/FVC ratio was less than 70% of predicted, FEV1 was less than 80%, with TLC, functional residual capacity (FRC), and residual volume (RV) normal or elevated. 3. Restrictive pattern = FEV1, FVC, and TLC ≤ 80% of predicted, with normal, or increased FEV1/FVC ratio or reduced TLC and $DL_{CO}$ ≤80% of the predicted value. 4. Mixed obstructive and restrictive pattern = FEV1/FVC ratio, TLC, FRC, and RV reduced to less than 80% of predicted. 5. Isolated = decreased DLco with all other normal parameters.

***Six minute walk test (6MWT).*** The 6MWT was performed according to ATS guidelines and was supervised by a qualified respiratory technician.[17] Before the test, blood pressure, heart rates and oxygen saturation were recorded (CriticareVital Signs Monitor, Wisconsin, USA). The awareness of dyspnea was assessed using a printed modified Borg scale, where 0 = "no dyspnea" and 10 = "maximum or intolerable." Patients were asked to walk at their own pace along a 30 m corridor and to cover as much ground as possible. Subjects were allowed to stop or rest if they developed leg cramps, dyspnea or other symptoms, and then asked to continue as soon as possible. At the conclusion of the test, patients were evaluated for any symptoms and again underwent measurements of blood pressure, heart rate and oxygen saturation and were assessed using a Borg scale. As there is no published data on

the predicted 6-minute walk distance (6MWD) for the Saudi population, results were compared to the age-, gender- and body mass index (BMI)-matched healthy subjects (controls).

***Echocardiography.*** Two dimensional, mode (M) 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 criteria.[18] 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 (PAP) was estimated by measuring tricuspid valve regurgitant jet velocity using continuous-wave Doppler ultrasound.

Statistical analysis was performed using statistical package for the social sciences (SPSS) software for Windows (version 13.0, Chicago, Illinois). Qualitative variables were analyzed using chi-square tests. A 2-sample Student's t-test was used to compare continuous variables between 2 groups. Pearson correlations were used to determine the relationship between physiological (dyspnea score, 6MWD, echocardiographic, and PFT parameters) and hematological [total Hb, HbF, HbS, lactate dehydrogenase (LDH), S/ferritin, and bilirubin level] variables. All data were expressed as mean±SD and *p* values less than 0.05 were considered to indicate a significant difference.

**Results.** Thirty-nine consecutive SCD patients were recruited for the study. Patients' demographic data are shown in **Table 1**. There were 20 female and 19 male patients, with a mean age of 22.7 years (range 14-41 years). Patients showed signs of mild hemolysis, elevated reticulocyte levels, elevated LDH, and elevated indirect bilirubin levels. Male and female patients were similar in terms of age, BMI, hematological profiles, PFT variables, and echocardiographic parameters. There were 21 patients on hydroxyurea and 18 on no treatment. The patients on hydroxyurea were significantly older than patients not on hydroxyurea (24.33±6.938 versus 19.78±6.449, $p$=0.042). However, there was no significant difference in other demographic features, hematological indices, or physiological parameters between the 2 groups.

***Dyspnea in SCD patients.*** Before commencement of the 6MWT, the mean Borg score for all patients was 0.6±0.9, and 16 patients (41%) had dyspnea. At the termination of the 6MWT, the mean Borg Score for all patients was 1.3±1.8, and 24 patients (61%) had dyspnea. This final Borg score was similar for both males and females. There was a significant difference between the Borg scores at the beginning and end of the 6MWT ($p$<0.0001), and the mean Borg scores for SCD patients and matched healthy subjects ($p$=0.002). Dyspnea did not correlate with any PFT, echocardiographic or hematological variable.

***Pulmonary function test.*** Twenty patients (51%) showed abnormal PFT results. Lung volume was mildly lower than predicted, with TLC. The predicted DLco were corrected for the level of Hb. Diffusion capacity of carbon monoxide was similar in both female and male patients ($p$=0.067). Restrictive physiology was the

**Table 1 -** Characteristics and pulmonary function test results for 39 patients with sickle cell disease.

| Variables (n=39) | Mean±SD |
|---|---|
| Sex (male/female) | 19/20 |
| Age (years) | 22.7 ± 7.1 |
| BMI | 23.0 ± 6.3 |
| Total Hb (g/L) | 95.5 ± 14.6 |
| HTC % | 28.5 ± 4.8 |
| WBC (x10$^9$/L) | 11.2 ± 5.2 |
| Platelets (x10$^9$/L) | 416 ± 152 |
| Reticulocyte % | 7.5 ± 3.7 |
| HbF % | 13.7 ± 8.6 |
| HbS % | 72.49 ± 17.39 |
| Ferritin (ng/mL) | 628 ± 743 |
| LDH (U/L) | 393 ± 227 |
| Total Bilirubin (µmol/L) | 50 ± 44 |
| Indirect Bilirubin (µmol/L) | 42.8 ± 30.4 |
| ALT (U/L) | 41.5 ± 10.5 |
| Alkaline phosphatase (U/L) | 173 ± 199 |
| Albumin (g/L) | 40.9 ± 5.2 |
| GGT (U/L) | 41.4 ± 29.4 |
| Urea (mmol/L) | 3.2 ± 3.1 |
| Creatinine (µmol/L) | 70 ± 118 |
| FVC % (pred) | 79 ± 18 |
| FEV1 % (pred) | 79 ± 19 |
| RATIO % (FEV1/FVC) | 89 ± 6 |
| TLC % (pred) | 78 ± 17 |
| FRC % (pred) | 81 ± 22 |
| DLco % (pred) | 80 ± 24 |
| PAP (mmHg) | 26 ± 6 |

ALT - alanine aminotransferase, BMI - body mass index, DLco - diffusion capacity of carbon monoxide, FVC - forced vital capacity FEV1 - forced expiratory volume in one second, FRC - functional residual capacity, GGT - gamma glutamyl transpeptidase, Hb - hemoglobin, HbF - fetal hemoglobin; HbS - sickle hemoglobin, HTC - hematocrit, LDH - lactate dehydrogenase, PAP - pulmonary artery pressure, TLC - total lung capacity, WBC - white blood cell.

**Table 2 -** Comparison of demographic and physiological characteristics between SCD patients and healthy controls at rest and at the end of the 6-minute walk test.

| *Variables* | *Control (N=36)* | *SCD Patients (N=39)* | *P* - value |
|---|---|---|---|
| Age (years) | 23.9 ± 5.9 | 22.2 ± 7.0 | 0.268 |
| BMI | 24.6 ± 5.5 | 23.1 ± 6.4 | 0.261 |
| HR base (b/m) | 82 ± 13 | 88 ± 13 | 0.084 |
| HR end (b/m) | 88 ± 16 | 99 ± 20 | 0.010 |
| $O_2$ base (%) | 98.5 ± 0.6 | 97.3 ± 2.4 | 0.002 |
| $O_2$ end (%) | 98.4 ± 1.5 | 96.9 ± 2.8 | 0.008 |
| Borg Scale base | 0.03 ± 0.17 | 0.60 ± 0.91 | 0.0001 |
| Borg Scale end | 0.25 ± 0.65 | 1.33 ± 1.88 | 0.002 |
| 6MWD | 407.6 ± 47.9 | 368.2 ± 67.8 | 0.005 |

Base - beginning of test, End - end of test, HR - heart rate at beat/minute, BMI - body mass index, $O_2$ - oxygen saturation, 6MWD - 6-minute walk distance

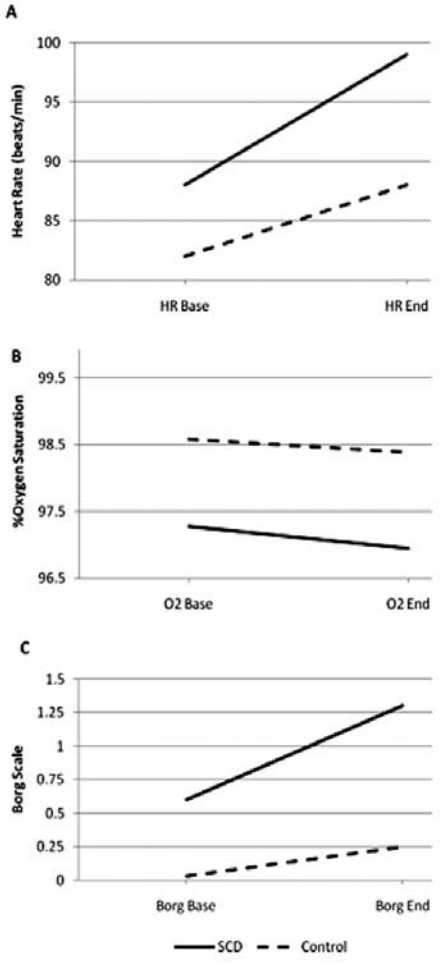


**Figure 1 -** Variables measured at the beginning (Base) and at end (End) of the 6-minute walk test for SCD patients and control subjects. **a**) Heart rate, **b**) oxygen saturation, **c**) Borg dyspnea score.

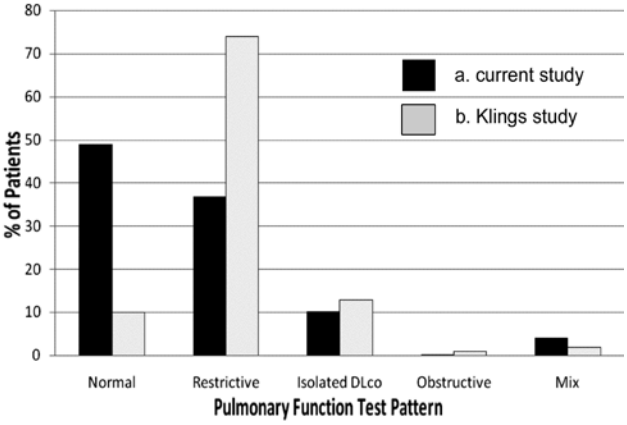


**Figure 2 -** Pulmonary function test patterns for the current and Klings studies. Isolated DLco = isolated decrease in diffusion capacity of carbon monoxide, Mix = mixed obstructive and restrictive physiology.

most common abnormality observed, and was noted in 15 patients (35.8%). Isolated decrease in DLco was observed in 4 patients (10.1%), and was the second most common presentation. While a mixed pattern was seen in only one patient, there were no physiological changes suggestive of obstructive impairment. A negative linear correlation was observed between LDH and both FEV1 (r=-0.413, $p$=0.019) and FVC (r=-0.397, $p$=0.039). A lower DLco value was associated with older age (r=-0.398, $p$=0.040). Patients with normal pulmonary function appeared to be younger (average age 19 versus 24 years). Patients with abnormal pulmonary function were similar to those with normal function in terms of hematological parameters, dyspnea level, oxygen saturation, and echocardiographic findings.

***Exercise capacity.*** All SCD patients completed the 6MWT. The demographic and physiological variables of SCD patients and controls are shown in **Table 2**. The average distance walked by SCD patients was less than that for controls (368±67 versus 407±47 m, $p$=0.005). Patients with abnormal PFT walked less than patients with normal PFT (346 versus 390 m, $p$=0.042). The distance walked was associated only with the level of FEV1. **Figure 1** shows data relating to variables measured before and after the 6MWT. Oxygen saturation was greater in controls (98.6%) compared to the SCD patients (97.3%). While control subjects showed no significant changes in oxygen saturation before and after the 6MWT, oxygen saturation dropped in SCD patients (from 97.3-96.9%, $p$<0.0001). Oxygen saturation at the beginning and end of the test correlated with the hemoglobin level. Sickle cell disease patients had a steeper heart rate increase in response to exercise than controls (5.9% versus 2.9% increase in predicted maximum heart rate, $p$=0.034).

***Echocardiography in SCD patients.*** A mild rise in systolic pulmonary artery pressure of >30 mmHg was observed in 36% of SCD patients. There was no correlation between echocardiographic findings and dyspnea, 6MWD, or pulmonary function data.

**Discussion.** The present study found that 41% of SCD patients experienced mild dyspnea at rest, 51% of SCD patients had abnormal pulmonary function, and that SCD patients had less exercise capacity than healthy subjects. Sickle cell disease affects the respiratory physiology resulting in respiratory symptoms and physical limitations.[19] While pulmonary complications in adults with SCD have been examined in a variety of ethnic populations.[1,4,20-22] The present study found that 41% of patients with stable SCD had dyspnea (a Borg score ranging from 1-4). The frequency and the magnitude of dyspnea increased after exertion, and were not associated with age, anemia, pulmonary function parameters or echocardiographic findings. Dyspnea is a complex phenomenon which is generally the result of multiple mechanisms.[23] Few studies have examined dyspnea symptoms in SCD patients. A recent study reported that higher levels of dyspnea awareness were associated with lower levels of DLco, but was not associated with other physiological markers,[10] consistent with the present study. It is possible that dyspnea causes were multifactorial in the current population with the presence of mild anemia, mild pulmonary vascular disease, and mild ventilatory impairment all possibly contributing to breathlessness in this cohort. Abnormal pulmonary function was observed in approximately half of the current SCD patients (51%), and a restrictive physiological pattern was noted in 38% of all SCD patients and in 75% of those with abnormal PFT results. Klings et al[9] demonstrated PFT abnormalities in up to 90% of patients, and restrictive changes in 74%. Differences in the frequencies of PFT patterns between the 2 studies are shown in **Figure 2**. The average TLC was 78 and DLco was 80 in our study compared to 70 and 64, subsequently, in the Klings et al study. These findings support the concept that the SCD is generally milder in Saudi Arabia, with some complications being infrequent and lesser pulmonary involvement. While the pathophysiology of chronic lung disease in SCD patients is not completely understood, 2 mechanisms have been proposed.[24] The first mechanism describes an initial endothelial injury causing alveolar wall necrosis, pulmonary edema, and subsequent interstitial fibrosis. Physiologically, this may be reflected in reduced lung volume with or without a DLco decrease. A clinical example of this mechanism is found in a study by Hijazi et al[23] of 21 children (average age 12 years) with Arab-Indian haplotype HbSS. The restrictive ventilatory pattern was predominant in those patients and none had a DLco abnormality. The second proposed mechanism describes pulmonary vaso-occlusive disease and increased capillary artery pressure resulting in pulmonary hypertension. This is most likely characterized by the observation of a decrease in DLco in PFT. In the present study, an isolated decrease in DLco was observed in 10% of patients, raising the possibility that pulmonary vascular diseases were present. We hypothesize from these findings that the 2 mechanisms can progress independently, the former (restrictive impairment) can occur at a younger age while the latter (isolated decrease in DLco) develops later. We currently have no specific evidence to support this theory, and thus the cause(s) for these differences remains unclear. Sickle cell anemia is known to limit physical capacity, and this has been investigated using both maximal and submaximal levels of exercise.[10,26-28]

In the current study, the distance walked by SCD patients was less than that of matched healthy subjects. Interestingly, the distance walked by the control subjects was less than that reported to be walked by their Caucasian counterparts.[29-31] Thus, while the present SCD patients walked less than SCD patients in other studies, this difference is likely to reflect the relatively shorter distance walked by healthy subjects instead of Saudi SCD being more severe than the SCD from other parts of the world. The only variables associated with the 6MWD were spirometric parameters, with neither lung volumes, nor DLco being associated. These findings differ from those of Delclaux who reported that DLco was associated with 6MWD in 49 patients with SCD.[10] The present findings are consistent with previous reports showing that hematological values and echocardiographic measurements do not correlate with the walk distance. Lower oxygen saturation in SCD patients was associated with lower levels of hemoglobin, which may explain the increased heart rate and relatively decreased oxygen saturation in response to exercise compared to the healthy individuals.

Pulmonary hypertension has been recognized a serious complication of SCD.[2] In a recent study, pulmonary hypertension was observed in 38% of adult Saudi SCD patients.[32] In the same study, 76% had mild and 8% had severed pulmonary hypertension. While hydroxyurea has been shown to decrease morbidity and mortality of SCD by reducing the acute chest syndrome events and painful crises,[33] it has no relation with the development of pulmonary hypertension.[34] In agreement with this finding, our study demonstrated no difference in the presence or the severity of pulmonary hypertension between the patients on hydroxyurea and patients who were not.

In addition, our study is the first to address the lack of association between treatment with this agent and the development of other chronic lung complications. Furthermore, we also found that the exercise capacity and perception of dyspnea were similar between the group who received and the group who did not receive hydroxyurea treatment. As hydroxyurea has an impact on mortality by decreasing the acute fatal events, the current observation may indicate that the long benefit of this treatment on chronic complications of SCD is still unknown.

The present study had some limitations. Firstly, most patients were referred from primary and secondary care hospitals, and were not followed-up primarily by our institution. Although data regarding the frequency of hospital admissions were available, documentations of vaso-occlusive crises and acute chest syndrome episodes were difficult to identify. Thus, we cannot evaluate the effect of these events on the outcome variables. However, several studies have shown that the frequency of acute chest syndrome was not associated with worse physiological parameters.[6,9] Secondly, several other variables were not considered in this study, including respiratory and musculoskeletal muscle strength and quality of life assessments that may influence the degree of dyspnea and the limitation in physical capacity which was beyond the objective of this study.

In summary, adult Saudi patients with SCD exhibited mild but frequent chronic pulmonary complications. They showed mild dyspnea and exercise limitations with no correlation to the level of anemia, pulmonary, or cardiac function. Mild restrictive lung disease and possible pulmonary vascular disease were present in half of the population, emphasizing the need for regular follow-up with a complete pulmonary function test, not just a spirometric test. Further, studies are required to evaluate the prognostic value and significance of these parameters in managing SCD patients.

## References


1. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. ***Medicine (Baltimore)*** 1988; 67: 66-76.
2. 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.
3. Miller GJ, Serjeant GR, Saunders MJ, Richardson C, Gilson RJ. Interpretation of lung function tests in the sickle-cell haemoglobinopathies. ***Thorax*** 1978; 33: 85-88.
4. Femi-Pearse D, Gazioglu KM, Yu PN. Pulmonary function studies in sickle cell disease. ***J Appl Physiol*** 1970; 28: 574-547.
5. Pianosi P, D'Souza SJ, Charge TD, Esseltine DE, Coates AL. Pulmonary function abnormalities in childhood sickle cell disease. ***J Pediatr*** 1993; 122: 366-371.
6. Santoli F, Zerah F, Vasile N, Bachir D, Galacteros F, Atlan G. Pulmonary function in sickle cell disease with or without acute chest syndrome. ***Eur Respir J*** 1998; 12: 1124-1129.
7. Siddiqui AK, Ahmed S. Pulmonary manifestations of sickle cell disease. ***Postgrad Med J*** 2003; 79: 384-390.
8. Sylvester KP, Patey RA, Milligan P, Dick M, Rafferty GF, Rees D, et al. Pulmonary function abnormalities in children with sickle cell disease. ***Thorax*** 2004; 59: 67-70.
9. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. ***Am J Respir Crit Care Med*** 2006; 173: 1264-1269.
10. Delclaux C, Zerah-Lancner F, Bachir D, Habibi A, Monin JL, Godeau B, et al. Factors associated with dyspnea in adult patients with sickle cell disease. ***Chest*** 2005; 128: 3336-3344.
11. Perrine RP, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabs. A study of 270 subjects. ***Ann Intern Med*** 1978; 88: 1-6.
12. Gelpi AP. Benign sickle cell disease in Saudi Arabia: survival estimate and population dynamics. ***Clin Genet*** 1979; 15: 307-310.
13. el Mouzan MI, al Awamy BH, al Torki MT. Clinical features of sickle cell disease in eastern Saudi Arab children. ***Am J Pediatr Hematol Oncol*** 1990; 12: 51-55.
14. Mulik R, Butikofer A, Aramouni G, Munshi N, Iliff P. A clinico-epidemiological study of sickle cell anaemia in Saudi Arabia. ***J Trop Pediatr*** 1991; 37: 100-105.
15. Standardization of Spirometry, 1994 Update. American Thoracic Society. ***Am J Respir Crit Care Med*** 1995; 152: 1107-11036.
16. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique--1995 update. ***Am J Respir Crit Care Me***d 1995; 152 (6 Pt 1): 2185-2198.
17. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. ***Am J Respir Crit Care Med*** 2003; 167: 1287.
18. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. ***J Am Soc Echocardiogr*** 1989; 2: 358-367.
19. Minter KR, Gladwin MT. Pulmonary complications of sickle cell anemia. A need for increased recognition, treatment, and research. ***Am J Respir Crit Care Med*** 2001; 164: 2016-2019.
20. Miller GJ, Serjeant GR. An assessment of lung volumes and gas transfer in sickle-cell anaemia. ***Thorax*** 1971; 26: 309-315.
21. Lemle A, Hazan EM, Mandel MB, Pinto JC. The defect in pulmonary gas transfer in patients with sickle cell disease. ***Rev Bras Pesqui Med Biol*** 1976; 9: 279-291.
22. Lonsdorfer J, Bogui P, Otayeck A, Bursaux E, Poyart C, Cabannes R. Cardiorespiratory adjustments in chronic sickle cell anemia. ***Bull Eur Physiopathol Respir*** 1983; 19: 339-344.
23. Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. ***N Engl J Med*** 1995; 333: 1547-1553.
24. Weil JV, Castro O, Malik AB, Rodgers G, Bonds DR, Jacobs TP. NHLBI Workshop Summary. Pathogenesis of lung disease in sickle hemoglobinopathies. ***Am Rev Respir Dis*** 1993; 148: 249-256.
25. Hijazi Z, Onadeko BO, Khadadah M, Haider MZ, Adekile AD, Al-Habashi H. Pulmonary function studies in Kuwaiti children with sickle cell disease and elevated Hb F. ***Int J Clin Pract*** 2005; 59: 163-167.
26. Pianosi P, D'Souza SJ, Esseltine DW, Charge TD, Coates AL. Ventilation and gas exchange during exercise in sickle cell anemia. ***Am Rev Respir Dis*** 1991; 143: 226-230.

27. Callahan LA, Woods KF, Mensah GA, Ramsey LT, Barbeau P, Gutin B. Cardiopulmonary responses to exercise in women with sickle cell anemia. ***Am J Respir Crit Care Med*** 2002; 165: 1309-1316.
28. Anthi A, Machado RF, Jison ML, Taveira-Dasilva AM, Rubin LJ, Hunter L, et al. Hemodynamic and Functional Assessment of Sickle Cell Disease Patients with Pulmonary Hypertension. ***Am J Respir Crit Care Med*** 2007.
29. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. ***Am J Respir Crit Care Med*** 1998; 158 (5 Pt 1): 1384-1387.
30. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. ***Eur Respir J*** 1999; 14: 270-274.
31. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. ***J Cardiopulm Rehabil*** 2001; 21: 87-93.
32. Aleem A, Jehangir A, Owais M, Al-Momen A, Al-Diab A, Abdulkarim H, et al. Echocardiographic abnormalities in adolescent and adult Saudi patients with sickle cell disease. ***Saudi Med J*** 2007; 28: 1072-1075.
33. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. ***JAMA*** 2003; 289: 1645-1651.
34. 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.