ORIGINAL COMMUNICATIONS

LUNG FUNCTION IN SICKLE CELL HEMOGLOBINOPATHY PATIENTS COMPARED WITH HEALTHY SUBJECTS

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Previous studies of lung function tests performed on patients with sickle cell disease have shown a restrictive ventilatory defect, usually a diffusion defect, and mild hypoxia at rest. The present study was undertaken to explain the pathophysiology of these changes and to extend these studies to include functional measurements not reported previously.

Lung function studies were performed at rest and during treadmill walking on 66 patients with sickle cell anemia and on 16 healthy control subjects. Patients had restrictive ventilatory defects, decreased lung compliance, and uneven ventilation-perfusion ratios. These abnormalities caused an increased alveolar-arterial oxygen tension difference that caused hypoxemia. The diffusion defects were because of the sickle cell disease.

Carboxyhemoglobin levels were increased in patients with sickle cell disease. This increase may be caused by a combination of factors, including increased cigarette smoking, hemolysis, and preferential survival of red blood cells that contain carbon monoxide and which do not sickle. During treadmill walking, the patients with sickle cell disease showed a decreased work tolerance caused by impaired oxygen delivery. The anaerobic threshold is reached sooner in patients with sickle cell disease and may also account for the limitations in work capacity of these patients.

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The sickle cell gene, an adaptation of nature, has arisen out of natural selection to protect man against the scourge of the malarial parasite in tropical and subtropical regions of the world.[1] The sickle cell trait is found in one in 12 live births or in approximately 2 million black Americans.

It is estimated that approximately 50,000 persons in the United States suffer from the disease,[2] one of 600 black Americans and one of every 1,200 white Americans. In patients with sickle cell anemia, the function of organ systems is variously impaired. This paper highlights a horizontal spectrum of lung function in patients with sickle cell hemoglobinopathies compared with that in healthy hemoglobin AA control subjects at rest and during treadmill walking.

TABLE 1. SMOKING HISTORY OF STUDY SUBJECTS

Study Groups	Smokers	Non-smokers	Ex-Smokers*
Controls			
(n = 16)	7	9	0
Pack-years**	2.4 ± 1.8	—	—
Sickle cell patients			
(n = 66)	32	31	3
Pack-years	7.2 ± 8.5	—	—

* Defined as a person who has abstained from smoking for at least one year
** Index of cigarettes smoked, mean and 1 SD

TABLE 2. NONCARDIOPULMONARY COMPLICATIONS* IN SICKLE HEMOGLOBINOPATHY PATIENTS (n = 66)

Complication	No. of Patients
Cholelithiasis/post-cholecystectomy state	34
Chronic leg ulcers	17
Aseptic necrosis of bone	15
Stroke	7
Priapism	3
Hematuria	7
Mental depression	3
Post-transfusion hepatitis	3
Transfusion reaction	3

* Complications are not mutually exclusive

METHODS

There were 82 subjects. Of these, 16 were healthy hemoglobin AA control subjects matched by age, racial group, and equal sex distribution. Control subjects lacked a previous history of cardiopulmonary disease. Sixty-six sickle cell anemia patients of the following genotypes were studied: 58 hemoglobin SS, 3 hemoglobin S β-thalassemia, and 5 hemoglobin SC. The mean age of patients was 27 years. The mean age of controls was 26 years. Smoking habits of both groups are shown in Table 1. Mean hemoglobin amount in the patients was 8.6 ± 1.2 g percent.

The crises seen in the 66 sickle cell anemia patients were vasco-occlusive in 85 percent and hemolytic (reticulocyte count of 10 or >) in 78 percent. No one experienced an aplastic crisis. The order of decreasing frequency of noncardiopulmonary complications due to sickle cell disease among the patients is seen in Table 2.

Research was carried out according to the principles of the Declaration of Helsinki; informed consent was obtained. The Howard University College of Medicine Human Experimentation Committee approved the study. History and physical examination were performed on each subject. Measurements were made of body size, including linear height, upper measurement, chest circumference (on inspiration and expiration), and body weight. Patients weighed less than controls with a mean of 59 vs 73 kg, respectively. There was no difference in height, upper measurement, and chest expansion.

Pulmonary function tests (PFTs) were performed during the symptom-free interval while the patient was not in crisis or having acute chest syndrome. PFTs consisted of spirometry and static lung volumes. Functional residual capacity was measured by plethysmographic and nitrogen washout methods. Tests of alveolar gas uniformity were also performed. Large airways function was assessed by spirometry and by measurement of airway resistance in a variable-pressure body plethysmograph. Small airways function was assessed by measurement of closing volume using the resident gas technique. In some subjects, helium-oxygen flow-volume curves were also measured. Lung compliance was measured by the esophageal balloon technique. Tests of ventilation and gas exchange, breath-holding carbon monoxide diffusing capacity, and arterial blood gases were measured at rest while breathing room air and during treadmill walking. Arterial blood spot samples were taken aerobically from the catheter in the brachial artery and analyzed in vitro on a blood gas analyzer. Oxyhemoglobin and carboxyhemoglobin saturations were analyzed on a cuvette oximeter.

End tidal and mixed expired gases and bloods were also measured simultaneously with dual medical mass spectrometers. The outputs were recorded by an ink-writing, multichannel recorder. Measurements were made at rest while breathing room air and during treadmill walking. Exercise studies were not performed on patients with either chronic leg ulcers or septic necrosis of the hip.

Prediction standards were used from equations as follows: for spirography, the Veterans Administration–Army Cooperative Study[3]; for static lung volumes, Goldman and Becklake[4]; for slope of phase III, Comroe and Fowler[5]; for closing volume, McCarthy and associates[6]; for carbon monoxide diffusing capacity, Burrows and associates[7]; and for Krogh's k, McGrath and Thomson.[8]

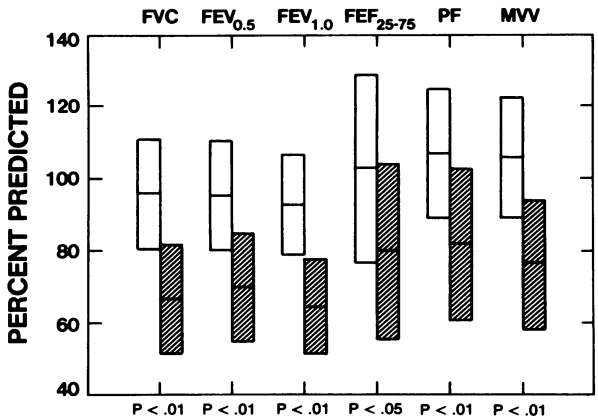

Figure 1. Bar graphs represent the percent predicted spirometric measurements and show mean and ±SD for each. Cross-hatched bars represent sickle cell patients; solid bars represent control subjects. FVC—forced vital capacity; FEV—forced expiratory volume; FEF—forced midexpiratory flow rate; PF—peak flow; MVV—maximum voluntary ventilation

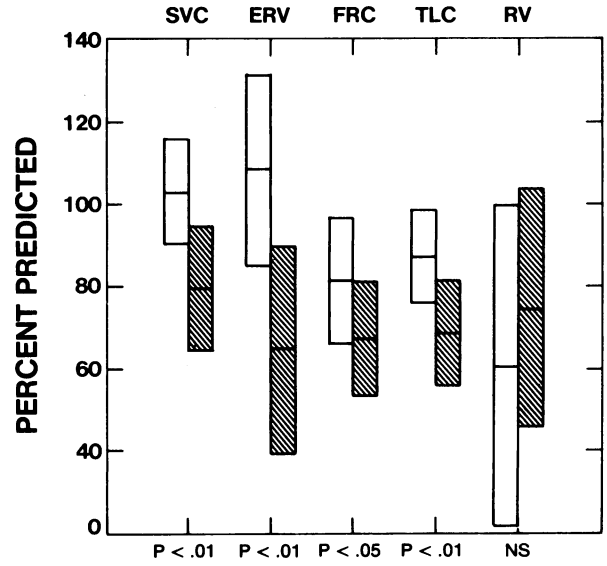

Figure 2. Bar graphs represent the percent predicted static lung volumes and show mean and ±SD for each. Cross-hatched bars represent the sickle cell patients; solid bars represent control subjects. SVC—stroke volume; ERV—expiratory reserve volume; FRC—functional residual capacity; TLC—total lung capacity; RV—residual volume

Statistical evaluation was performed on a mainframe computer using the SPSS program software package.[9] The evaluation consisted of descriptive statistics, Pearson correlation, multiple regression, and Student's *t* test.

RESULTS

Resting Studies

The percent predicted values for spirometric measurements in sickle cell patients was less than that of the control subjects (Figure 1). Mean airway resistance in the sickle cell patients was greater than in control patients (2.61 ± 1.07 vs 2.18 ± 0.57 cm H_2O/L/sec, respectively, $P < 0.05$). This difference was caused by the smaller lungs of the sickle cell patients. When corrected for lung size (specific airway conductance), no difference was found. Obstruction of small airways was absent in patients as measured by closing volume and helium-oxygen flow-volume curves.

The decrease in mean dynamic lung compliance of patients was significant when compared with control patients (0.11 vs 0.19 L/cm H_2O, $P < .01$). This decrease was due to lung stiffness. Mean compliance corrected for lung size and mean specific compliance was also decreased: 0.04 vs 0.097 cm H_2O, $P < .01$, respectively.

The percent predicted static lung volumes of sickle cell anemia patients were likewise decreased when compared with controls with the exception of the residual volume (Figure 2). Functional residual capacity measured in the body plethysmography was likewise decreased in the patients, 2.77 vs 3.42 L in controls, $P < .05$.

Present studies of alveolar gas uniformity indicated that nonuniform alveolar ventilation was not a problem for sickle cell anemia patients. Neither mean change in slope of phase III alveolar plateau nor the mean lung clearance index was significantly different from controls (lung clearance index = washout volume/functional residual capacity).

The mean percent predicted diffusing capacity and standard deviation (SD) for patients was decreased, 69.1 ± 13.9 vs 100.1 ± 24.9 for controls, $P < .01$. For Krogh's k, "the lung permeability," which is independent for lung volume, mean, and SD, was decreased, 75.8 ± 14.6 for sickle cell patients vs 99.1 ± 17.6 for controls, $P < .01$.

The partition of diffusing capacity into that of the lung membrane and pulmonary capillary blood volume was decreased in sickle cell patients when compared with controls. These gas-transfer abnormalities were due to the anemia. In Figure 3 are regression lines that show the effect of anemia on diffusing capacity.

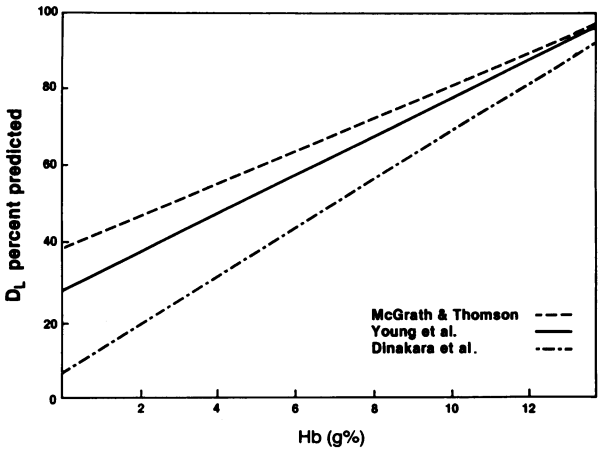

Figure 3. Regression (solid) line for percent predicted carbon monoxide diffusing capacity (DL) in patients with sickle cell anemia and control subjects. Percent predicted DL = 4.98 × Hb (g %) + 27.95 ± 0.71. r = 0.64, P < .01). Comparison is made with that of other workers[14,15] whose patients had all types of anemia. Regression for Krogh's k (graph not shown) and hemoglobin was percent predicted k = 4.34 × Hb (g %) + 39.01 ± 0.60, for the regression = 0.66, P < .01

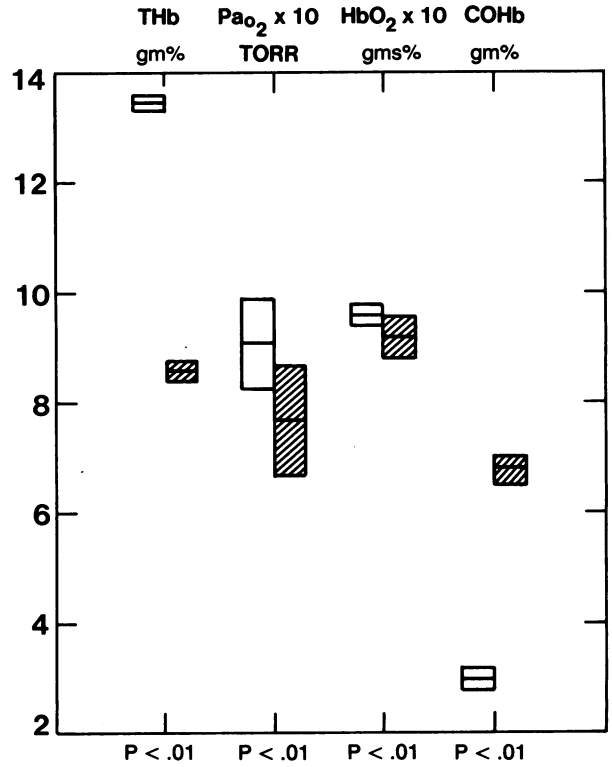

Figure 4. Bar graphs of hemoglobin saturations and arterial blood oxygenation showing mean and ±SD for each. Cross-hatched bars denote sickle cell patients; solid bars denote control subjects. Thb—total hemoglobin; Pa_{O_2}—partial arterial oxygen pressure; HbO_2—oxygenated hemoglobin; COHb—carboxyhemoglobin

Hemoglobin saturations and arterial blood oxygenation are shown in Figure 4. There was a decrease in arterial oxygen saturation and arterial oxygen tension of sickle cell anemia patients when compared with controls. Carboxyhemoglobin, however, was increased in the sickle cell patients.

Endogenous carbon monoxide (CO) production in man is about 0.42 ± 0.07 mL/h.[10] Additional CO is contributed by combustion (eg, smoking materials, automobile exhaust).

The increased carboxyhemoglobin in the blood of sickle cell anemia patients may be caused by a number of factors, the first of which is greater cigarette consumption; the second factor is hemolysis; and third is the preferential survival of red cells containing CO that do not sickle. In the present study, the effect of hemolysis was verified by having blood obtained from control subjects divided into two aliquots. One aliquot served as the nonhemolyzed control; the other was partially mechanically hemolyzed in vitro with a shaker. Carboxyhemoglobin concentrations of hemolyzed blood of control subjects as well as that of patients were significantly increased.

In the sickle cell anemia patients, the arterial carbon dioxide tension and pH were no different from the control subjects'. Alveolar-arterial oxygen tension gradient and contributions made by ventilation-perfusion inhomogeneity are shown in Figure 5. These gradients were increased in the sickle cell patients. The widened gradient for oxygen is caused by low ventilation-perfusion ratios, which is shown by the increased arterial-alveolar nitrogen difference. To a lesser extent, the increased venous admixture to the pulmonary circulation (blood) shunt also contributes to the widened gradient for oxygen.

Treadmill Walking

The arterial oxygen tension of sickle cell anemia patients was lower than that of the control subjects both at rest and during minimal work rates; it remained relatively constant (Figure 6). Minute ventilation was greater for patients at rest than it was for the control subjects, and it increased for both groups during minimal work rates.

The heart rate of patients and controls was similar at rest, but at minimal work rates it increased at a

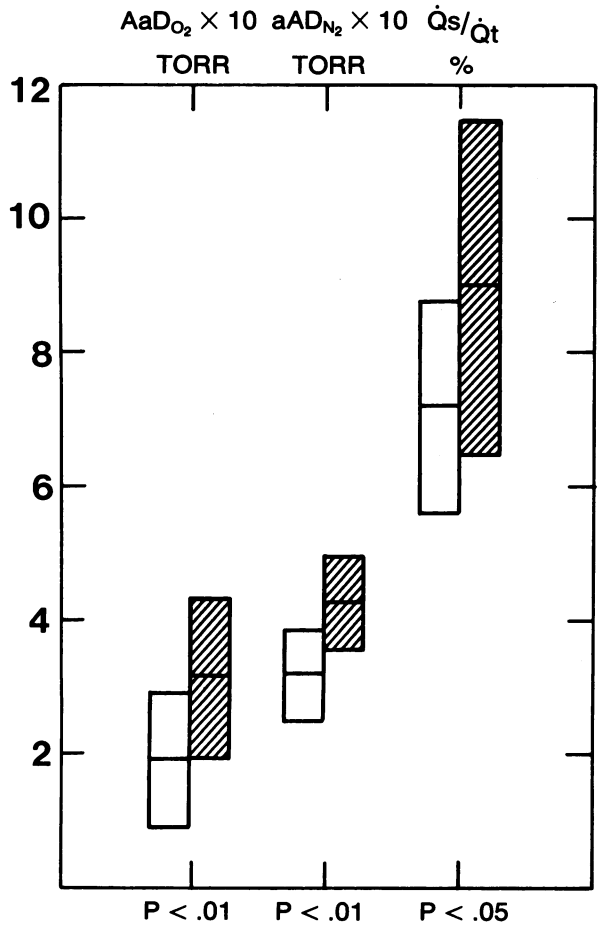

Figure 5. Bar graphs of the alveolar-arterial oxygen gradient and contributions made by ventilation-perfusion inhomogeneity. Note the increase in sickle cell patients for all variables shown. AaD_{O_2}—alveolar-arterial oxygen tension difference; aAD_{N_2}—alveolar-arterial nitrogen partial pressure

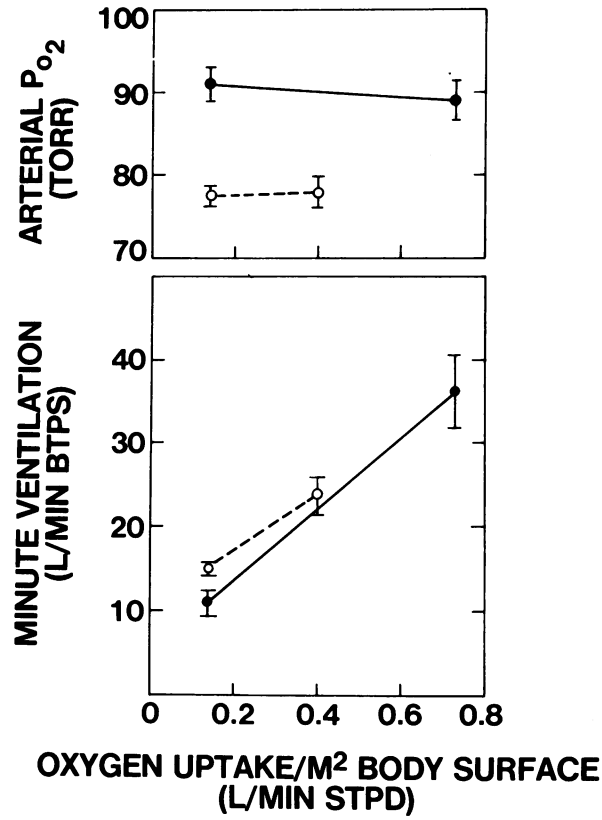

Figure 6. Arterial oxygen tension (top) of sickle cell anemia patients (open circles, dashed lines) is lower than that of controls (closed circles, solid lines) at rest and during minimal work rates and remains relatively constant in both groups. Minute ventilation (bottom) is greater for patients than for controls and it increased for both groups during minimal work rates

faster rate in the sickle cell patients. The respiratory-exchange ratio of 1 was exceeded at a lower oxygen consumption of 0.3 for patients vs 0.4 L/min standard temperature and pressure per m^2 body surface for controls. This ratio indicated that the patients reached the anaerobic threshold at lower work rates than did the controls.

DISCUSSION

Many workers have studied lung function in sickle hemoglobinopathy patients. Unlike the present study, they did not always include healthy controls, nor did they include a horizontal array of most available tests, both at rest and during exercise.

Femi-Pearse and co-workers[11] studied six hemoglobin SS patients, 4 hemoglobin SC patients, and 30 control subjects. They found vital capacity and total lung capacity were decreased without airway obstruction in patients with hemoglobinopathy. Miller and Serjeant[12] drew further attention to restricted lung volumes in sickle cell anemia. They suggested that the cause was anthropometric differences in these patients. The senior author confirmed restricted lung volumes in a preliminary study.[13]

Wall and co-workers[14] failed to find a decrease in lung volumes and expiratory flow rates in 12 children with sickle cell anemia. The normal values found in the 12 children were explained by the absence of repeated episodes of chest syndrome.

The diffusing capacity has also been found by many workers to be decreased.[11-13,15] Femi-Pearse and associates[11] partitioned diffusing capacity into its

components. Both the overall diffusing capacity and that of the pulmonary membrane were decreased; however, capillary blood volume was increased. This increase was attributed to "a chronically expanded pulmonary capillary bed." McGrath and Thomson[8] presented data showing the inverse relationship of diffusing capacity to quantitative hemoglobin in all types of anemia. Dinakara and co-workers[16] subsequently confirmed their work.

Becklake and associates[17] found that oxygen saturation in sickle cell anemia patients was later than in their control subjects; however, no difference existed in their arterial oxygen tensions. On the other hand, Moser and co-workers[18] emphasized the widened arterial oxygen tension gradients. Bromberg and Jensen[19] confirmed that the widened gradient was caused by a shunt. Fowler and co-workers[20] demonstrated a decreased alveolar-arterial oxygen tension gradient when sickle cell anemia patients breathed low-oxygen mixtures.

According to Wasserman and Whipp,[21] "the physiologic requirements for work performance involve a functional coupling of accelerated cardiovascular and respiratory activity to achieve gas transport between muscle cells and the atmosphere appropriate to the increased metabolic stress." Sickle cell anemia patients have both abnormal hemoglobin and anemia. The oxygen carrying capacity of the blood is a determinant in the adequacy of oxygen transport.

The respiratory exchange ratio (R) is a good indicator of aerobic and anaerobic glycolysis. It can be quantitated by inspection of the analog trace by end tidal N_2 wave-form analysis. The wave form is a crest for $R < 1$ at rest and at minimal work rates; rectilinear for $R = 1$ at moderate work rates; and is a trough for $R > 1$ at high work rates for anaerobic glycolysis. In sickle cell anemia patients, anaerobic glycolysis with production of lactate and metabolic acidosis is prominent at a relatively low work rate. The greater metabolic acidosis during anaerobic work induces disproportionate hyperpnea and ventilation. Care must be taken to prevent patients with sickle cell anemia from performing heavy workloads, for fear of inducing vaso-occlusive crises because oxygen transport in these patients is inadequate to support even moderate work.

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