Lung Function Abnormalities Occurring in Sickle Cell Hemoglobinopathies
A Preliminary Report

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ABNORMALITIES affecting the respiratory system in sickle cell hemoglobinopathies have been given scant attention. Moser and Shea[1] pointed out that episodes of chest pain, unexplained dyspnea or "pneumonitis" occurring in sickle cell anemia patients, should suggest the occurrence of in-situ pulmonary infarction, which is more frequent than realized. Recurrent episodes compromise lung function and because of concurrent anemia and cor pulmonale may be a consequence. This clinical entity, "sickle cell lung disease" is more common in older patients beyond 30.

This preliminary study was intended to ascertain to what extent pulmonary abnormalities occur in asymptomatic sickle cell anemia patients, to indicate which types of abnormalities are more frequent, and to point a direction for further study.

MATERIALS AND METHODS

Patients. To date, we have studied a total of nine homozygous patients, whose vital statistics are shown in Table 1. Patients 1 through 4 and 7 were studied during the symptom-free interval, while patients 5, 6, 8 and 9 were studied following recovery from in-situ pulmonary thromboses and infarction.

Studies. The following studies were performed on an Automated Pulmonary Function Laboratory*, the heart of which is a hot wire anemometer flow sensor. Volumes were obtained from electronic integration of a flow signal. Microprocessors automatically computed measured values, and percent predicted normal from standard prediction equations.[2] Digital displays, printed outputs and curves were recorded for each test. Forced vital capacity, its subdivisions and peak flow were computed from maximum expiratory flow-volume curves. Functional residual capacity was measured by the nitrogen washout method and distribution of ventilation measured by the nitrogen delta test. Small airways function was assessed by the closing volume test using the residual gas technique. Minute ventilation, tidal volume and respiratory fre-

Table 1. CHARACTERISTICS OF SICKLE CELL ANEMIA PATIENTS*

No.	*Initials*	*Age*	*Sex*	*Ht*	*Wt*	*Hb*
1	FJ	26	M	69	117	6.4
2	JC	49	M	66	167	8.6
3	ML	38	F	66	139	7.9
4	NO	37	M	74	179	9.0
5	AB	24	F	66	106	7.0
6	BC	23	M	67	152	8.2
7	SW	28	M	72	123	7.4
8	JJ	21	F	65	119	7.9
9	CS	44	M	69	147	8.1

*Ht = height in inches; Wt = weight in pounds
Hb = hemoglobin at time of study

*Work done during tenure of a 1975 Summer Medical Student Fellowship.

*Automated Pulmonary Function Laboratory. Available from SRL Medical, Inc. Dayton, Ohio.

Table 2. STATIC LUNG VOLUMES AND MAXIMAL EXPIRATORY FLOW RATE*

Patient	VC	(%)	FRC	(%)	RV_{TLC}	(%)	TLC%	FVC	(%)	$FEV_{FVC\ 100}$	$FEV_{3\ FVC\times 100}$	FEF_{25-75}	$\dot{V}max$	(%)
1	4.33	86	3.96	94	32	—	6.37	4.10	82	75	96	2.60 57	10.1	107
2	2.72	66	2.31	71	22	66	3.47	2.66	64	81	94	2.52 74	9.6	122
3	2.58	74	1.66	64	22	67	3.33	2.57	74	87	95	4.18 124	6.9	107
4	4.61	85	2.84	71	25	89	6.20	4.53	83	80	94	4.55 105	8.2	83
5	2.13	57	1.77	53	28	92	2.97	2.08	55	88	94	2.92 77	8.0	117
6	3.05	65	2.81	85	27	114	4.19	2.96	63	88	94	3.50 77	5.3	59
7	3.46	64	3.44	74	41	158	5.84	3.57	66	63	89	1.45 31	5.5	56
8	1.92	52	—	—	—	—	—	1.92	52	80	100	1.90 50	—	—
9	3.18	69	3.89	100	45	145	5.80	3.18	69	80	100	3.20 85	—	—

*VC = Vital capacity (L), FRC = Functional residual capacity (L), RV/TLC — Residual volume total lung capacity ratio, TLC — Total lung capacity (L), FVC = Forced vital capacity, $FEV_1/FVCx100$ = Forced expiratory volume in one second expressed as percent of Forced vital capacity. $FEV_3/FVCx100$ = Forced expiratory volume in three seconds expressed as percent of Forced vital capacity, FEF_{25-75} — Forced expiratory flow between 25 and 75 percent of the Forced vital capacity (L/Sec), V max = peak flow.

quency were measured breathing both room air and then 100% oxygen. Breath-holding diffusing capacity for carbon monoxide was measured with calculation of Krogh's K.

Large airways function was assessed directly by measurement of airways resistance and thoracic gas volume, in a variable pressure body plethysmograph.* Resistance was expressed as its reciprocal, conductance per liter of lung volume. Lung compliance was measured as dynamic lung compliance, using the esophageal balloon technique, at low respiratory frequencies.+

Single stick arterial blood samples were taken from the brachial artery at rest, breathing ambient air and analyzed for gas tensions, pH with polarographic electrodes and for oxygen saturation and hemoglobin in a cuvette oximeter.‡

A complete clinical assessment was made of each patient, complete with history, physical examination, chest radiographs and lung scans.

RESULTS

The majority of patients had restrictive lung disease, Table 2. Patients 2 through 7 had low total lung capacities and all but patients 1 and 4 had low vital capacities. Patients 7 and 9 also had hyperinflation of lung tissue as shown by large RV/TLC ratios. Patient 7 had an element of obstruction of large airways in addition to the restrictive element as shown by a low FEV_1/FVC x 100 and FEV_3/FVC x 100. This patient's FEF_{25-75} and $\dot{V}$ max were among the lowest in the group. The remainder of patients had pure restrictive patterns.

Figure 1 demonstrates the typical maximal expiratory $\dot{V}$ V curve of restrictive lung dis-

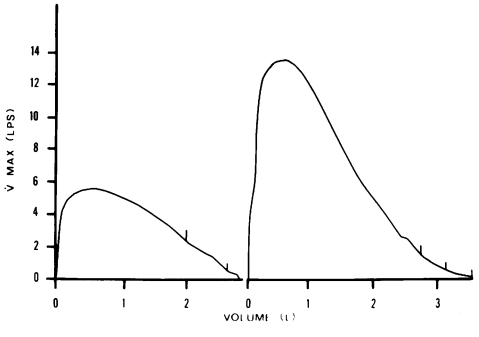

Fig. 1. Typical maximal expiratory V V curve of restrictive lung disease in the sickle cell anemia patient (left), compared with that of a healthy hemoglobin aa subject (right). Note that the sickle cell anemia patient has a decreased V max (y axis) and decreased FVC (x axis). One second time marks are shown on the tail of each curve.

ease in the sickle cell anemia patient compared with that of a healthy hemoglobin aa subject matched for age and sex for comparison. In the sickle cell anemia patient, both FVC and $\dot{V}$ max are decreased. Expiration was complete in a little over two seconds.

Table 3 reveals non-uniform distribution of inspired gases in only one patient, patient 5. We consider the upper limit of normal for

*Body Plethysmograph from Warren E. Collins, Inc. Braintree, Mass., Recorder from Electronics for Medicine, White Plains, N.Y.

+Godart Compliance Test, Instrumentation-Associates, N.Y., N.Y.

‡IL 213 and 182 Scientific Products, Columbia, Maryland.

Table 3. DISTRIBUTION OF INSPIRED GASES, GAS EXCHANGE AND LUNG MECHANICS*

Patient	$N_2\Delta$	LCI	(%)	$\%CV_{VC/CV}$	(%)	$\cdot D_L$	(%)	K	(%)	V_{TG}	S_{GAW}	C_{Ldyn}	C_{Lsp}
1	1.1	7.8	112	13	117	15	57	2.3	48	3.36	0.12	—	—
2	0.9	8.1	117	0	—	24	86	4.2	106	3.08	0.13	—	—
3	—	8.8	126	0	—	15	69	3.6	83	2.29	0.26	—	—
4	0.7	6.9	99	0	—	19	66	2.9	67	2.72	0.11	—	—
5	2.5	8.6	123	10	98	12	55	2.8	58	1.97	0.18	0.05	0.03
6	1.0	7.0	101	4	43	21	72	3.8	76	2.80	0.19	0.08	0.03
7	1.3	8.2	117	13	110	17	62	2.7	57	3.87	0.06	0.14	0.04
8	—	—	—	—	—	18	80	—	—	2.40	0.18	0.06	0.03
9	—	—	—	—	—	21	87	—	—	4.42	0.22	0.15	0.04

*N_2 = Single breath oxygen test, percent N_2 between 750 and 1250 ml gas expired. LCI = Lung clearance index, % CV/VC/VC = closing volume expressed as percent of vital capacity, DL = Diffusing capacity for carbon monoxide (ml/min/mm Hg), K = Krogh's "lung permeability" (min^{-1}), VTG = Thoracic gas volume measured at FRC (L), SG_{AW} = Specific airways conductance (cmH_2O^{-1}), C_{Ldyn} = Lung compliance (L/cmH_2O), C_{Lsp} = Specific lung compliance (cmH_2O^{-1}).

the N_2 delta test to be 2.0 % N_2. Lung clearance induces, the amount of oxygen required to washout the FRC, were slightly increased in patient 2 and patient 5. Significant peripheral small airways disease was absent in ALL sickle cell anemia patients in whom it was measured. Three patients lacked a discernable closing volume. Ironically, these were older patients (Patients 2, 3 and 4).

Carbon monoxide diffusing capacity was decreased in 6 of 9 of the patients studied. The low diffusing capacity was not due to small lungs alone, because k, the "permeability" of the lungs was often decreased as well. This measurement is independent of lung size, and depends on the characteristics of the pulmonary membrane and reaction rate with red cells in lung capillaries. At least part of the decrease in diffusing capacity and permeability is related to the anemia present. Jouasset-Strieder and associates[3] have demonstrated in dogs, that both diffusing capacity of the lungs as well as diffusing capacity of the lung membrane are decreased proportionate to the amount of hemoglobin present.

Specific airways conductance was significantly low only in patient 7, confirming the previously noted obstruction of large central airways in this patient. The low lung compliances in patients 5, 6 and 8 were due to small lungs and NOT changes in the elastic properties of the lung, because specific compliance, (compliance per liter of lung volume) was normal.

Measured arterial oxygen saturations and tensions are shown in Figure 2, superimposed over standard oxyhemoglobin dissociation curves at the pH values shown. With the exception of one patient, we failed to demonstrate lower measured O_2 saturations for corresponding arterial oxygen tensions in these sickle cell patients.

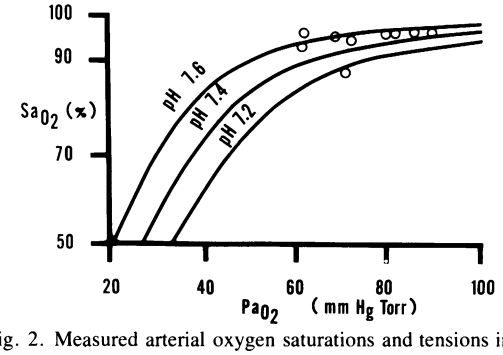

Fig. 2. Measured arterial oxygen saturations and tensions in 9 sickle cell anemia patients superimposed over standard oxyhemoglobin dissociation curves at pH values shown. Although 5 patients were hypoxemic (arterial Po_2 below 80), with the exception of one patient, we failed to demonstrate lower saturations for corresponding Po_2.

Lastly, Table 4 shows the direction and magnitude of response of minute ventilation and tidal volume, breathing 100% oxygen as compared with air breathing. The decrease in minute ventilation in 6 of 7 patients and decrease in tidal volume and presumably alveolar ventilation in 4 of 7 patients, suggests the possibility of hypoxic drive to respiration, at least in some sickle cell anemia patients.

DISCUSSION

"Sickle cell lung disease" is common in older patients with sickle cell anemia in

whom sickle cell potentiators (recurrent or extensive infection, acidosis, demands for greater O_2 utilization or left heart failure) make patients more prone to develop recurrent pulmonary infarction.[1] Opphenheimer and Esterly[4] reviewed 36 necropsied patients with sickle hemoglobinopathy in Baltimore and Chicago and noted that pneumonia was no more common in sickle cell patient than among age matched controls. They further suggested that in-situ pulmonary infarction was often mistaken for pneumonia in the sickle cell anemia patient. When pneumonitis *did* occur it was caused by a variety of bacteria and correlated well with hyperplasia of lymphoid tissue. Repeated scarring because of multiple infarctions and unresolved pneumonias was thought to lead to smaller lungs and decreased lung volumes.

Table 4. RESPONSE OF MINUTE VENTILATION AND TIDAL VOLUME BREATHING 100% OXYGEN, AS COMPARED WITH AIR BREATHING*

Patient	V_E (L/*min*)	V_T (L/*breath*)
1	4.4 increase	0.28 decrease
2	0.3 decrease	0.55 increase
3	3.0 decrease	0.20 decrease
4	3.0 decrease	0.23 decrease
5	2.6 decrease	0.17 increase
6	4.4 decrease	0.11 decrease
7	2.5 decrease	0.20 increase

/ V_E = minute ventilation (L/min); V_T = tidal volume (L/breath)

Femi-Pearse and Associates,[5] like the present authors, measured lung function using modern techniques of flow-volume curves, helium dilution functional residual capacity and breath-holding diffusing capacity, which they divided into its components, that of the lung membrane and volume of blood in the lung capillaries. They studied six patients with SS hemoglobinopathy, four with SC and 30 healthy adult control subjects. Like the present workers, they found vital capacity and total lung capacity were decreased without airways obstruction. They attributed these abnormalities to multiple pulmonary infarcts. Although diffusion capacity of the lung was decreased, they believed it was disproportionately high with respect to the anemia present. It was thought to represent a "chronically expanded pulmonary capillary bed".

Miller and Serjeant[6] drew further attention to the restricted lung volumes in sickle cell anemia, noting that 13 of 25 patients had a history of previous lung disease. Their static lung volumes were likewise decreased. They postulated smaller lung volumes as due to a short thorax relative to body stature, and a narrower chest diameter than is present in healthy subjects of the same ethnic, and is attributed to their having performed anthropometric measurements. Their values for diffusing capacity like ours, were decreased.

Ishikawa[7] recently presented data on eight patients with sickle cell anemia. He essentially confirmed the restrictive lung disease and low diffusing capacity demonstrated by the present workers and by others.[5,6]

Many workers[7,8] emphasized the low arterial oxygen tensions found in patients with sickle cell anemia. Increased alveolar-arterial oxygen tension gradients have been demonstrated. Moser and co-workers,[8] believed that some of the widened gradients were due to shunt or venous admixture due to physiologic blood shunts through unventilated lung. They presented data however, which demonstrated the increase in membrane but not the shunt component. Fowler and co-workers,[9] demonstrated a decreased alveolar-arterial oxygen gradient when sickle cell anemia patients breathed low oxygen mixtures suggesting that the widened gradient was not due to a "membrane component", but rather a "shunt component".

Becklake and associates[10] and later others,[8,9] found that oxygen saturations in sickle cell anemia were lower than those of control subjects, although no difference existed in the arterial oxygen tensions. The oxyhemoglobin dissociation curve in sickle cell anemia has been shown to be displaced to the right, causing the oxygen tension at which hemoglobin is half saturated, to be higher (increased P_{50}). It is related to increased amounts of 2,3 diphosphoglyceric acid in red cells of these patients, a homeostatic mechanism, which when combined with increased cardiac output of anemia, enhances oxygen delivery to the tissues.

The present authors noted low arterial oxygen tensions and presumed widened alveolar-arterial oxygen tension gradients in five of nine patients (Fig. 2). However, with the exception of one patient, we failed to demonstrate lower measured oxygen saturations for corresponding arterial oxygen tensions (plotted against standard oxyhemoglobin dissociation curves for human blood, corrected for pH). The reasons for this is not apparent, since all patients studied had moderate degrees of anemia. Perhaps the number of patients studied was too small.

The hypoxic drive to respiration shown in the majority of patients studied, suggests blunting of respiratory control mechanisms in the sickle cell anemic patient. This facet deserves further study. Additional, investigation should also include statics, anthropometric measurements and partition of diffusing capacity.

We support the view that pulmonary function abnormalities in sickle cell hemoglobinopathies consists of a decrease in lung volumes and abnormalities in gas transfer. Lack of specificity of the alveolar-arterial oxygen tension gradient for demonstrating physiologic mechanism of gas exchange abnormality is clearly recognized. Additional work is required in areas of gas exchange in evaluation of ventilation blood-flow inhomogeneities in sickle cell lung disease. Finally, the difficulties in evaluation of lung function in the sickle cell anemia patient should not be overlooked. These patients, with multiple hospitalizations and medical complications in life, are poor performers and lie on the low end of the motivation scale, unlike the cystic fibrosis patient. Perhaps psychological testing of large groups of sickle cell anemia patients may also bring new answers to these questions.

SUMMARY

The majority of adults with sickle cell anemia have restrictive lung disease when compared with predicted normal values. Whether this is due to smaller scarred lungs of repeated episodes of in-situ pulmonary thromboses and infarction or a smaller thorax to total height measurement, remains to be defined.

Abnormalities in gas transfer across the pulmonary membrane are present, while any increase in lung stiffness is likely due to small lung size. In general, obstruction of either large or small airways is infrequent. We were unable to demonstrate the rightward shift in the oxyhemglobin dissociation curve said to occur in sickle cell anemia.

Finally, a decrease in minute ventilation and tidal volume breathing 100% oxygen as compared with air, suggests that hypoxic drive to respiration is present in some patients.

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