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Pulmonary function in sickle cell disease with or without acute chest syndrome

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Pulmonary function in sickle cell disease with or without acute chest syndrome. F. Santoli, F. Zerah, N. Vasile, D. Bachir, F. Galacteros, G. Atlan. ©ERS Journals Ltd 1998.

ABSTRACT: Recurrent acute chest syndrome (ACS) has been suggested as a risk factor for chronic lung dysfunction in sickle cell disease.

To investigate this hypothesis, lung function tests were performed in 49 sickle cell disease outpatients whose condition was stable, including 23 patients with a history of two to four episodes of ACS (ACS+) and 26 with no history of ACS (ACS-). The two groups were comparable regarding the sex ratio, body mass index, smoking history, physical characteristics, clinical history and usual lung function tests.

Respiratory resistance (R_{rs}), measured using the forced oscillation technique, increased with the number of ACS episodes (r=0.55, p<0.0001) and a significant relationship was observed between R_{rs} as an independent variable and the expiratory flow rates at 25, 50 and 25–75% of the forced vital capacity as explanatory variables (r= 0.36, p<0.02; r=0.35, p<0.02; and r=0.4, p<0.006, respectively), with higher R_{rs} being associated with lower expiratory flow rates. The transfer factor ($T_{L,CO}$) and transfer coefficient (K_{CO}) for CO were significantly higher in the ACS+ group than in the ACS- group ($T_{L,CO}$=84±4 *versus* 71±3%, p<0.004 and K_{CO}=102±5 *versus* 90±3%, p<0.05, res-pectively).

The data demonstrate that obstructive lung dysfunction is fairly common in sickle cell disease and suggest that recurrent acute chest syndrome may contribute specific obstructive defects. The increase in respiratory resistance associated with acute chest syndrome was accompanied by an increase in diffusion capacity, suggesting that it may have been related to an increase in lung blood volume.

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Pulmonary involvement in sickle cell disease (SCD) is a source of acute morbidity and, in the long term, a major determinant of survival. However, some confusion surrounds the two main pulmonary complications described in SCD, as a result of gaps in the understanding of their cause and pathophysiology. One of these complications, often called sickle chronic lung disease (SCLD), is believed to be initiated by recurrent acute events characterized by vascular injury, possibly responsible for pulmonary oedema [1, 2], with the ultimate result being chronic fibrosis. Other factors, including infections and infarctions, are superimposed on this background [3], further worsening the lung damage and leading to pulmonary hypertension [1, 2]. Most studies of lung function in SCLD have demonstrated a restrictive defect [1, 4, 5], and a reduction in total lung capacity (TLC) of ð50% has been reported in advanced forms [1]. An obstructive pattern has also been reported [4, 6] in a few patients with SCLD. Alterations in diffusion capacity (transfer factor of the lung for carbon monoxide ($T_{L,CO}$)) were found in most studies [4, 5].

The other pulmonary complication is an acute clinical event called acute chest syndrome (ACS), which is distinct from acute vaso-occlusive painful crisis [7]. ACS has been defined as "a new pulmonary infiltrate with fever and often bone pain" [8]. Its pathogenesis is uncertain. Although ACS is one of the most frequent causes of hospitalization in SCD, it is relatively rare: in a study of 3,751 patients with SCLD [9], a total of 2,100 episodes of ACS occurred in 1,085 patients; most patients with ACS experienced a single episode (55.9%) and only 5.9% had four episodes. However, ACS is a potentially life-threatening event and it has been suggested that recurrent ACS may be associated with an increased risk of SCLD [2, 10]. The present study was undertaken to investigate this suggestion. The patients studied did not have marked respiratory symptoms at the time of the study and were divided into two groups according to whether or not they had a history of recurrent ACS.

Patients and methods

Study population

Forty-nine outpatients (25 males and 24 females) aged 16–49 yrs (mean±SD 27.7±7.1) receiving regular follow-up at the Sickle Cell Disease Centre of the authors' institution were entered into the study. All patients were studied during a crisis-free period. Lung function tests were performed at least 2 months after the last acute event or blood transfusion. Forty-two patients had sickle cell SS-haemoglobin disease, four had sickle cell SC-haemoglobin disease and three had sickle cell β-thalassaemia disease.

None of the study patients had a history of smoking, alcohol misuse, immunodeficiency, heart disease or liver disease, and none was taking medications other than folic acid. None had a history of asthma or chronic bronchitis and none had respiratory symptoms that forced them to stop their usual activities. Thirty-nine patients were actively employed at the time of the lung function tests, five were homemakers, four were students and one was on a disability pension.

Of the 49 patients, 23 had a history of ACS (ACS+ group). All of the episodes of ACS had been severe enough to require inpatient treatment. The number of patients who had experienced two, three and four episodes was 15, four and four, respectively. After recovery from ACS, these 23 patients did not have any distinctive clinical features allowing them to be differentiated from the patients without ACS (ACS-). The physical characteristics in the ACS+ and ACS- groups are listed in table 1. The diagnosis of ACS was established based on chest pain, dyspnoea, fever and the development of a pulmonary infiltrate and neutrophil count elevation in the absence of any evidence of pulmonary infection. In most patients, arterial oxygen tension (P_{a,O_2}) values during the hospital stay were significantly lower than the baseline value in the same individual. On average, only one-third of the ACS events required partial exchange transfusion. The duration of hospital stay was 7–13 days.

At the time of lung function testing, each patient underwent a thin section computed tomographic scan of the thorax (with 1.0 or 1.5 mm collimation and a bone algorithm) in suspended maximum inspiration in the supine position. The following signs were assessed by two ob-servers: interlobular septal thickening, parenchymal bands or nodes, subpleural lines, pleural tags, honeycombing and areas of attenuated vasculature. For none of these signs were any significant differences seen between ACS+ and ACS- patients or according to the severity of ventilatory defects.

Lung volumes and flows

Lung volumes and flows were measured in the sitting position, using a closed-circuit spirometer (VG 2000; Mijnhardt BV, Bunnik, The Netherlands). Functional residual capacity (FRC) was measured using either the helium dilution technique with a closed-circuit spirometer (VG 2000) or the nitrogen wash-out technique (PF/Dx 1085 D; MedGraphics St Paul, MN, USA). The mean of two determinations was used. Forced expiratory flows were measured using the MedGraphics flowmeter system, which was coupled to a computer that expressed usual maximal forced expiratory flows at different levels of the forced vital capacity (FVC), *i.e.* (forced expiratory flow at 50% and 25% of FVC peak flow, (FEF_{50}, FEF_{25}) and maximal forced mid-expiratory flow ($FEF_{75–25}$)). Since most patients in this study were from the West Indies or Africa, the reference values determined by MILLER *et al.* [11] were used. The values in the few Caucasian patients were compared to the predicted values reported by QUANJER *et al.* [12]. Spirometry measurement techniques met international standards [12].

Table 1. – Physical characteristics and types of haemoglobinopathy the study patients

	ACS+	ACS-
Subjects n	23	26
SS disease	17	25
S β-thalassaemia disease	3	1
SC disease	3	0
Regular transfusions	5	7
Age yrs	26.0±6.2	29.1±7.7
Sex ratio M/F	9/14	16/10
BMI $kg \cdot m^{-2}$	20.8±3.6	21.4±4.2
Height cm	167±9	169±9
Weight kg	59±13	60±11
Hb $g \cdot dL^{-1}$	10.2±1.7	9.3±1.8

Values are expressed as means±SD. No significant differences were observed between the groups. ACS+: patients with a history of acute chest syndrome; ACS-: patients without a history of ACS; SS disease: sickle cell SS-haemoglobin disease; S β-thalassaemia disease: sickle cell β-thalassaemia disease; SC disease; sickle cell SC-haemoglobin disease. M: male; F: female; BMI: body mass index (weight/height^2); Hb: haemoglobin.

Diffusing capacity

$T_{L,CO}$ was measured using the single breath-holding carbon monoxide method, as described by COTES *et al.* [13]. Neon was used as the inert gas to evaluate the alveolar volume (V_A), which served to calculate the carbon monoxide transfer coefficient ($K_{CO} = T_{L,CO}/V_A$). T_L was corrected for haemoglobin concentration. The predicted values for this parameter were those determined by QUANJER *et al.* [12].

Arterial blood gas analysis

Arterial blood was drawn from the radial artery with the patient awake and semi-supine. Blood samples were analysed for pH, carbon dioxide tension, and oxygen tension (ABL 30 Blood gas analyser; Radiometer, Copenhagen, Denmark). Oxygen saturation was determined using a spectrometer (OSM3, Hemoximeter; Radiometer). Arterial gas levels were measured at rest and, in 18 patients, after a short period of exercise on a bicycle ergometer. Thirty-one patients were unable to use the bicycle because of musculoskeletal lesions caused by bone infarctions.

Respiratory system resistance

Respiratory system resistance (R_{rs}) was measured using the previously described forced oscillation method [14]. In brief, a pseudorandom noise signal of 3–32 Hz was generated by loudspeakers and superimposed on the spontaneous breathing of the subject, who was equipped with a mouthpiece and noseclip. The subject's cheeks were held firmly. Mouth flow was measured using a screen pneumotachograph (Jaeger, Würzburg, Germany) connected to a differential transducer (LX 0600ID; Sensym, Sunnyvale, CA, USA). An identical transducer was used to measure mouth pressure. Signals were low-pass filtered to prevent aliasing, *i.e.* to eliminate the possible influence of low or high frequencies. Signals were sampled at a frequency of 128 Hz and fed into a microcomputer for spectral analysis using a 512-point fast fourier transform algorithm. The real part (relating to the resistive properties of the system) and the imaginary part (corresponding to inertance and compliance properties) of the respiratory impedance were computed every 0.25 Hz from 3 to 32 Hz and displayed as a function of frequency. For each of these frequencies, a coherence function ranging from 0–1 was calculated to enable evaluation of the reproducibility of the impedance

measurement and 0.9 was chosen as the lower limit of data acceptance. The real part of impedance was submitted to linear regression analysis which yielded the R_{rs} extrapolated to zero frequency and the slope (S) of the linear relationship of the resistive impedance *versus* frequency. As described previously [15], fitting of the real part of the impedance by a linear model enabled use of the impedance value extrapolated to zero frequency as an index of R_{rs} during spontaneous breathing.

Statistical analysis

Data are expressed as mean±SD. The ACS+ and ACS- groups were compared using the t-test. Frequency data were analysed using the Chi-squared test, with Yates' correction when necessary. Correlations between variables were analysed using least-squares linear regression techniques; multiple regression analysis was also performed. For all comparisons, p-values <0.05 were considered statistically significant.

Results

The physical characteristics of the two groups of patients are presented in table 1. Anthropometric data and the sex ratio were not significantly different between the two groups.

Lung volumes and expiratory flows

Lung volumes and expiratory flow rates were not significantly different between the ACS+ and ACS- groups (table 2).

In the overall study group, mean TLC was slightly reduced (83%; range 47–109%; no clear explanation was found for the more substantially reduced TLC values seen in three patients). Twenty (41%) patients exhibited a restrictive ventilatory defect, as defined by a TLC value <80% of the predicted value. These patients were evenly distributed between the two patient groups (35% and 46% in the ACS+ and ACS- groups, respectively), (table 3) and no correlation was found between the number of ACS episodes and the reduction in TLC.

Twenty-eight patients (57%) had an obstructive defect, as defined by a forced expiratory volume in one second (FEV_1)/vital capacity (VC) value <80%. Ten of these patients also had a restrictive defect. The patients with obstructive patterns were evenly distributed between the two groups (table 3, 56% and 58% in the ACS+ and ACS- groups, respectively, NS). The severity of obstruction was not correlated with the number of ACS episodes.

Respiratory system resistance

In the overall population, significant increases in R_{rs} were observed with decreasing expiratory flow rates (FEF_{25} FEF_{50} and FEF_{25-75}: r=0.36, p<0.02; r=0.35, p<0.02, and r=0.4, p<0006, respectively). No significant relationships were noted between R_{rs} and FEV_1 (table 2).

R_{rs} values were significantly higher in the ACS+ group than in the ACS- group (4.8±1.8 *versus* 3.9±0.8 $cmH_2O \cdot L^{-1} \cdot s^{-1}$, p<0.03) (fig. 1). Regression analysis with R_{rs} as a continuous dependent variable and the number of ACS episodes as an independent variable yielded similar results (p<0.0001, r=0.55). The magnitude of the R_{rs} increased with the number of ACS episodes. Similarly, there was a significant correlation between the slope of the linear relationship of the resistive impedance *versus* frequency as an independent variable and the number of ACS episodes (r= 0.46, p<0.002).

Table 2. – Lung function and arterial blood gas values in patients with (ACS+) and without (ACS-) a history of acute chest syndrome

	Total	ACS+	ACS-	p-value
Subjects n	49	23	26	
TLC % pred	83±12	83±13	83±10	NS
FVC % pred	83±13	83±14	82±11	NS
FRC % pred	78±18	76±18	81±18	NS
FEV_1 % pred	86±17	86±19	86±14	NS
FEV_1/VC % pred	84±12	83±13	85±12	NS
FEF_{50} % pred	72±27	73±29	71±26	NS
FEF_{25} % pred	57±24	58±25	56±24	NS
FEF_{25-75} % pred	67±24	69±25	66±22	NS
R_{rs} $cmH_2O \cdot L^{-1} \cdot s^{-1}$	4.4±1.4	4.8±1.8	3.9±0.8	<0.03
K_{CO} % pred	96±20	102±22	91±17	<0.05
$T_{L,CO}$ % pred	77±17	84±17	71±15	<0.004
P_{a,O_2} R mmHg	87±9	88±10	87±9	NS
P_{a,O_2} E mmHg	85±10	87±11	83±9	NS
P_{a,CO_2} R mmHg	39±4	39±4	39±4	NS
P_{a,CO_2} E mmHg	39±3	38±4	40±3	NS
S_{a,O_2} %	96±2	95.9±2.6	96.1±1.9	NS

Values are expressed as mean±SD. pred: predicted values from [12, 16]. TLC: total lung capacity; FVC; forced vital capacity; FRC: functional residual capacity: FEV_1: forced expiratory volume in one second; VC: vital capacity; FEF_{50} and FEF_{25}: forced expiratory flow at 50% and 25% of FVC; FEF_{25-75}: maximal mid-expiratory flow; R_{rs}: respiratory system resistance; K_{CO}: transfer coefficient for CO; $T_{L,CO}$: transfer factor of lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; S_{a,O_2}: arterial oxygen saturation; R: at rest; E: after exercise testing (n=18). (1 mmHg=0·133kPa.)

Arterial blood gas values

Arterial blood gas values were normal in every patient at rest (n=49), as well as during exercise (n=18), with no significant differences between the two groups. However, the mean P_{a,O_2} value was lower in the 20 patients with a restrictive pattern (TLC<80% predicted) than in the 29 other patients (11.1±0.7 kPa (83±5mmHg) and 12.1±1.5 kPa (91±11 mmHg), respectively, p<0.005) (see table 2).

Table 3. – Distribution of ventilatory defects in the overall patient population and in the groups with (ACS+) and without (ACS-) a history of acute chest syndrome

	Total	ACS+	ACS-
Subjects n	49	23	26
TLC Š80% and FEV_1 VC Š80%	11	7	4
TLC Š80% and FEV_1/VC <80%	18	8	10
TLC <80% and FEV_1/VC Š80%	10	3	7
TLC <80% and FEV_1/VC <80%	10	5	5

Lung function parameters are expressed as percentages of predicted values [12, 16]. All comparisons between patients with and without ACS were nonsignificant. TLC: total lung capacity; FEV_1: forced expiratory volume in one second; VC: vital capacity.

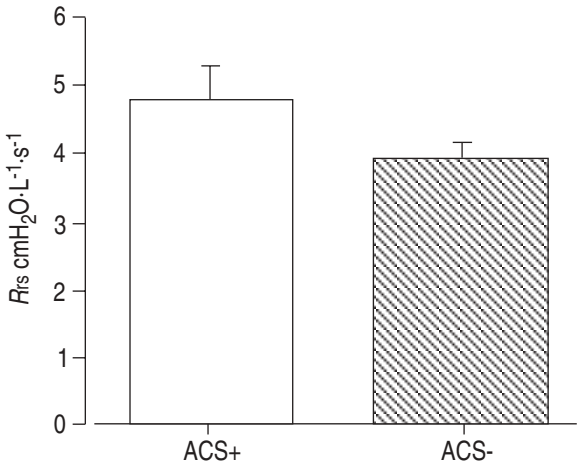

Fig. 1. – Respiratory system resistance (R_{rs}) measured using the forced oscillation technique, was significantly higher ($p<0.03$) in the patients with a history of acute chest syndrome (ACS+) than in those without (ACS-). Values are presented as mean±SD.

Significant correlations were found between P_{a,O_2} and FEV_1, FEF_{25}, FEF_{50} and FEF_{25-75}: $r=0.35$, $p<0.02$; $r=0.35$, $p<0.02$; $r=0.33$, $p<0.03$; and $r=0.4$, $p<0.009$, respectively.

No correlations were noted between the number of ACS episodes and blood gas values.

Diffusing capacity

$T_{L,CO}$ was reduced relative to the TLC (or V_A), 77±17% pred; range 45–132). However, the mean K_{CO} for the overall population was virtually normal (96±20% pred; range 58–142) and K_{CO} was not influenced by the presence of a restrictive or obstructive defect (table 2, fig. 2). Although significant differences in K_{CO} and $T_{L,CO}$ values were seen between the two groups, the number of ACS episodes was not significantly correlated with K_{CO} and $T_{L,CO}$ values, probably because of the large SD.

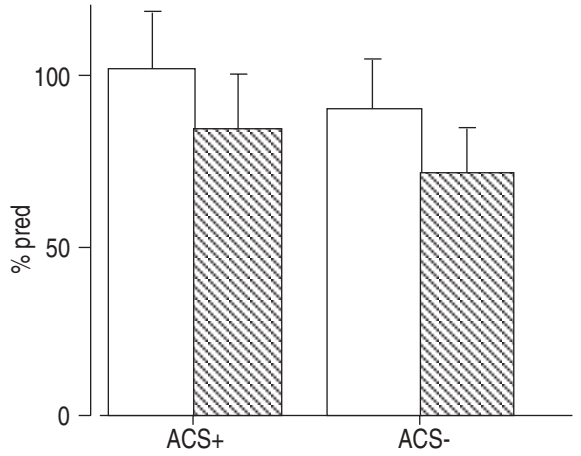

Fig. 2. – Diffusing capacity parameters (transfer coefficient for carbon monoxide (K_{CO}, ▭) and transfer factor of the lung for carbon monoxide ($T_{L,CO}$, ▨)) measured using the carbon monoxide breath-holding technique were significantly higher in the patients with a history of acute chest syndrome (ACS+) than in those without (ACS-). % pred: percentage of predicted value. $p<0.05$, significant difference in K_{CO}; $p<0.004$, significant difference in $T_{L,CO}$ between groups.

Discussion

The present data were from SCD patients in a stable condition who differed regarding their history of ACS but were comparable regarding anthropometric data and smoking history. The goal was to evaluate the effects of ACS episodes on lung function. The two main findings were: 1) in addition to the restrictive pattern classically observed in SCD, an obstructive pattern was common, and 2) a history of ACS was associated with higher values for $T_{L,CO}$ and R_{rs} but not with more severe ventilatory defects.

Earlier studies [4, 5, 10, 17, 18] found a restrictive ventilatory defect in patients with SCLD. It has been suggested that endothelial injury induced by sickled red cells may initiate a chain of reactions leading to pulmonary oedema, which may in turn give rise to the fibrotic process [1, 2]. Other factors superimposed on this process may worsen the lung damage. Thus, infections, fat embolism following bone infarction and increased intravascular coagulation may contribute substantially to the pulmonary hypertension seen in advanced SCLD.

Based on a review of 29 patients, POWARS *et al.* [10] found that the natural history of SCLD evolved through four successive stages that could be differentiated by pulmonary function tests, chest radiographs, blood gas values and noninvasive cardiac studies. Patients with stage I disease, or incipient SCLD, had a mean age of 23.8 yrs, were usually free of respiratory symptoms (except during acute events) and exhibited only a moderate ventilatory defect (which was not characterized as restrictive or obstructive). Most of the ACS+ group patients in this study met this description, although a large proportion of them had near normal pulmonary function.

POWARS *et al.* [10] reported that ACS episodes were an important risk factor for the development of SCLD. In the present large group of patients with a history of ACS, no association was found between a history of ACS episodes and the severity of ventilatory defects. This discrepancy is probably due to the fact that the cases of SCLD in this study were early-stage, whereas POWARS *et al.* [10] studied their patients over the long term and consequently accumulated a large number of ACS episodes. The findings from the present study may have been different if patients with five or more episodes of ACS had been included. However, in the authors' institution such patients were treated with hydroxyurea (HYDREA®), which is known to increase haemaglobin F concentrations and to reduce the occurrence of ACS. Nevertheless, the present data allow the conclusion to be reached that a small number of ACS episodes is not a risk factor for SCLD.

Another striking finding from the present study is that, in contrast to widely held belief [4, 5] restriction was far from being the only pattern of ventilatory defect, since 18 of the patients had a purely obstructive defect and 10 others had both a restrictive and an obstructive defect. Obstructive defects have been occasionally reported in the literature, usually in the context of acute events [19]. Low peak flow rates and a favourable response to β-agonist therapy in children have also been reported during ACS. It is difficult to explain this unexpected finding, although it may be related to sequelae of bronchial infections. Are obstructive defects more frequent in patients with ACS? In the present study, the R_{rs} and S parameters were sensitive to a history of ACS and to the number of ACS episodes, whereas the

usual indices of obstruction (FEV_1 and FEV_1/FVC) were not. Although all of the patients were nonsmokers and free of chronic bronchitis or asthma, R_{rs} increased significantly with the number of ACS episodes ($r=0.55$, $p<0.0001$).

R_{rs} is known to be influenced by height, body mass index and sex. No significant differences in any of these parameters were found between the two groups. The significant increase in R_{rs} with the number of ACS episodes ($r=0.55$, $p<0.0001$) may be ascribable to obstruction of the peripheral airways. The regression analysis demonstrated significant correlations between R_{rs} as the dependent variable and the expiratory flow rates FEF_{50}, FEF_{25} and FEF_{25-75} as the explanatory variables ($r=0.35$, $p<0.02$; $r=0.36$, $p<0.02$, and $r=0.4$, $p<0.006$; respectively). The frequency dependence of resistance increased significantly with the number of ACS episodes ($r=0.46$, $p<0.002$). This parameter, the S of the relationship between R_{rs} and oscillation frequency, was also closely correlated with the expiratory flow rates FEF_{50}, FEF_{25}, and FEF_{25-75} ($r=0.4$, $p< 0.009$; $r=0.4$, $p<0.008$ and $r=0.41$, $p<0.006$, respectively). R_{rs} is a global parameter that includes chest wall impedance, but the significant correlations found between R_{rs} and expiratory flow rates indicate that distal airway obstruction was partly responsible for the observed alterations, consistent with the present results and with the results of earlier studies [15].

To define the role of peripheral obstruction, the data were analysed further using multiple regression analysis with R_{rs} as the dependent variable and FEF_{25-75} and the number of ACS episodes as the explanatory variables. This significant multiple regression ($r=0.67$, $p<0.0001$) demonstrated a highly significant correlation ($p<0.0001$) between R_{rs} and ACS and a significant correlation ($p<0.0015$) between R_{rs} and FEF_{25-75}. Results were similar when S was used as the dependent variable and FEF_{25-75} and ACS were used as the explanatory variables ($r=0.6$, $p<0.0001$): significant correlations were demonstrated between S and FEF_{25-75} ($p<0.0035$) and between S and ACS ($p<0.0015$). In other words, even when peripheral obstruction was taken into account, R_{rs} was still influenced by the number of ACS episodes.

Many pathological processes associated with SCD have been implicated in the development of ACS. Although interest is moving away from infection, at least in adults, increasing attention is being directed to infarction due to *in situ* thrombosis [20], hypoventilation due to painful chest wall lesions [21], fat emboli from bone marrow infarcts [22, 23], and intravascular overload [24]. Regarding this last factor, a study found that a slight increase in thoracic blood volume, obtained by pneumatic trouser inflation, resulted in an increase in R_{rs} in normal subjects [16]. A marked increase in R_{rs} with a fall in FEV_1 was also demonstrated during large thoracic blood volume increases, such as those produced by volume expansion [25], both in normal subjects and in asthma patients. In asthma patients, an increase in the capillary bed within airway walls has been found.

Results regarding $T_{L,CO}$ lend further support to the intravascular overload hypothesis. $T_{L,CO}$ was usually decreased [5, 17]. When the two components of $T_{L,CO}$ were measured separately, the membrane diffusing capacity was decreased, whereas pulmonary capillary blood volume was increased. The two components of $T_{L,CO}$ were not measured in the present study. Although a decrease in mean $T_{L,CO}$ was found, this decrease was roughly of the same order of magnitude as the decrease in TLC and mean K_{CO} was close to the predicted value. More importantly, $T_{L,CO}$ and K_{CO} were substantially higher in those patients who had a history of ACS. Moreover, $T_{L,CO}$ tended to be higher in the patients who had experienced more than two ACS episodes, although this increase did not reach statistical significance. Although these facts are difficult to interpret, they suggest that lung blood volume may be increased in patients with a history of ACS compared to those without and that this increase may be responsible for the increase in R_{rs} seen in ACS+ patients. If this is the case, the concern arises that ACS may result in lung alterations that persist after recovery from ACS. Further work is necessary to investigate some of the hypotheses raised by this study, including the possible irreversibility of alterations induced by the acute event.

In conclusion, this study found no evidence that recurrent acute chest syndrome may be associated with more severe lung damage as assessed by lung function tests. Obstructive ventilatory defects were fairly common and were evenly distributed between patients with and without a history of acute chest syndrome. The distinctive features evidenced in patients with acute chest syndrome were increases in both respiratory resistance and diffusion capacity, which suggest an increase in thoracic blood volume.

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References

1. Powars DR. Sickle cell anemia and major organ failure. *Hemoglobin* 1990; 14: 573–598.
2. Weil JV, Castro O, Malik AB, Rodgers G, Bonds DR, Jacobs TP. Pathogenesis of lung disease in sickle hemoglobinopathies. *Am Rev Respir Dis* 1993; 148: 249–256.
3. Haupt HM, Moore CM, Bauer TW, Hutchins GM. The lung in sickle cell disease. *Chest* 1982; 81: 332–337.
4. Bromberg A. Pulmonary aspects of sickle cell disease. *Arch Intern Med* 1974; 133: 652–657.
5. Femi-Pearse D, Gazioglu KM, Yu PN. Pulmonary function studies in sickle cell disease. *J Appl Physiol* 1970; 28: 574–577.
6. Danon G. La fonction respiratoire de sujets drépanocytaires. *Bull Eur Physiopathol Respir* 1976; 12: 333–348.
7. Charache S, Scott JC, Charache P. Acute chest syndrome in adults with sickle cell anemia. *Arch Intern Med* 1979; 139: 67–69.
8. Poncz M, Kane E, Gill FM. Acute chest syndrome in sickle cell disease: etiology and clinical correlates. *J Pediatr* 1985; 107: 861–866.
9. Castro O, Brambilla DJ, Thorington B, *et al*. The acute chest syndrome in sickle disease: incidence and risk factors. The cooperative study of sickle cell disease. *Blood* 1994; 84: 643–649.
10. 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* 1988; 67: 66–76.
11. Miller GJ, Cotes JE, Hall AM, Salvosa CB. Lung func-

tion and exercise performance of healthy Caribbean men and women of African ethnic origin. *Q J Exp Physiol* 1972; 57: 325–341.
12. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
13. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurements of transfer factor (diffusing capacity). *Eur Respir J* 1993; 6: Suppl. 16, 41–52.
14. Pelle G, Lorino A, Lorino H, Mariette C, Harf A. A microcomputer-based system to calculate respiratory impedance from forced random noise data. *Med Biol Eng Comput* 1986; 24: 541–544.
15. Brochard L, Pelle G, De Palmas J, *et al*. Density and frequency dependence of resistance in early airway obstruction. *Am Rev Respir Dis* 1987; 135: 579–584.
16. Lorino A, Lofaso F, Lorino H, Harf A. Changes in respiratory resistance to low dose carbachol inhalation and to pneumatic trouser inflation are correlated. *Eur Respir J* 1994; 7: 2000–2004.
17. Miller GJ, Serjeant CR. An assessment of lung volumes and gas transfer in sickle cell anaemia. *Thorax* 1971; 26: 309–315.
18. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell disease. *N Engl J Med* 1995; 333: 699–703.
19. Handelsman E, Voulalas D. Albuterol inhalations in acute chest syndrome. *Am J Dis Child* 1991; 145: 603–604.
20. Bhalla M, Abboud MR, McLoud TC, *et al*. Acute chest syndrome in sickle cell disease: CT evidence of microvascular occlusion. *Radiology* 1993; 187: 45–49.
21. Gelfand MJ, Daya SA, Rucknagel DL, Kalintak KA, Paltiel HJ. Simultaneous occurrence of rib infarction and pulmonary infiltrates in sickle cell patients with acute chest syndrome. *J Nucl Med* 1993; 34: 614–618.
22. Charache S, Page DL. Infarction of bone marrow in the sickle cell disorders. *Ann Intern Med* 1967; 67: 1195–1200.
23. Godeau B, Schaeffer A, Bachir D, *et al*. Bronchoalveolar lavage in adult sickle cell patients with acute chest syndrome: value for diagnostic assessment of fat embolism. *Am J Respi Crit Care Med* 1996; 153: 1691–1696.
24. Haynes J, Allison R. Pulmonary edema: complication in the management of sickle cell pain crisis. *Am J Med* 1986; 80: 833–840.
25. Gilbert I, Regnard J, Lenner K, Nelson J, McFadden JE. Pulmonary mechanics following vascular volume expansion with intravenous saline or dextran in normals and asthmatics. *Clin Res* 1990; 39: 484S.