

## INCENTIVE SPIROMETRY TO PREVENT ACUTE PULMONARY COMPLICATIONS IN SICKLE CELL DISEASES

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**Abstract** *Background.* This study was designed to determine the incidence of thoracic bone infarction in patients with sickle cell diseases who were hospitalized with acute chest or back pain above the diaphragm and to test the hypothesis that incentive spirometry can decrease the incidence of atelectasis and pulmonary infiltrates.

*Methods.* We conducted a prospective, randomized trial in 29 patients between 8 and 21 years of age with sickle cell diseases who had 38 episodes of acute chest or back pain above the diaphragm and were hospitalized. Each episode of pain was considered to be an independent event. At each hospitalization, patients with normal or unchanged chest radiographs on admission were randomly assigned to treatment with spirometry or to a control nonspirometry group. Each patient in the spirometry group took 10 maximal inspirations using an incentive spirometer every two hours between 8 a.m. and 10 p.m. and while awake during the night until the chest pain subsided. A second radiograph was obtained three or more days after admission, or sooner if clinically necessary, to determine the incidence of pulmonary complications. Bone

scanning was performed no sooner than two days after hospital admission to determine the incidence of thoracic bone infarction.

*Results.* The incidence of thoracic bone infarction was 39.5 percent (15 of 38 hospitalizations). Pulmonary complications (atelectasis or infiltrates) developed during only 1 of 19 hospitalizations of patients assigned to the spirometry group, as compared with 8 of 19 hospitalizations of patients in the nonspirometry group ( $P=0.019$ ). Among patients with thoracic bone infarction, no pulmonary complications developed in those assigned to the spirometry group during a total of seven hospitalizations, whereas they developed during five of eight hospitalizations in the nonspirometry group ( $P=0.025$ ).

*Conclusions.* Thoracic bone infarction is common in patients with sickle cell diseases who are hospitalized with acute chest pain. Incentive spirometry can prevent the pulmonary complications (atelectasis and infiltrates) associated with the acute chest syndrome in patients with sickle cell diseases who are hospitalized with chest or back pain above the diaphragm. (*N Engl J Med* 1995;333:699-703.)

**P**ATIENTS with sickle cell diseases are prone to an acute chest syndrome of chest pain and the presence of pulmonary infiltrates on chest radiography.<sup>1</sup> The cause of most cases of the acute chest syndrome is uncertain.<sup>2</sup> Pneumonia is often among the causes considered, but bacterial, viral, or mycoplasma infection is infrequently documented.<sup>3-8</sup> Vaso-occlusion due to intravascular sickling of red cells in the lung and embolism of thrombus or bone marrow<sup>9</sup> have never been shown conclusively to be present in the majority of cases. Although the illness is frequently self-limited when the infiltrate is confined to a small area, it can progress rapidly and may be fatal.<sup>10</sup>

In some patients with the acute chest syndrome, radionuclide imaging showed focal changes in the bony thorax (ribs, sternum, and thoracic vertebrae) indicative of bone infarction.<sup>11</sup> In a retrospective analysis of bone scans, we found a high degree of correlation between thoracic bone infarction and the presence of a pulmonary infiltrate.<sup>12</sup> We propose that in many cases the primary event leading to the acute chest syndrome is thoracic bone infarction, which predisposes patients to the development of the acute pulmonary complica-

tions of atelectasis or infiltrates. Analgesia to relieve the pain of splinting and the use of the incentive spirometer to ensure lung aeration may prevent these complications. The incentive spirometer measures the inspiratory capacity of the lungs and is designed to encourage deeper inspiratory effort. To test our hypothesis, we conducted a prospective, randomized trial of incentive spirometry in patients with sickle cell diseases who were hospitalized with acute chest or back pain above the diaphragm. The incidence of thoracic bone infarction was also determined.

### METHODS

#### Patients and Study Design

All patients received health care at the Comprehensive Sickle Cell Center at Children's Hospital Medical Center, Cincinnati. Twenty-nine patients (14 female and 15 male) between 8 and 21 years of age with sickle cell diseases who had acute chest or back pain above the diaphragm and who were admitted to the hospital were enrolled in the study between October 1, 1990, and August 1, 1994. Twenty-three patients had homozygous sickle cell anemia, three had sickle cell-hemoglobin C disease, two had sickle cell- $\beta^+$ -thalassemia, and one had sickle cell-hemoglobin D disease (Los Angeles). Reasons for hospital admission included acute chest or back pain, usually unrelieved by two doses of intravenous morphine; fever; respiratory distress; a sharp decrease in the hemoglobin concentration; and a need for oxygen. These 29 patients were hospitalized a total of 38 times — 21 had 1 hospitalization, 7 had 2, and 1 had 3. Patients less than 7 years old were not enrolled because of their difficulty in learning how to use the incentive spirometer effectively. Patients were admitted to the Hematology-Oncology Service of the Children's Hospital Medical Center, and the attending hematologist was responsible for their treatment. The investigators supervised the use of the incentive spirometer and the collection of data. The study protocol was approved by the institutional review board, and

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informed consent was obtained from all study patients or their parents or legal guardians.

A complete history was taken and a physical examination performed when the patients presented to the Comprehensive Sickle Cell Center or the emergency department. Some had pain elsewhere than in the chest or back, and others did not. The following tests were performed: complete blood and differential counts, reticulocyte count, measurement of hemoglobin F and S concentrations, blood culture if the patient was febrile, measurement of oxygen saturation with a pulse oximeter while the patient breathed room air, and chest radiography. At each hospitalization, patients with normal chest radiographs or radiographs that were unchanged since the previous examination were randomly assigned to one of two groups — a spirometry group that received standard care as well as the use of the incentive spirometer, and a nonspirometry group that received standard care only. Bone scanning was performed during each hospitalization to determine the incidence of thoracic bone infarction.

Incentive spirometry was used by patients in the spirometry group every two hours between 8 a.m. and 10 p.m. and while they were awake at night until the chest pain had subsided. The standard Volurex volumetric incentive spirometer (Diemolding Healthcare Division, Canastota, N.Y.) was used to measure inspiratory capacity. The patients were asked to take 10 maximal inspirations, and the inspiratory capacities on the 4th, 5th, and 6th inspirations were measured and recorded. A second chest radiograph was obtained at least three days after admission to the hospital, or sooner if clinically necessary, to determine whether pulmonary complications (atelectasis or infiltrates) had developed. We grouped atelectasis and infiltrates together because it is often difficult to distinguish between them radiographically. The chest radiographs were interpreted in a blinded manner; that is, the radiologists did not know whether a patient was assigned to the spirometry group or the nonspirometry group during a given hospitalization. Bone scanning was performed two hours after the intravenous administration of technetium Tc 99m medronate (0.185 mCi per kilogram of body weight; maximum, 12 mCi) no sooner than two days after admission to the hospital to determine the incidence of thoracic bone infarction. General-purpose or high-resolution parallel-hole collimation was used. Intravenous fluid — 5 percent dextrose in 0.45 percent sodium chloride — was routinely given at 1 to 1.5 times the maintenance rate for at least the initial 24 hours of hospitalization. Antibiotics were given for oral temperatures greater than 38°C and for suspected or known bacterial infection. Blood transfusions were given when the hemoglobin concentration fell below 6 g per deciliter.

Different analgesic agents were used to treat pain. The narcotics included morphine, hydromorphone, meperidine, methadone, fentanyl, oxycodone, and codeine (with acetaminophen). The dosage was adjusted according to the patient's comfort or tolerance. Non-narcotic analgesic agents included ketorolac, naproxen, ibuprofen, and acetaminophen. The amount of narcotics given during each hospitalization was recorded in milligrams of morphine equivalents per kilogram of body weight<sup>13</sup> and for ketorolac in milligrams of morphine equivalents per kilogram, assuming that 30 mg of intravenous ketorolac equals 12 mg of intravenous morphine.<sup>14</sup> The total narcotic dosage was compared in the spirometry and nonspirometry groups (Table 1) as a measure of the amount of pain that was experienced.

### Statistical Analysis

The data were entered in our computer data base and analyzed with SAS software. Patients were randomly assigned to the spirometry or nonspirometry group at each hospitalization, according to the forced-randomization procedure of Taves.<sup>15</sup> All dichotomized data were analyzed with Fisher's exact test for two-by-two tables, and all continuous data were analyzed with Student's t-test. All the tests were two-tailed. Logistic-regression analysis was used to assess the effect of incentive spirometry on decreasing the incidence of pulmonary complications (atelectasis or infiltrates), independent of other confounding variables.

Since 8 of 29 patients had more than one hospitalization, we in-

**Table 1. Selected Clinical Features of Patients Assigned to Spirometry or Standard Care without Spirometry during Hospitalization.\***

CLINICAL FEATURE	SPIROMETRY (N = 19)†	NONSPIROMETRY (N = 19)‡
Sex — F/M	8/11	11/8
Age — yr	15.0±4.2	16.8±3.0
Genotype — no.		
Homozygous sickle cell anemia	14	16
Sickle cell–hemoglobin C disease	3	1
Sickle cell–hemoglobin D disease (Los Angeles)	0	2
Sickle cell–β <sup>+</sup> -thalassemia	2	0
Temperature (oral) on admission — °C	37.6±1.2	37.3±0.8
Respiratory rate — per min	24.2±6.5	22.1±4.3
Pleuritic pain — no. (%)	10 (53)	9 (47)
Nonpleuritic pain — no. (%)	9 (47)	10 (53)
Abdominal pain — no. (%)	6 (32)	9 (47)
Back pain — no. (%)	10 (53)	14 (74)
Long-bone pain — no. (%)	13 (68)	10 (53)
Sternal pain — no. (%)	15 (79)	12 (63)
Cough — no. (%)	5 (26)	2 (11)
Rales — no. (%)	1 (5)	1 (5)
Rib tenderness — no. (%)	13 (68)	8 (42)
Chest-wall tenderness — no. (%)	11 (58)	9 (47)
Sternum tenderness — no. (%)	13 (68)	8 (42)
Thoracic-spine tenderness — no. (%)	3 (16)	2 (11)
Oxygen saturation by pulse oximetry while breathing room air — %	92.6±6.2‡	93.5±4.0§
White-cell count — ×10 <sup>3</sup> /mm <sup>3</sup>	14.2±4.8	17.7±6.5
Segmented neutrophils — %	63±11.4	66±13.0
Hemoglobin — g/dl	8.8±2.1	8.9±1.4
Reticulocyte count — %	9.6±8.1	10.3±7.1
Hemoglobin S — %	71.2±21.0¶	74.0±21.8§
Hemoglobin F — %	4.5±3.1§	5.1±4.4§
Infarction of bones other than thoracic — no. (%)	6 (32)	5 (26)
Intravenous fluids — no. (%)	18 (95)	18 (95)
Oxygen — no. (%)	11 (58)	10 (53)
Antibiotics — no. (%)	12 (63)	11 (58)
Blood transfusion — no. (%)	6 (32)	6 (32)
Exchange transfusion — no. (%)	0 (0)	1 (5)
Narcotics — mg of morphine equivalents/kg	2.9±4.5	3.3±3.9
Narcotics plus ketorolac — mg of morphine equivalents/kg	4.2±5.1	4.8±5.4
Days between first and second chest radiographs	2.6±1.7	2.6±1.6
Bone scanning — days after admission	5.0±2.1	4.9±3.6
Duration of chest pain before hospitaliza- tion — days	2.4±3.1	1.1±1.6
Total duration of chest pain — days	6.2±4.6	5.5±2.9
Hospital stay — days	3.8±2.0	4.7±2.7

\*Plus-minus values are means ±SD.

†N denotes number of hospitalizations. Patients were assigned to one of the two groups at each admission.

‡N = 14.

§N = 16.

¶N = 17.

vestigated whether each hospitalization could be treated as an independent event. To do this, we used the method described by Liang and Zeger.<sup>16</sup> Two sets of analyses were compared to assess the effectiveness of incentive spirometry in preventing pulmonary complications. In one analysis, the existence of within-patient correlation was assumed, whereas in the other, a within-patient correlation of zero was assumed. The P values for the regression coefficients for treatment effect were almost identical (0.0252 and 0.0261 for the independence model and the exchangeable-correlation model, respectively). These two Liang-Zeger analyses gave P values close to that obtained with Fisher's exact test (P = 0.019). Therefore, Fisher's exact test, which assumes the independence of events, could be used in the analysis to determine whether incentive spirometry prevents pulmonary complications.

As a measure of the effectiveness of the patient's performance in

using the incentive spirometer, the mean ratio of observed inspiratory capacity to expected inspiratory capacity was calculated at each hospitalization. The mean observed inspiratory capacity was determined on hospital days 1, 2, and 3 and for the entire hospital course. We calculated the expected vital capacity using the method of Hsu et al.<sup>17</sup> The expected inspiratory capacity was assumed to be 75 percent of the vital capacity.<sup>18</sup>

## RESULTS

Table 1 lists selected clinical features of the spirometry and non-spirometry groups. The groups were well balanced. In eight patients in the spirometry group and eight in the nonspirometry group, the oxygen saturation measured by pulse oximetry was less than 90 percent or arterial-blood gas analysis was performed because of suspected hypoxemia. Of 25 bacterial blood cultures, none were positive. One viral blood culture was positive for cytomegalovirus. No sputum or pleural-fluid cultures were obtained. There were no deaths.

During 15 of the 38 hospitalizations, thoracic bone infarction was demonstrated by bone scanning (39.5 percent; 95 percent confidence interval, 24 to 55 percent). Segmental rib infarction was observed during 14 hospitalizations (one rib was involved in 5 cases, two to five ribs in 5, and six or more ribs in 4), and isolated thoracic vertebral infarction was observed during 1 hospitalization. Infarction of one or more thoracic vertebral bodies was found during seven of these hospitalizations, and infarction of the sternum was found once.

Pulmonary complications developed during only 1 of 19 hospitalizations of patients assigned to receive spirometry, as compared with 8 of 19 hospitalizations in the nonspirometry group ( $P=0.019$ ). Of seven hospitalizations in which a patient in the spirometry group had thoracic bone infarction, none involved pulmonary complications, as compared with five of eight hospitalizations in the nonspirometry group ( $P=0.025$ ). Logistic-regression analysis confirmed that the risk of pulmonary complications was lower during spirometry hospitalizations than during nonspirometry hospitalizations, even when adjusted for the amount of narcotics used during each hospitalization ( $P=0.02$ ).

Table 2 describes the abnormalities on the second chest radiograph in eight patients assigned to the non-spirometry group and one in the spirometry group. The left lower lobe was involved in all nine cases. Four of five patients with thoracic bone infarction also had involvement of the right lower lobe. The parenchymal lesions consisted of patches and densities, which ranged from 1 cm in greatest dimension to involvement of the entire lobe. Five patients had small pleural effusions; in three they were bilateral. Two pa-

Table 2. Abnormalities on Chest Radiography That Developed in Patients Assigned to Spirometry or Standard Care without Spirometry during Hospitalization.\*

PATIENT No.	ASSIGNMENT DURING HOSPITALIZATION	SIZE (cm)†	APPEARANCE	ANATOMICAL LOCATION	PLEURAL EFFUSION	THORACIC BONE INFARCTION
1	N	4	Patch	RLL	None	+
		5	Patch	LLL		
2	N	1	Patch	RLL	None	+
		4	Linear density	LLL		
3	N	Lobar	Density	RLL	None	+
		5	Density	LLL		
4	N	4.5	Linear density	RLL	Small, right side	+
		5.5	Density	LLL		
5	N	2.5	Patch	LLL	Small, bilateral	+
6	N	3.5	Linear density	LLL	Small, bilateral	-
7	N	5	Density	LLL	Small, left side	-
8	N	7	Density	LLL	None	-
9	S	5	Density	LLL	Small, bilateral	-

\*Plus signs denote positive results, minus signs negative results, N nonspirometry, S spirometry, RLL right lower lobe, and LLL left lower lobe.

†Values are greatest dimensions.

tients with demonstrable thoracic bone infarction had pleural effusions. In the 9 hospitalizations during which pulmonary complications occurred, the mean hospital stay was  $6.4 \pm 1.9$  days, as compared with  $3.6 \pm 2.1$  days in the 29 hospitalizations during which no pulmonary complications occurred ( $P=0.001$ ). The mean number of days between the first and second chest radiographs in these 9 hospitalizations was  $2.4 \pm 1.0$  days, as compared with  $2.8 \pm 1.8$  days for the 29 hospitalizations during which no pulmonary complications occurred ( $P=0.58$ ).

The spirometric data were analyzed for 17 of the 19 hospitalizations in which the spirometer was used; the data for 2 hospitalizations were lost. The mean ratio of observed inspiratory capacity to expected inspiratory capacity during these hospitalizations was 75 percent on day 1, 75 percent on day 2, 70 percent on day 3, and 74 percent for the entire hospital course. This ratio was similar during hospitalizations of patients who did and patients who did not have thoracic bone infarction on day 1 (67 percent vs. 80 percent,  $P=0.39$ ), day 2 (67 percent vs. 79 percent,  $P=0.36$ ), or day 3 (69 percent vs. 70 percent,  $P=0.94$ ).

## DISCUSSION

The results of this prospective, randomized trial demonstrate that use of the incentive spirometer with 10 maximal inspirations every two hours from 8 a.m. to 10 p.m. and when the patients were awake at night significantly decreased the incidence of pulmonary complications (atelectasis or infiltrates) in patients with sickle cell diseases who were hospitalized with acute chest or back pain above the diaphragm. When patients with thoracic bone infarction were analyzed separately, the effect of incentive spirometry was also statistically significant.

The incentive spirometer has been used successfully for many years to prevent pulmonary atelectasis and its

complications in postoperative patients.<sup>19-21</sup> Bendixen et al. have shown that healthy people usually take deep breaths or sigh 9 to 10 times per hour to prevent alveolar collapse.<sup>22</sup> The absence of these periodic deep breaths during spontaneous ventilation in anesthetized patients, even when breathing is adequate to eliminate carbon dioxide, contributes to atelectasis and hypoxemia.<sup>23</sup> Incentive spirometry presumably counteracts the effect of splinting in patients with sickle cell diseases who are unable to take deep breaths because of chest pain and helps prevent the development of atelectasis or infiltrates.

The characteristic recurrent pain and organ damage of sickle cell diseases are thought to be due to vaso-occlusion resulting from decreased deformability of sickle cells and their adherence to vascular endothelium<sup>24,25</sup> and to each other.<sup>26</sup> Much of the pain is due to vaso-occlusion in bone, which may progress to frank infarction.<sup>27</sup> In our study no clinical, hematologic, or plain radiographic measure could reliably diagnose thoracic bone infarction, which can be suspected when rib or vertebral tenderness is present. The diagnosis of thoracic bone infarction can be confirmed only by radionuclide scintigraphy. Thoracic bone infarction in patients with sickle cell disease has been demonstrated previously by bone scanning,<sup>11,12,28-30</sup> but the present study estimates the frequency of the problem. The incidence of 39 percent for thoracic bone infarction in our group of patients is likely to be an underestimate, since scanning may not detect small areas of infarction because of limited spatial resolution. Moreover, some of the scans may have been obtained too early in the clinical course of the episode to demonstrate bone infarction. In some patients, not enough time may have elapsed for the bone scan to reveal increased uptake of the radiopharmaceutical agent by osteoblasts, which are mobilized to repair the damaged bone. It is not known how long the findings of bone infarction persist on bone scans, but in this study, three patients with evidence of thoracic bone infarction on the first scan did not have any evidence of infarction on subsequent scans obtained 24, 133, and 483 days later, respectively.

Some investigators have proposed that narcotics may predispose patients with sickle cell diseases to hypoventilation and atelectasis or infiltrates.<sup>6,31</sup> In our study, it is unlikely that the higher complication rate in the non-spirometry group was due to greater use of narcotics, because the amount of narcotics used in the spirometry and nonspirometry groups did not differ significantly. Moreover, logistic-regression analysis showed that incentive spirometry was effective even when we adjusted for the amount of narcotics used.

Prevention of the radiographically evident abnormalities of atelectasis and infiltrates is important in the short-term prognosis of the acute chest syndrome. Although the acute chest syndrome is usually self-limited, single episodes may progress and cause substantial morbidity and even death. We do not know whether the association of the acute chest syndrome with a poor

long-term outcome in patients with sickle cell diseases is related to presentation with symptoms localized to the thorax or to the presence of abnormalities on the chest radiograph. Powars et al.<sup>32</sup> reported that the most important risk factor associated with chronic lung disease in patients with sickle cell diseases was the total number of episodes of the acute chest syndrome. Platt et al.<sup>33</sup> determined that the acute chest syndrome was a significant risk factor for early death in patients with sickle cell anemia who were 20 years of age or older. Whether these acute episodes alone lead to terminal pulmonary dysfunction, or whether they punctuate an ongoing occlusion of the pulmonary vascular bed by sickling, is unknown.

Our findings suggest that in many cases thoracic bone infarction with subsequent atelectasis or development of an infiltrate due to chest splinting is the primary pathogenesis of the acute chest syndrome. We found that incentive spirometry can prevent the pulmonary complications (atelectasis or infiltrates) associated with the acute chest syndrome in patients with sickle cell diseases who are hospitalized with chest or back pain above the diaphragm. This inexpensive intervention might prevent chronic lung disease and early death in patients with sickle cell diseases.

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