SMOKING IS A FACTOR IN CAUSING ACUTE CHEST SYNDROME IN SICKLE CELL ANEMIA

Roscoe C. Young, Jr, MD, Raylinda E. Rachal, MD, Robert L. Hackney, Jr, MD,
Corazon G. Uy, MD, and Roland B. Scott, MD, ScD
New Orleans, Louisiana and Washington, DC

A link between cigarette smoking and "acute chest syndrome" in sickle cell anemia is suggested. Acute chest syndrome in the patient with sickle cell anemia is characterized by fever, leukocytosis, cough, chest pain, and pulmonary infiltrates in the chest radiograph. This article describes the results of a study of 69 adolescent and young adult sickle cell anemia patients. Twenty-nine of these patients were smokers, three were former smokers, and 37 were nonsmokers.

Patients completed respiratory questionnaires that focused on smoking habits and included a history of chest syndrome. Information obtained was confirmed by review of clinical records. The chi-square test demonstrated a strong relationship between cigarette smoking and chest syndrome in sickle cell anemia. All 29 smokers had a history of chest syndrome, but only 24 of 37 nonsmokers had such a history.

Although the exact mechanism of the relationship between smoking and the development of acute chest syndrome remains speculative, cigarette smoking joins infection, hypoxia, acidosis, infarction, dehydration, and analgesics as a causative factor in adolescent and adult patients with sickle cell anemia. Behavioral modification of the smoking habit in patients with sickle cell anemia may decrease the frequency of acute chest syndrome and sequelae of sickle cell lung disease. (*J Natl Med Assoc.* 1992;84:267-271.)

Key words • sickle cell anemia • smoking • chest pain • pulmonary vaso-occlusive disease • hemoglobin SC disease

Acute chest syndrome (ACS) in patients with sickle cell anemia consists of chest pain, fever, leukocytosis, cough, and pulmonary infiltrates on the chest radiograph. It often constitutes a difficult diagnostic problem, and therapy is often poorly focused. Acute chest syndrome and other common pulmonary problems in sickle cell anemia have been reviewed previously.[1] Heterogeneous contributing factors causing ACS in sickle cell anemia include infection, hypoxemia, acidosis, infarction, dehydration,[2] and analgesic therapy.[3]

It is recognized that cigarette smoking in the general population causes classical "cigarette diseases" (eg, chronic bronchitis and emphysema, carcinoma of the lung, and other cancers), and increases the risk for a cardiovascular event. Unreported new findings suggest

From the College of Pharmacy, Xavier University of Louisiana, New Orleans, Louisiana, and the Pulmonary Division and the Center for Sickle Cell Disease, Howard University College of Medicine, Washington, DC. Presented as a scientific poster exhibit at the Annual Meeting of the American Lung Association and American Thoracic Society, May 8-11, 1988, Las Vegas, Nevada; the 93rd Annual Meeting of the National Medical Association, July 30-August 4, 1988, Los Angeles, California; the 82nd Annual Meeting of the Southern Medical Association, November 6, 1988, New Orleans, Louisiana; and the 32nd Navy Occupational Health and Preventive Medicine Workshop, March 24-29, 1990, Virginia Beach, Virginia. Requests for reprints should be addressed to Dr Roscoe C. Young, Jr, Xavier University of Louisiana, College of Pharmacy, 7325 Palmetto St, New Orleans, LA 70125.

TABLE 1. OXYGEN AND CARBON MONOXIDE IN ARTERIAL BLOOD OF SICKLE CELL ANEMIA PATIENTS

	Smokers (N=35)			Nonsmokers and Former Smokers (N=34)			
	Mean	SD	SEM	Mean	SD	SEM	Significance*
Po_2	75.1	±8.7	±1.5	78.3	±11.1	±1.9	NS
HbO_2	91.3	±4.0	±0.68	92.5	±6.2	±1.1	NS
HbCO	7.3	±2.5	±0.43	5.6	±2.6	±0.44	$P<.01$

*Student's *t* test.

a link between cigarette smoking and the development of ACS in patients with sickle cell anemia, placing this population in greater jeopardy. A prospective study was performed to determine if a relationship exists between cigarette smoking and the occurrence of ACS in patients with sickle cell anemia.

MATERIALS AND METHODS

Sixty-nine subejcts were age- and sex-matched patients with sickle cell hemoglobinopathy of the following genotypes: 61 Hb SS, 3 Hb S/Beta-Thalassemia, and 5 Hb SC. They were selected from adolescent and adult sickle cell anemia patients enrolled for medical and social support services at the Center for Sickle Cell Disease, Howard University College of Medicine, between 1983 and 1985.

The National Heart, Lung, and Blood Institute (NHLBI) respiratory questionnaire for epidemiologic studies[4] was administered to each patient. The questionnaire focused on the patient's smoking history and a past history of "pneumonia" or ACS. None of the patients was employed in a dusty occupation. The majority of patients were disabled by their disease and its complications, and unable to work.

History of ACS was supplemented by careful review of the patients' clinical records. The mean age was 27 years, and mean weight was 59 kg. Age, sex, height, and weight of the smokers did not differ significantly from that of nonsmokers. Ten of the patients were adolescents ≤18 years of age. Eighty-five percent of the patients had painful crises, and 78% also had hemolytic crises (based on bilirubin levels over 5 mg/dL and reticulocyte counts over 10%).

Arterial blood gases were measured while patients were at rest and breathing room air. They were done during the symptom-free interval while patients were not in a painful crisis or experiencing ACS. Oxygen tension (Po_2) was measured with a Clark oxygen electrode. Oxyhemoglobin saturation (HbO_2) and carboxyhemoglobin saturation (HbCO) were measured with a cuvette oximeter.*

Statistical evaluation was performed on a mainframe computer using the SPSS program software package.[5] The evaluation consisted of descriptive statistics, Pearson's correlation, Student's *t* test, contingency table for chi-square analysis, and phi statistic. Yates correction for continuity[6] was applied, which is recommended for 2×2 contingency tables when any of the observed frequencies is less than five. Research was carried out according to the principles of the Declaration of Helsinki. The institutional review committee approved the study. Confidentiality was protected, and informed consent was obtained from participants.

Thirty-one of the patients with sickle cell anemia were nonsmokers. Three former cigarette smokers (persons who successfully abstained from smoking for more than a year) were added to the nonsmokers for calculations involving HbCO, since smoking causes increases in HbCO that last 18 to 20 hours following the last cigarette.

RESULTS

Thirty-five smokers with sickle hemoglobinopathy had a mean lifetime smoking history of 1.2 pack-years (index of lifetime cigarette consumption is the product of the number of packs smoked a day and the total number of years smoked). The majority of smokers were "light" smokers, since they smoked less than 10 pack-years. Acute chest syndrome was not more frequent in Hb SS patients than among Hb S variants. Table 1 shows that for mean arterial Po_2 and HbO_2, the difference was not significant when smokers were compared with nonsmokers and former smokers. The significant increase in mean HbCO in smokers when compared with nonsmokers and former smokers is likely due to continued smoking, since urban exposures

*IL 813 blood gas analyzer was used to measure arterial Po_2. A comparison IL 289 CO-Oximeter was used to measure COHb. These tests are available from Instrumentation Laboratory, 113 Hartwell Ave, Lexington, MA 02173-3190.

TABLE 2. 2×2 CONTINGENCY TABLE FOR SMOKING AND CHEST SYNDROME HISTORY (N=66)

	Smokers	Nonsmokers
History of chest	Observed frequency = 29 Expected frequency = 23.3	Observed frequency = 24 Expected frequency = 29.7
Negative history of chest	Observed frequency = 0 Expected frequency = 5.7	Observed frequency = 13 Expected frequency = 7.3

Total chi-square = 1.40 + 1.10 + 5.71 + 4.48 = 12.69; *df* = 1
Phi = 0.44, $P < .001$

Ex-cigarette smokers were omitted from the chi-square calculation. Chi-square indicates that a systematic relationship exists between the two variables, chest syndrome and cigarette smoking. The phi statistic is a measure of the strength of the association. Phi = 0 when no relationship exists and takes on the value of +1 when the variables are perfectly related.

were similar in both groups. Pearson's correlation was negative and significant for HbCO versus Po_2, $r = -0.33$, and $P<.01$, and for HbCO and HbO_2, $r = -0.24$, and $P<.05$.

Table 2 is a 2×2 contingency table showing the relationship between ACS and cigarette smoking in patients with sickle cell anemia. The frequency of occurrence of ACS among smokers was significantly increased when compared with nonsmokers ($\chi^2 = 12.69$, 1 *df*, phi statistic +0.44, and $P<.001$). Thus, a major disadvantage of cigarette smoking in patients with sickle cell anemia is the increased frequency of ACS.

DISCUSSION

The suggestion that smoking might influence ACS came about in the summer of 1982 when a preliminary study was performed to determine whether cigarette smoking had an effect on the incidence and severity of painful crises and associated complications in patients with sickle cell anemia. The study used an interview method and also screened the clinical records of 26 smokers and 36 nonsmokers. Although smoking did not affect the number or length of vaso-occlusive pain crises, smokers were hospitalized 1.5 times more often than nonsmokers and experienced 1.25 times more cases of "pneumonia" (Adler S, Scott RB. Unpublished data).

Possible Sources of Bias

Several possible sources of bias exist in the present study. The assumption was made that patients' clinical records were accurate pertaining to the diagnosis of homozygous SS hemoglobinopathy or a variant S hemoglobinopathy. Ascertainment and detection of ACS could have been a source of error in as much as ACS is often confused with infectious pneumonia although ACS is more likely in adolescents and adults.[1] For smokers, the estimate of cigarette smoke exposure could be another source of error in respect to patients' recall of the number and duration of cigarettes smoked. For former smokers, the number of cycle(s) of starting and stopping, until complete abstinence, and for nonsmokers, the role of confounding variables of "passive smoking," and indoor and outdoor urban atmospheric pollutants could have been a source of error. Interviewer error as a source of bias was minimized by limiting the number of interviewers to a single trained person and by following a standard epidemiologically acceptable outline. Measurement error may have been introduced in that the oxygen electrode in the blood gas analyzer is accurate to 2 or 3 mm Hg. Rounding instrument readout to the nearest integer is acceptable practice but may increase error. Measurement error was minimized by adding a correction factor to compensate for oxygen consumed by the electrode during measurements (1% of the reading was added if ≤80 mm Hg, and 2% was added for readings >80 mm Hg).

Relative risk of development of ACS in smoking sickle cell anemia patients could not be calculated since one cell in the 2×2 contingency table contained zero (Table 2).

Cigarette Smoke

Sickle cell anemia patients are already at a disadvantage because they have low oxygen saturations compared with healthy Hb AA subjects.[1,7,8] The present study demonstrates a strong relationship between cigarette smoking and the frequency of ACS in patients with sickle cell anemia.

Cigarette smoke is a heterogeneous mixture of gases,

uncondensed vapors, and liquid particulate matter. More than 500 different compounds occur in cigarette smoke including nicotine and its related companion alkaloids, hydrocarbons, alcohols, esters, sterols, aldehydes, ketones, acids, and gases, which include CO and acroline.[9] Values for HbCO in nonsmoking sickle cell anemia patients were higher than expected for Hb AA nonsmokers because of hemolysis of the patient's cells.[8]

W.P. Winter has suggested that a component of cigarette smoke other than CO may be implicated in causing ACS in sickle cell anemia (unpublished data). He based his suggestion on the inhibition of sickling, which decreases the likelihood of vaso-occlusion in pulmonary small blood vessels. An increase in nicotine blood levels in nonsmoking patients who chew nicotine gum does not increase sickling. Perhaps components of cigarette smoke other than CO and nicotine may enhance vaso-occlusion of small vessels. It is therefore unlikely that either CO or nicotine in cigarette smoke cause ACS in sickle cell anemia patients.

Hebbel and associates[10] have demonstrated a good correlation between clinical severity of vaso-occlusive crises and erythrocyte adherence to cultured endothelium in vitro. They suggested that abnormal interactions between the two may initiate crises. It is reasonable to suspect that oxidants from cigarette smoke acting as electron acceptors may generate free radicals that cause injury to the alveolar-capillary interface locally (lipid oxidation, sulfhydryl oxidation, and DNA damage).[11] It is also reasonable to suspect that this chain of events might increase electrostatic attraction of negatively charged erythrocytes[12] and subsequent adherence to pulmonary capillary endothelium, thereby initiating ACS. Recently, Sowemimo-Coker and associates[13] reported on increased endothelial cells in plasma, which suggests endothelial cell injury in both sickle cell anemia patients during painful crisis and also in "normal" smokers.

While irreversibly sickled red cells have received attention as a cause of vaso-occlusive crises, some workers found no change in the number of irreversibly sickled cells,[14] and others reported a decrease.[15] In the present study, a wide variance (0 to 14) was found in the percentage of irreversibly sickled cells. Lack of correlation existed with either smoking history or ACS. Attention has shifted to red cell density, but again the issue is controversial, with some authors finding an increase in the number of dense cells during crisis[16] and others finding a decrease.[17] Polymorphonuclear leukocytes also participate in abnormal reactions. Lachant and Oseae[18] demonstrated polymorphonuclear leukocyte aggregation in sickle cell anemia patients during their pain-free state. Polymorphonuclear leukocyte chemotaxis also was increased during crisis. These authors suggested that alterations in polymorphonuclear leukocyte function may play a role in the development of ACS, as well as increase infection risk.

CONCLUSION

The exact mechanism by which the smoking habit contributes to the development of ACS in sickle cell anemia patients remains speculative. In addition to the traditional hazards of smoking, the sickle cell anemia patient has additional reasons for behavioral modification of the smoking habit: to decrease the possibility of developing ACS and to minimize the sequelae of sickle cell lung disease (ie, pulmonary fibrosis, restrictive ventilatory defect, and cor-pulmonale). Additional studies in this area are needed.

Acknowledgments

This research was supported by Grant #NHL-BI-DBDR-8IG-A from the Sickle Cell Disease Branch, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, National Institutes of Health, and the Xavier-Tulane Center for Bioenvironmental Research.

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