Pulmonary and Cardiac Function in Sickle Cell Lung Disease: Preliminary Report

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Physicians have long been intrigued by the unusual cardiac and pulmonary manifestations which may occur in patients with sickle cell anemia. Cardiomegaly, systolic and diastolic murmurs, recurrent bouts of pulmonary infiltration and chest pain, episodic or chronic dyspnea—all of these may appear in the sicklemic individual.

In recent years, considerable investigation has been carried out to define the anatomic and physiologic substrates upon which these fascinating clinical abnormalities are based. Such study has indicated that patients with sickle cell anemia have three major defects which may influence cardiopulmonary function: (1) a chronic and usually severe anemia; (2) an abnormal form of hemoglobin, designated as S hemoglobin; and (3) a tendency to develop multiple zones of pulmonary thrombosis. While each of these factors contributes to clinical disability, it is the occurrence of repeated pulmonary thromboses which may lead to the development of the interesting clinical entity which we have labeled "sickle cell lung disease."

Clinically, sickle cell lung disease parallels the well-known syndrome of multiple pulmonary emboli. Characteristically, the symptoms and signs of thrombosis vary widely. Recurrent episodes of poorly-defined chest discomfort or frank, pleuritic chest pain may occur. Fever and some dyspnea are common with these episodes, although hemoptysis is rare. Small infiltrations which heal by linear scarring may appear on serial chest roentgenograms (Fig. 1). A variable degree of leucocytosis may occur. In our experience, the search for pathogens in the sputum is usually unrewarding. Furthermore, resolution of the fever, leucocytosis and roentgenographic abnormalities occur in the same time-period whether or not antibiotic therapy is instituted. These thrombotic episodes are usually diagnosed as "pneumonitis" or non-specific manifestations of sickle cell "crisis."

Occasionally, in patients who have experienced this syndrome repeatedly, evidence suggesting residual cardiopulmonary disease appears in the form of excessive fatigue, dyspnea with mild exercise and cardiac enlargement especially of the right ventricular type. Cyanosis is rarely seen, however, probably because of the severity of the anemia.

Microscopic sections of the lung indicate that sickle thrombi occur chiefly in the pulmonary capillaries and smaller arterioles (Figs. 2, 3). If widespread obstruction has occurred, right ventricular enlargement may be found at direct examination.

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These clinical and pathological observations suggest that thrombotic obstruction in the pulmonary vascular bed is not uncommon in sickle cell subjects. However, two major unknowns exist regarding the process: (1) why do these thromboses occur; and (2) what are the cardiopulmonary consequences of these occlusions?

In order to answer these questions, combined cardiac catheterization and pulmonary function study was carried out in ten patients with electrophoretically-pure S hemoglobin.* The technique and procedure of these studies has been described elsewhere. The data acquired from this small group permit us to make some preliminary comments upon both the causes and the consequences of thrombotic sickle cell lung disease.

Mechanisms of Pulmonary Thrombosis in Sickle Cell Subjects

At the present time, it appears that thrombosis in the pulmonary vasculature of these patients is a consequence of simple obstruction of the smaller pulmonary vessels by sickled red blood cells. The capillaries and terminal arterioles of the lung are of such calibre as to enforce

*We are indebted to the Hematology Sections of the Georgetown and George Washington University Services of the D. C. General Hospital for obtaining the electrophoretic hemoglobin patterns in these patients.

FIGURE 1: Chest roentgenograms of a 28 year old colored man with sickle cell anemia who entered the hospital with fever and pleuritic left chest pain. At the left is roentgenogram on admission showing wedge-shaped infiltrate at the left base. On the right is roentgenogram two weeks after admission showing linear healing characteristic of pulmonary infarction.
"single file" passage upon the normal red cell. If cells containing S hemoglobin have assumed bizarre shapes prior to entering these small vessels, mechanical obstruction would appear a likely consequence. Should even partial obstruction develop, the associated stagnation of flow might well be sufficient to administer the thrombotic coup-de-grace.

Presumably, then, a key factor in sickle thrombosis in the lung is the presence of a great percentage of sickled red cells in blood reaching the lungs. Therefore, in searching for the mechanisms of thrombosis, attention should be directed toward those factors which may potentiate sickling in the venous blood.

![Microscopic section from lung of 29 year old colored man with sickle cell anemia who succumbed after multiple admissions for pulmonary infarction and progressive right ventricular failure. Section demonstrates thrombosed pulmonary capillary. (x44). FIGURE 2: FIGURE 3: Microscopic section of lung from same patient as Figure 2 showing thrombosed pulmonary arteriole. (x3.5).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21341/ on 06/25/2017)
Since exposure of susceptible cells to low oxygen tensions is a potent method for inducing the sickling phenomenon, low venous oxygen concentrations may be expected to produce intense sickling of the red cells entering the lungs. That this mechanism may be operative in vivo is suggested by our experimental data which indicate that low venous oxygen values are common in patients with sickle cell anemia. When the saturation of the mixed venous blood of these patients is compared with the expected saturation according to the oxygen uptake (VO₂), these values are almost uniformly below normal or at the lower limits of normal (Fig. 4). The average mixed venous saturation was 59.8 per cent at rest and decreased to 43.9 per cent with exercise. At such low oxygen concentrations, a high degree of sickling might be expected among red cells reaching the pulmonary bed.

The obvious question posed by these findings is, “Why do these patients have this unfortunate tendency toward low oxygen saturation of the mixed venous blood?” While this question cannot be answered with precision at the present time, it appears that at least three independent factors may play a part in producing this abnormality (Fig. 5). First, several investigators have indicated that the oxyhemoglobin dissociation curve for sickle (S) hemoglobin lies to the right of that for normal (A) hemoglobin. This shift means that a given oxygen tension will not saturate S hemoglobin as fully as normal hemoglobin would be saturated. Conversely, when oxygen tensions and saturations are both measured in these patients, the presence of S hemoglobin should lead to oxygen tensions consistently in excess of those predicted from saturation values using the oxyhemoglobin dissociation curve for normal hemoglobin. This situation is confirmed by our experimental data, though an unexplained patient variability does exist (Fig. 6). In view of this behavior of S hemoglobin, sickle patients have a “built in” de-

**FIGURE 4:** Mixed venous oxygen saturations in sicklemic subjects at various levels of oxygen uptake. Normal range is indicated by hatched area. Closed circles are resting values; open circles are exercise values.
gree of arterial and venous desaturation, for red cells containing this hemoglobin will leave the pulmonary capillary with below-normal saturation despite exposure to normal alveolar oxygen tensions.

By itself, this defect in S hemoglobin would not produce severe desaturation of the venous blood. Unfortunately, most of these subjects also have a marked anemia. Hemoglobin values in our patients were extremely low, averaging 7.3 gms per cent. This degree of anemia can be responsible for an additional lowering of the venous saturation. When low hemoglobin concentrations exist in the blood, tissues must extract a larger proportion of the available oxygen from red cells as they pass through the peripheral capillary bed. This adaptive phenomenon in anemia results in an abnormally low saturation of the mixed venous blood. When anemic subjects exercise, the per cent peripheral utilization may be quite high and extremely low levels of venous saturation may be reached.

In addition to the presence of S hemoglobin and anemia, a third factor may contribute to abnormally low venous saturations in these patients. As will be indicated in greater detail below, those sickle subjects who have suffered widespread pulmonary thrombi may develop a diffusion insufficiency for oxygen in the lung. This defect also leads to incomplete saturation of the blood leaving the lungs, and, thereby, exaggerates venous desaturation.

While exposure to low oxygen tensions is regarded as a dominant influence, exposure of red cells to acid pH and heat also potentiates sickling. Increased venous acidity may appear if the peripheral oxygen

\[ \text{SHIFT OF DISSOCIATION CURVE TO RIGHT} \] \text{ANEMIA} \[ \text{DIFFUSION INSUFFICIENCY} \]

\[ \text{LOW VENOUS } O_2 \text{ SATURATION} \]

\[ \text{ACID VENOUS pH} \] \[ \text{HEAT} \] \[ \text{HYPOVENTILATION} \]

**FIGURE 5:** Diagrammatic representation of the potentiators of the sickling phenomenon.
lack in anemia forces cells to utilize anaerobic metabolic pathways which release acid end-products. Increased temperature of the venous blood may occur with the fever of sickle "crises."

Finally, in this analysis of factors inducing sickle cell pulmonary thrombosis, it should be recalled that a certain portion of the pulmonary blood flow normally perfuses poorly-ventilated alveoli. This "physiologic shunting" contributes to arterial and venous desaturation. More important, however, is the fact that arteriolar constriction may develop in such hypoventilated areas. This constriction would render vessels especially vulnerable to plugging by sickled cells.

**Cardiopulmonary Consequences of Pulmonary Thrombosis**

The anatomic defect imposed by widespread thrombotic events is a decrease in available "capacity" of the pulmonary vascular bed. Such anatomic diminution is significant because the low-pressure, low-resistance hemodynamics of the pulmonary circulation are dependent upon the tremendous reserve capacity of this vascular bed. This reserve permits the pulmonary vascular bed to accept large increases in blood flow with minimal increases in pulmonary arterial pressure or right ventricular work. Thus, preservation of normal hemodynamics is accomplished by "opening" new vascular capacity in the lung.

**FIGURE 6:** Relationship of the measured arterial oxygen tensions in sicklemic subjects to the tensions predicted from pH and oxygen saturation using the oxyhemoglobin dissociation curve for normal (A) hemoglobin. Solid line indicates expected relationship.
of events by which pulmonary arterial pressure and right ventricular work escape abnormal elevations may be expressed in another way; viz., the normal individual is able to lower the calculated "pulmonary vascular resistance" as pulmonary blood flow is increased.13,14

Pulmonary thrombotic disease decreases this vital reserve capacity of the pulmonary vascular bed. Fortunately, the unused reserve is so vast that considerable thrombotic obstruction must occur before hemodynamic abnormalities appear. However, if thromboses are sufficiently widespread, the expandable reserve is depleted. Resistance in the pulmonary circuit then becomes fixed. When this fixation occurs, any increase in the pulmonary blood flow can be achieved only at the expense of an abnormal increase in both the pulmonary artery pressure and the work of the right ventricle.

Severe reduction of the pulmonary vascular bed results in an increased velocity of blood flow through the remaining vessels. Normally, venous blood achieves virtually full equilibration with alveolar oxygen tension during its transit through the alveolar capillary. End-capillary and alveolar oxygen tensions are therefore almost identical. While addition of the "venous admixture" does lead to a slightly lower oxygen tension in the arterial blood, the difference between alveolar and arterial oxygen tensions normally is quite small (below 20 mm Hg). Therefore, at normal flow rates, there is a small difference, or gradient, between the oxygen tension of arterial blood and that present in alveolar gas. This difference is referred to as the alveolo-arterial (or A-a) oxygen tension gradient.

![Diagrammatic representation of effect exerted by excessive velocity of capillary blood flow in a depleted pulmonary vascular bed. Dotted area shows normal change from venous oxygen tension (P_vO_2) to end-capillary (P_cO_2) and arterial (P_aO_2) oxygen tensions as blood passes alveolus. Dotted portion of box at right shows "normal" gradient between alveolar (P_aO_2) and arterial oxygen tensions. Dashed line shows failure of equilibration which occurs when "contact time" is decreased. The A-a gradient increases, as indicated by the whole box at right. The effect of venous admixture is not indicated.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21341/)
If large areas of the pulmonary capillary bed are obstructed, blood may flow through the remaining capillaries with extreme speed. The time of contact between capillary blood and alveolar gas is reduced. If this acceleration of velocity reaches a critical level, flow through the pulmonary capillaries may become so rapid that blood leaves contact with alveolar gas before normal oxygen tension can be achieved. This produces an abnormal gradient between alveolar and end-capillary oxygen tensions (Fig. 7). This failure of equilibration is reflected as an abnormally-wide gradient between alveolar and arterial oxygen tensions, i.e., a widened “A-a gradient.” The term “diffusion insufficiency for oxygen” is used to describe this failure of oxygen equilibration in the lung. Therefore, the wide A-a gradient of diffusion insufficiency is another indication of severe capillary bed depletion.

The total pattern of abnormalities which may be expected in patients who have suffered extensive obstruction (or destruction) of pulmonary vessels by sickle thrombi (or by any other mechanism) may be summarized as follows: The primary anatomic defect is a diminution of available capillary bed area. This leads to the twin physiologic defects of fixed pulmonary vascular resistance and increased velocity of blood flow. Depending on the level of pulmonary blood flow, these defects may produce a variable degree of diffusion insufficiency (with widening of the A-a gradient), pulmonary hypertension and increased right ventricular work.

With minimal vascular obstruction, these abnormalities are absent. With moderately extensive damage, the aberrations are manifested only when pulmonary blood flow is increased, as by exercise. If severe loss of cross-sectional area has occurred, these defects are present at rest and exaggerated by exercise. Because their anemia is associated with abnormally high pulmonary blood flows,¹⁹ sickle subjects should develop these abnormalities at less marked degrees of pulmonary vascular compromise than the normal individual. In our series, resting blood

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FIGURE 8: Representative cardiopulmonary data from a 19 year old sicklemic subject with pulmonary vascular compromise. (See Text).
flows averaged 4.4 L./min./m² and increased to an average of 8.7 L./min./m² with exercise.

Of the 10 patients studied, three demonstrated the pattern which suggests moderate to severe pulmonary vascular obstruction. Representative data from one of these patients is shown in Figure 8. At rest, with a pulmonary blood flow of 4.7 L./min., no striking abnormality is present, although the A-a gradient is somewhat widened. However, during exercise, several pathologic responses of the pulmonary bed are apparent. Despite an increase in pulmonary blood flow to 10.9 L./min., the pulmonary arteriolar resistance remained virtually fixed, failing to show the expected decline. The mean pulmonary arterial pressure rose to an abnormal value of 30.5 mm Hg., and the right ventricular work increased six-fold. Furthermore, the A-a gradient widened to a distinctly abnormal value of 43 mm Hg.

Since almost two-thirds of the pulmonary bed must be obliterated before abnormalities of this severity appear, it is not surprising that such patients are not common. However, data obtained during exercise suggests that a number of patients may have a milder degree of pulmonary vascular compromise (Fig. 9). In eight patients, the pulmonary arterial pressure rose during exercise. In six cases, it equalled or exceeded the high normal value of 20 mm Hg. Changes in A-a gradient were also conspicuous. If 20 mm Hg is taken as a generous upper-limit-of-normal, abnormalities of the A-a gradient were frequent at rest. With exercise, seven patients showed further widening of this gradient. Thus, these findings suggest that other patients in this group may have a degree of

![FIGURE 9: Changes in pulmonary arterial mean pressure and A-a oxygen tension gradient in sicklemic subjects with exercise. (Pressure measurements in one patient and gradient determinations in two were incomplete or unsatisfactory).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21341/)
pulmonary vascular compromise which is not apparent at rest, but becomes detectable when pulmonary blood flow is raised by exercise.

**Comments**

The clinical observations indicating that pulmonary thrombosis is a frequent complication in individuals with "pure S" hemoglobin assume greater significance in the light of the data presented here. It is apparent that considerable hemodynamic aberration may result from these small, repeated insults to the pulmonary vascular bed. One patient in this series succumbed, at age 29, after repeated hospital admissions during which evidence of pulmonary infarction and progressive right ventricular failure were the dominant features. At autopsy, fresh and old thrombotic occlusion was rampant throughout the smaller arterioles and the capillaries of the pulmonary vascular bed (Figs. 2, 3). A dilated pulmonary artery, hypertrophied and dilated right ventricle and evidence of passive congestion of the viscera were present. In another case in which autopsy was performed, pulmonary vascular thrombosis was considerably less widespread, and minimal right ventricular hypertrophy was present.

There is obviously a marked variation in the extent to which various "S-S" subjects occlude the pulmonary vascular bed. While age may play some role, it is not the only factor, since one of the most severely affected patients in this series was only 19 years old. Perhaps the extent of concurrent hemolysis of red cells may play a crucial role, since evidence recently has appeared indicating the thrombogenic potential of red cell stroma. Other events, such as transitory hypoventilation in small pulmonary segments due to bronchitis or pneumonitis, may be sufficient to encourage thrombosis in sickle subjects, while they would be of little significance in the normal individual.

It is apparent that elucidation of those factors which influence the extent, frequency and, possibly, the duration of pulmonary thrombosis in these patients poses a challenge requiring further study. This challenge must be met if therapeutic devices are to be developed which can alter the prognosis of sickle cell subjects. At the present time, avoidance of extremes of exertion, especially during periods of marked anemia, and perhaps administration of alkali in the acute situation are the only therapeutic suggestions which can be offered. Anticoagulation, in our experience, has proved of questionable benefit, as might be expected in view of the probable "mechanical" pathogenesis of sickle thrombosis. It appears that real therapeutic advance will await the development of techniques whereby cells containing S hemoglobin can be induced to retain a normal contour.

**SUMMARY**

1. Pulmonary thrombosis in sickle subjects appears to be a consequence of mechanical obstruction of small pulmonary vessels by sickled cells. Such cells may gain entrance into the pulmonary vascular bed in high concentration because of abnormally low oxygen concentrations in the venous blood. This desaturation is the end-result of several independent factors. Fever and an acid pH of venous blood also may potentiate sickling. Vessels in hypoventilated areas of the lung may constrict under the influence of abnormal alveolar oxygen and carbon dioxide tensions, rendering them especially susceptible to thrombotic occlusion by the sickled cells.

2. If thrombotic events involve a large area of the pulmonary vascular bed, cardiopulmonary abnormalities may develop. These include fixation of pulmonary vascular resistance, pulmonary hypertension, increased right ventricular work and diffusion insufficiency for oxygen. The high cardiac output imposed by anemia in these patients tends to exaggerate these abnormalities. However, the extent of vascular loss may become apparent only when the pulmonary blood flow is raised, as by exercise.

3. The variability in extent of pulmonary thrombotic involvement among patients with S-S hemoglobin remains unexplained, though a number of possibilities exist.

4. Effective prophylaxis and therapy in these patients awaits the discovery of satisfactory methods for preventing or reversing the sickling phenomenon in vivo.

**RESUMEN**

1. La trombosis pulmonar en los sujetos con el fenómeno de las ceidillas en hoz (sickled cells) parece ser una consecuencia de la obstrucción mecánica de los pequeños vasos pulmonares por las ceidillas con ese fenómeno. Tales ceidillas pueden lograr acceso a estas arteriolas no obstante, la desaturación es el resultado final de varios factores independientes. La fiebre y un pH ácido de la sangre venosa, puede también potenciar el fenómeno. Los vasos en los tejido pulmonar, capilar pulmón en elevada concentración a causa de las bajos concentraciones anormales de la sangre venosa. Esta desaturación es el resultado final de varios factores independientes. La fiebre y un pH ácido de la sangre venosa, puede también potenciar el fenómeno. Los vasos en las áreas hipoventiladas pulmonar se pueden encontrar bajo la influencia del oxígeno alveolar anormal y de las tensiones de dióxido de carbono haciéndolos especialmente susceptibles a la oclusión trombótica por esas ceidillas en hoz.

2. Si la trombosis compromete un área grande del lecho vascular pulmonar pueden desarrollarse anomalías cardipulmonares. Estas incluyen la fijación de la resistencia...
vascular pulmonar, la hipertensión pulmonar, el aumento del trabajo del ventrículo derecho y la insuficiencia de difusión del oxígeno. El elevado rendimiento cardíaco impuesto por la anemia en estos enfermos, tiende a exagerar las anormalidades. Sin embargo, la extensión de la pérdida vascular puede hacerse aparente sólo cuando el flujo pulmonar sanguíneo aumenta como en el ejercicio.

3. La variabilidad en la extensión del compromiso trombótico pulmonar entre los enfermos con hemoglobina S-s, permanece inexplicada, aunque cierto número de posibilidades existe.

4. La profilaxis efectiva y el tratamiento de estos enfermos está en espera del descubrimiento de métodos efectivos para evitar o obtener la reversión del fenómeno de células en vivo.

**RESUMÉ**

1. La trombosis pulmonar que los sujetos atípicos de drépanocitosis parece ser la consecuencia de una obstrucción mecánica de los pequeños vasos pulmonares por células falciformes. De las células pueden penetrarse en el lit vascular pulmonar a alta concentración a causa de la concentración de oxígeno anormalmente baja dentro del sangui

2. Si des faits produits par la thrombose atteignent une large zone du lit pulmonaire vascular, des anormalidades cardiovasculaires peuvent se développer. Celles-ci comprennent la fixation de la résistance vasculaire pulmonaire, l'hypertension pulmonaire, l'augmentation du travail du ventricule d

3. La variabilidad de la extension de l'atteinte pulmonaire trombotique parmi les malades con hémoglobine S reste inexplicada, bien qu'un grand nombre de possibilités existent.

4. La prophylaxie et le traitement efficaces chez ces malades ne seront possibles que le jour où l'on aura découvert des méthodes satisftantes pour prévenir ou guérir le phénomène in vivo.

**ZUSAMMENFASSUNG**


2. Betrifft ein thrombotisches Geschehen einen großen Bereich des pulmonalen Gefäßbettes, so können daraus kardiopulmonale Veränderungen entstehen. Hier-hin gehören die Fixationen des pulmonalen Gefäßwiderstandes, pulmonaler Hochdruck, erhöhte Belastung des rechten Herzens und Insuffizienz der Sauerstoffdiffusion. Das durch die Anaemie bewirkte große Herzminutenvolumen führt bei diesen Kranken dazu, diese Veränderungen noch zu verstärken. Es kann jedoch so sein, daß das Ausmaß des Gefäßverlustes nur in Erscheinung tritt, wenn sich die pulmonale Durchströmung verstärkt, etwa bei Belastung.


4. Eine effektive Prophylaxe und Therapie bei diesen Kranken sieht noch de-r Ent-

**REFERENCES**


