Editorial

Respiratory repercussions of sickle cell anemia

Gustavo Antonio Moreira

Sickle cell anemia is a disease with autosomal recessive inheritance, secondary to a mutation in the gene of the hemoglobin β chain, transforming normal hemoglobin (HbA) into sickle cell hemoglobin (HbS). When oxygenated, HbS presents normal function. At low oxygen tension, HbS undergoes polymerization, leading to the distortion of erythrocytes, which take on a characteristic sickle shape. This deformation results in vascular occlusion, ischemia, and tissue infarction. This vicious cycle between hypoxemia and deformation of the erythrocytes leads to known complications of sickle cell anemia, such as cerebral vascular accident, vaso-occlusive crisis, and acute thoracic syndrome. Therefore, the detection and treatment of hypoxia are vital for patients with sickle cell anemia.

Pulmonary complications account for 20-30% of deaths in adults with sickle cell anemia. Pulmonary alterations usually appear in the second decade of life and result in death in the fourth decade. A series of pulmonary lesions caused by upper-airway obstruction, pulmonary infections, and a proinflammatory state lead to obstructive or restrictive respiratory disorder, resulting in pulmonary hypertension and death.

Children and adolescents frequently present respiratory diseases of the upper and lower airways, which can lead to decreased oxygen availability. Adenotonsillar hypertrophy frequently leads to obstructive sleep apnea-hypopnea syndrome (OSAHS), characterized by intermittent obstruction of the upper airway and nocturnal hypoxemia. Cerebrovascular accidents are more common in sickle cell anemia patients between the ages of 5 and 7, a period that coincides with greater adenotonsillar growth. These children present a higher risk of having OSAHS, due to adenotonsillar compensatory growth after autosplenectomy caused by an increased reactive response to multiple infections with encapsulated germs and by increased hematopoietic needs resulting from hemolytic anemia. Obstructive sleep apnea in children has been associated with a higher frequency of morning vaso-occlusive crises, which become less frequent after adenotonsillectomy.[1] Since obstructive sleep apnea in children is easily treated, it is of utmost importance to perform clinical and laboratory investigation in children with a history of habitual snoring, morning vaso-occlusive crises, or both. However, pulmonary infections and repeated acute thoracic syndromes can lead to multiple pulmonary infarctions, evolving to gradual loss of the pulmonary function and sudden death.[2-3]

The technological advances made in recent decades have allowed the noninvasive measurement of peripheral oxygen saturation (SpO_2). Oxygen saturation is currently considered the fifth vital sign and has been universally used in intensive care units, operating rooms, emergency rooms, and outpatient clinics. Knowing the SpO_2 level is fundamental to clinical decision-making by pulmonologists, informing decisions such as whether to use oxygen therapy or therapy with positive airway pressure. However, the physician should always be alert to situations in which this measurement could be spurious. The article by de Souza and Viegas on sleep and pulmonary function in sickle cell anemia, in this issue of the Brazilian Journal of Pulmonology, is an example of how the interpretation of SpO_2, in special situations, can be confusing.[4]

The accuracy of SpO_2 in sickle cell anemia has already been studied in various situations. The pulse oximeter can overestimate or underestimate arterial oxygenation. Various aspects contribute to this variability. The pulse oximeter emits light with two wavelengths (red and infrared), which pass through the vascular bed and measure light absorption by oxyhemoglobin and deoxyhemoglobin. The analyzer calculates the saturation value, based on experimental data from normal volunteers. Most of the blood gas analysis equipment available in Brazil calculates oxyhemoglobin saturation by measuring arterial oxygen tension (PaO_2) and applying a standard HbA dissociation curve. Patients with sickle cell anemia present a hemoglobin dissociation curve shifted to the right. Hemoglobin is 50% saturated (P_{50}) at a PaO2 of 42-56 mmHg in patients with sickle cell anemia, compared with a mean of 26.5 mmHg in the general population. Therefore, patients with sickle cell anemia can present an SpO_2 < 90% and, nevertheless, present a PaO_2 > 80 mmHg.[4-5] In other words, using the HbA dissociation curve to calculate SpO_2 in patients with sickle cell anemia generates misleading data. Therefore, the PaO_2 measurement provides a more precise evaluation of arterial oxygenation in sickle cell anemia. Polymerization

of HbS increases at PaO_2 < 75 mmHg, and PaO_2 is therefore the best indicator of the risk of vaso-occlusive crises.

The blood gas analysis equipment with a co-oximeter uses a method of calculating arterial oxygen saturation (SaO_2) that is similar to that used by the pulse oximeter. The co-oximeter is more accurate at measuring SaO_2, since it uses light in 4-6 wavelengths, thereby allowing values for oxygenated hemoglobin, deoxygenated hemoglobin, methemoglobin (MetHb) and carboxyhemoglobin (COHb) to be determined. Therefore, it is possible to calculate the fraction of oxygenated hemoglobin:

fraction of oxygenated hemoglobin = oxygenated Hb/(oxygenated Hb + deoxygenated Hb + MetHb + COHb) (1)

At approximately 660 nm, the absorption of COHb is similar to that of oxyhemoglobin, leading the pulse oximeter to overestimate SpO_2. In cases of hemolytic anemia, there is an increase in COHb, and the co-oximeter is therefore necessary in order to obtain a precise SaO_2 measurement. The discrepancy between SpO_2 and SaO_2 in sickle cell anemia is due to the presence of COHb and MetHb, as well as to the differences in the dissociation curves. A recent study, involving 390 patients with sickle cell anemia, demonstrated that basal SpO_2, during regularly scheduled appointments, can range from 86 to 99%. However, only 2.3% of the patients presented an SpO_2 < 90%. In the multivariate analysis, the authors found that the SpO_2 was inversely related to hemoglobin, whereas it was directly related to the reticulocytes, to age and to male gender. However, no relationship between SpO_2 and the frequency of acute thoracic syndrome events was demonstrated.[5]

The second particularity in the interpretation of polysomnographic data of children and adolescents depends on their age bracket. The polysomnographic criteria in prepubescent children are different from those defined for adults. Obstructive apnea in children within two or more respiratory cycles (<10 s) is considered abnormal. In addition, healthy children rarely present obstructive events, and an obstructive apnea index > 1 event/h is therefore considered abnormal. In adolescents, there is as yet no clear definition in the literature regarding the criterion to be used, the criterion of children or that of adults (apnea-hypopnea index > 5 events/h). Simplified tests used in place of polysomnography, such as nocturnal oximetry, in isolation, are not routinely recommended for the triage of sleep-disordered breathing, due to their low specificity. For these reasons, nocturnal oximetry, in isolation, should not be used in sickle cell anemia patients. The ideal testing for these patients is to perform polysomnography measuring airflow through a pressure tube, which increases sensitivity in the detection of obstructive events, in addition to the transcutaneous oxygen tension and transcutaneous carbon dioxide tension measurements, thus avoiding misleading SpO_2 measurements. These measurements are important not only for the diagnosis of obstructive sleep apnea but also for the early diagnosis of nocturnal hypoxemia, lest the patient develop a permanent pulmonary lesion.

Adolescents with sickle cell anemia present significant pulmonary function alterations. In the above-mentioned study, ventilatory defects were observed in over one-third of the clinically stable adolescents.[4] The ventilatory defects found were either obstructive or restrictive. It is believed that pulmonary restriction results from inefficacious inspiration, due to pain, infarction of the ribs during growth, osteoporosis, or rib osteomalacia. Frequent episodes of acute thoracic syndrome can contribute to the development of pulmonary fibrosis. Evidence suggests that sickle cell anemia involves a proinflammatory process, due to leukocytosis, greater numbers of vascular adhesion molecules, and increased production of cytokines (tumor necrosis factor alpha, interleukin-1β and interleukin-6). This proinflammatory process is the probable causal agent of the reversible obstruction of lower airways. Other factors that accelerate the pulmonary lesion, such as repeated infections, fat embolism after bone infarction, and hypercoagulability, also contribute substantially to the development of pulmonary hypertension.

Since pulmonary complications are responsible for 20-30% of the deaths in adults with sickle cell anemia, the early detection of these alterations is fundamental for the initiation of therapeutic interventions, such as fluid replacement, judicious blood transfusion, prevention of infections, and hydroxyurea. Investigations involving patients at the early stages of the disease, such as that described by de Souza and Viegas in this issue of the Brazilian Journal of Pulmonology, are of utmost importance

for the early detection of respiratory alterations, resulting in interventions that can have an impact on the morbidity and mortality of patients with sickle cell anemia.

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