Gas Exchange Abnormality during Sleep in Non-Snoring Severe Thalassemia Children

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Objective: *To study the prevalence and associated factors of gas exchange abnormality during sleep in non-snoring severe thalassemia children.*
Material and Method: *Non-snoring severe thalassemia children aged 6 to 15 years who had been followed up at King Chulalongkorn Memorial Hospital between June 2009 and March 2010 were studied. Overnight pulse oximetry and end-tidal carbon dioxide tension ($P_{ET}CO_2$) monitoring as well as pulmonary function tests were evaluated.*
Results: *Fifty-eight non-snoring severe thalassemia children (aged 10.5 $\pm$ 2.6 years, 43% male) were studied. 67.2% showed abnormal gas exchange during sleep. All of them had nocturnal desaturation (nadir SpO_2 87 $\pm$ 6.9%; range 65 to 94%). 33.3% of those who had nocturnal desaturation had associated lung function abnormality. Abnormal lung function was found in 32.8% of the present study patients. Of these, 68.4% had associated nocturnal desaturation. Age, gender, nutritional status, size of liver and spleen, history of splenectomy, hemoglobin and serum ferritin level, and lung function were not associated with abnormal gas exchange during sleep.*
Conclusion: *Nocturnal desaturation was demonstrated in more than a half of non-snoring severe thalassemia children. Normal lung function did not guarantee normal gas exchange during sleep. However, more than a half of those who had lung function abnormality had associated nocturnal desaturation. Evaluation of gas exchange during sleep would be merited in this group of patients.*

Keywords: *Thalassemia, Abnormal blood gases, Lung function*

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Significant hypoxemia or desaturation has been reported in some patients with thalassemia, either during awake[1-4] or during sleep[5]. Mechanism of daytime hypoxemia has not been known yet. Histopathologic findings of pulmonary arterial occlusion and pulmonary thromboembolism were reported and suggested to be a potential cause of hypoxemia during awake in these patients[6,7]. However, studies of gas exchange during sleep in thalassemia patients are scanty. There was one report of nocturnal desaturation in a thalassemic child who snored and had obstructive sleep apnea (OSA)[5]. Gas exchange abnormality during sleep in non-snoring severe thalassemia children has never been investigated and can lead to many serious sequelae including cardiovascular problems if it is left untreated. Therefore, the authors were interested in studying the prevalence and associated factors of gas exchange abnormality during sleep in this group of children.

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Material and Method

Children aged 6 to 15 years who were diagnosed with severe thalassemia and had been followed-up at King Chulalongkorn Memorial Hospital were studied. Severe thalassemia was defined if the child had homozygous β-thalassemia or β-thalassemia/hemoblobin E and required at least one blood transfusion every 3 to 4 weeks. Exclusion criteria included those who had bone marrow transplantation, habitual snoring (snore $\geq$ 3 nights/week), other comorbid respiratory diseases (such as

asthma, chronic lung diseases, airway obstruction, acute respiratory tract infection within two weeks prior to the present study), neuromuscular diseases, congenital cyanotic heart diseases or were uncooperative with the overnight pulse oximetry, end-tidal carbon dioxide ($P_{ET}CO_2$) monitoring, and pulmonary function test. Written informed consent and assent (where applicable) were obtained from legal guardians and patients aged $\geq$ 7-years, respectively, prior to the present study. The present study protocol was approved by the Ethics Committee for Human Research Study of the Faculty of Medicine, Chulalongkorn University.

Gas exchange during sleep was evaluated by overnight pulse oximetry and $P_{ET}CO_2$ monitoring (Capnocheck PLUS®, BCI International, WI) while the patient was sleeping overnight in the hospital. The total recording time was 6 to 8 hours. A parent or caregiver was allowed to stay with the patient throughout the present study night. Movement artifact was noted if the patient showed irregularity of the pulse waveform signal and was confirmed with the parent or caregiver's observation. Desaturation was defined if the patient had arterial pulse oxygen saturation (SpO_2) < 94% for more than 5% of total sleep time. This was in accordance to the British Thoracic Society Guideline for home oxygen therapy in children[8]. Hypoventilation was defined if there was an elevation of $P_{ET}CO_2$ > 50 mmHg for more than 25% of total sleep time in accordance to the American Academy of Sleep Medicine (AASM) criteria[9].

Pulmonary functions (spirometry and lung volumes [measured by body plethysmography]) were evaluated by Vmax 6200 Autobox® (SensorMedics, Yorba Linda, CA) on the following day after the overnight pulse oximetry and $P_{ET}CO_2$ monitoring. Pulmonary function parameters included in the present study were forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, forced expiratory flow rate between 25 to 75% of vital capacity ($FEF_{25-75\%}$), total lung capacity (TLC), residual volume (RV) and RV/TLC ratio. All parameters except for FEV_1/FVC and RV/TLC ratio were expressed as the percentage of predicted value calculated from the normal value for an Asian population (European Respiratory Society 1993, Update). Obstructive defect was defined if the FEV_1 was less than 80% of predicted value (and/or $FEF_{25-75\%}$ was less than 70% of predicted value) with the FEV_1/FVC ratio lower than 0.85[10,11]. Restrictive defect was defined if the TLC was less than 80% of predicted value[12,13]. Hyperinflation was defined if the RV was greater than 135% of predicted value and the RV/TLC ratio was greater than 0.35[10].

Collected data included demographic data, nutritional status, history of splenectomy and iron chelation, the presence of hepatosplenomegaly, hemoglobin and serum ferritin levels within four to six weeks, respectively, prior to the present study, PFT parameters and overnight recorded SpO_2 and $P_{ET}CO_2$. Clinical data (in term of range, mean $\pm$ standard deviation (SD) and percentage) was compared between those who had normal and abnormal gas exchange during sleep (either desaturation or hypoventilation or both) by using Student's t-test for continuous variables and Fisher exact test for categorical variables to identify factors associated with abnormal gas exchange during sleep. A two-tailed p-value of less than 0.05 was considered for a statistical significance. The statistical analysis was performed by using GraphPad InStat (GraphPad Software Inc., San Diego, CA).

Results

Between June 1, 2009 and March 31, 2010, there were 110 severe thalassemia children aged 6 to 15 years who were followed-up at the Pediatric Hematology Clinic, King Chulalongkorn Memorial Hospital. Fifty-two patients were excluded from the present study. These included those who had habitual snoring (25 cases), bone marrow transplantation (9 cases), asthma (2 cases), chronic lung disease (1 case), movement artifact during SpO_2 and $P_{ET}CO_2$ monitoring, (2 cases) and poor compliance with pulmonary function test (1 case). Twelve parents refused to participate in the present study.

Fifty-eight patients were eligible to the study. The mean age was 10.5 $\pm$ 2.6 years (range 6 to 15 years). The male:female ratio was 1:1.3. Five patients (8.6%) were obese (percentage of weight for height $\geq$ 120%). Fifty-seven patients (98.3%) had beta-thalassemia/Hb E while one patient (1.7%) had Hb Bart's. All patients had desferrioxamine for iron chelation therapy. Nine patients (15.5%) had splenectomy. The time interval from splenectomy to the present study was 5.9 $\pm$ 3.9 years (range 6 months to 11.4 years). The mean platelet count after splenectomy was 726,055 $\pm$ 212,343 mm^3 (range 307,000-938,000 mm^3). Other clinical data are shown in Table 1.

Nocturnal desaturation was demonstrated in 39 patients (67.2%). The nadir SpO_2 was 87 $\pm$ 6.9% (65-94%). No nocturnal hypoventilation was observed.

The results of pulmonary function study were showed in Table 2. Nineteen patients (32.8%) demonstrated abnormal lung function. The most common was restrictive defect (7 patients; 36.8%). Other abnormal lung functions included hyperinflation (5 cases; 26.3%), obstructive defect (4 cases; 21.1%) and mixed restrictive/obstructive defects (3 cases; 15.8%).

Among 19 patients with abnormal lung function, 13 (68.4%) had associated nocturnal desaturation. These included four patients with restrictive defect, four patients with hyperinflation, three patients with obstructive defect and two patients with mixed restrictive/obstructive defects.

Comparison between those who had nocturnal desaturation and those who had not found no difference between the two groups in age, gender, history of splenectomy, nutritional status, liver span, size of spleen, hemoglobin level, serum ferritin level, and the presence of abnormal lung function (Table 3).

Table 1. Clinical data of the study patients (n = 58)

Clinical data	Mean ± SD (range)
Liver span (cm)	7.7 ± 1.9 (4-12)
Size of spleen below left costal margin (cm)	1.7 ± 1.6 (1-7)
Hemoglobin level (g/dl)	8.9 ± 1.2 (6-12)
Serum ferritin level (ng/ml)	2,838.0 ± 1,565.0 (312-7,465)
Awake SpO_2 (%)	98.0 ± 1.0 (96-99)
Awake $P_{ET}CO_2$ (mmHg)	40.0 ± 4.0 (30-49)
SpO_2 during sleep (%)	97.3 ± 0.9 (65-98)
$P_{ET}CO_2$ during sleep (mmHg)	39.4 ± 3.9 (28-55)

Table 2. The results of pulmonary function test (n = 58)

Pulmonary function parameters	Mean ± SD (range)
FVC (% predicted value)	84.3 ± 9.6 (67-108)
FEV_1 (% predicted value)	91.0 ± 11.2 (72-116)
FEV_1/FVC	0.92 ± 0.04 (0.8-1.0)
$FEF_{25-75\%}$ (% predicted value)	57.8 ± 15.3 (37-101)
TLC (% predicted value)	87.8 ± 9.8 (63-106)
RV (% predicted value)	102.8 ± 27.1 (49-179)
RV/TLC	0.30 ± 0.06 (0.2-0.5)

Discussion

In the present study, the authors found abnormal lung function in 32.8% and nocturnal desaturation in 67.2% of children aged 6 to 15 years who were non-snoring, severe thalassemia. Neither desaturation nor hypoventilation was found during awake. Several studies evaluated lung function and gas exchange during awake in thalassemia patients[1-4,14,15]. However, the causative relationship between abnormal lung function and hypoxemia while awake has not been established and still needs to be investigated.

Gas exchange capability can be decreased during sleep even though in normal healthy individuals[16]. Children with respiratory problems secondary to various etiologies such as upper airway obstruction, poor lung mechanics, etc. are even more risk for having gas exchange abnormalities during sleep. This can lead to several serious sequelae, especially cardiovascular complications if it is left untreated.

Nocturnal desaturation has been reported in many children with sickle cell disease, which is another inherited hemoglobinopathy presenting with the clinical features of chronic hemolysis and transfusion dependent liked severe thalassemia[17-20].

Table 3. Comparison of clinical parameters between those who had nocturnal desaturation and those who had not

Clinical parameters	Nocturnal desaturation (n = 39)	No nocturnal desaturation (n = 19)	p-value
Age (years) at the time of the study	11.1 ± 2.9 (6-15)*	10.3 ± 2.4 (6-15)*	0.28
Male : Female	1:1.7	1:1.2	0.69
History of splenectomy	4 (21 %)	5 (12.8 %)	0.67
Obesity (%)	2 (10.5 %)	3 (7.7 %)	1.00
Liver span (cm)	8.4 ± 1.8 (4-10)*	7.4 ± 1.8 (5-12)*	0.08
Size of spleen below left costal margin (cm)	1.9 ± 1.9 (0-7)*	1.7 ± 1.6 (0-7)*	0.63
Hemoglobin level (g/dL)	8.7 ± 1.2 (6.9-12)*	9.0 ± 1.2 (6-11.9)*	0.44
Serum ferritin level (ng/ml)	2,622.9 ± 1,518.3 (312-7,465)*	2,943.0 ± 1,597.5 (1,000-6,722)*	0.47
Abnormal lung function	13 (33.3 %)	6 (31.6%)	1.00

* Data were presented as mean ± SD (range)

Most of the desaturation events were associated with OSA secondary to adenotonsillar hypertrophy[17-19]. However, some children who had sickle cell disease presented with daytime and nighttime desaturations without having OSA[20,21]. The proposed mechanism of desaturation in these children is V/Q mismatching secondary to pulmonary thromboembolism induced by vascular endothelial cell injuries and hypercoagulable stage[20-23]. Other proposed mechanisms include low oxygen affinity of the HbS and increased level of methemoglobin and carboxyhemobglobin in these children[24-27].

Studies of gas exchange during sleep in thalassemia patients are scanty. There was only one report of nocturnal desaturation secondary to OSA in a child who had thalassemia intermedia[5]. Previous studies reported abnormal lung function and hypoxemia during awake in thalassemia patients[1-4]. However, some studies reported abnormal lung function without associated hypoxemia in these patients[14,15]. Whether abnormal lung function contributes to abnormal gas exchange during sleep or not has never been investigated. In the present study, the authors found that 67.2% of non-snoring, severe thalassemia children had nocturnal desaturation. Only one-third of these (33.3%) had associated lung function abnormality. That meant 67% had nocturnal desaturation despite having normal lung function. In the present study, pulmonary function tests were evaluated while the patients were in the upright position. Many children with severe thalassemia have hepatosplenomegaly, which can restrict diaphragm function and decrease lung volumes, especially when they are in the supine position. Those who have normal lung volumes assessed in the upright position may have decreased lung volumes and gas exchange capability when they are in the supine position. In other words, normal lung function assessed in the upright position did not guarantee normal gas exchange during sleep.

Another possible mechanism of nocturnal desaturation in severe thalassemia children is V/Q mismatching secondary to pulmonary capillary occlusions. Histopathological studies in thalassemic adults showed evidences of multiple microthormbi in pulmonary circulation, especially in those who had splenectomy[6,7]. Platelet hyperaggregration and increased serum protein C and protein S levels were reported in many thalassemia patients[14,28-30]. This hypercoagulable stage could be a leading cause of pulmonary thromboembolism in these patients[31]. It could be possible that some of the patients in the present study who showed nocturnal desaturation without having abnormal lung function had pulmonary microvascular occlusions that were not severe enough to cause abnormal lung function and desaturation during awake but induce desaturation during sleep. Further studies including ventilation/perfusion lung scan would be helpful in verifying this hypothesis.

In the present study, the authors could not demonstrate the association between nocturnal desaturation and age, gender, history of splenectomy, nutritional status, liver span, size of spleen, hemoglobin level, serum ferritin level and the presence of abnormal lung function in non-snoring severe thalassemia children. However, nearly 70% of those who had abnormal lung function demonstrated desaturation during sleep. This finding suggests that gas exchange monitoring during sleep may be needed in those who have abnormal lung function in order to plan for the appropriate long-term oxygen therapy.

In conclusions, the authors found nocturnal desaturation in more than a half of non-snoring severe thalassemia children. Normal lung function evaluated during awake did not warrant normal gas exchange during sleep. However, evaluation of gas exchange during sleep would be merited for the appropriate planning of the long term oxygen therapy in those who have abnormal lung function. This would be helpful in preventing the serious cardiovascular complications caused by nocturnal hypoxemia in severe thalassemic children.

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Abbreviations

$FEF_{25-75\%}$	Forced expiratory flow rate between 25-75% of vital capacity
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
$P_{ET}CO_2$	End-tidal carbon dioxide tension
RV	Residual volume
SpO_2	Arterial pulse oxygen saturation
TLC	Total lung capacity

Potential conflicts of interest

None.

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ความชุกของภาวะผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับในผู้ป่วยเด็กธาลัสซีเมียชนิดรุนแรงที่ไม่มีอาการนอนกรน

สุชาดา ศรีทิพยวรรณ, ไกลตา ศรีสิงห์, อิศรางค์ นุชประยูร, รุจิภัตต์ สำราญสำรวจกิจ, จิตลัดดา ดีโรจนวงศ์, นวลจันทร์ ปราบพาล

วัตถุประสงค์: *เพื่อศึกษาความชุกของภาวะผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับในผู้ป่วยเด็กธาลัสซีเมียชนิดรุนแรงที่ไม่มีอาการนอนกรนและปัจจัยที่เกี่ยวข้อง*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงวิเคราะห์ในผู้ป่วยเด็กธาลัสซีเมียชนิดรุนแรงที่ไม่มีอาการนอนกรน อายุ 6-15 ปี ที่มารับการตรวจรักษาที่ฝ่ายกุมารเวชศาสตร์ โรงพยาบาลจุฬาลงกรณ์ ระหว่างวันที่ 1 มิถุนายน พ.ศ. 2552 ถึงวันที่ 31 มีนาคม พ.ศ. 2553 ผู้ป่วยทุกรายได้รับการตรวจวัดค่าความอิ่มตัวของออกซิเจนในเลือดแดง (SpO_2) และระดับก๊าซคาร์บอนไดออกไซด์ในลมหายใจออก ($P_{ET}CO_2$) ขณะหลับในโรงพยาบาล 1 คืน และตรวจสมรรถภาพปอด (spiromtery และ body plethysmography) ในเช้าวันถัดไป*

ผลการศึกษา: *มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 58 ราย อายุเฉลี่ย 10.5 $\pm$ 2.6 ปี เพศชาย: เพศหญิง 1:1.3 พบความผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับร้อยละ 67.2 โดยเป็นภาวะ desaturation เพียงอย่างเดียว ค่าเฉลี่ยของ nadir SpO_2 เท่ากับ 87 $\pm$ 6.9 % (range 65-94%) ร้อยละ 33.3 ของผู้ป่วยที่มี desaturation มีสมรรถภาพปอดผิดปกติร่วมด้วย ร้อยละ 32.8 ของผู้ป่วยที่ทำการศึกษามีสมรรถภาพปอดผิดปกติ โดยร้อยละ 68.4 ของผู้ป่วยกลุ่มนี้มีความผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับร่วมด้วย การศึกษานี้ไม่พบความสัมพันธ์ระหว่างอายุเมื่อเข้าร่วมโครงการวิจัย, เพศ, ภาวะโภชนาการ, ขนาดของตับและม้าม, ประวัติการตัดม้าม, ระดับ hemoglobin ก่อนได้รับเลือด, ระดับ ferritin ในเลือด และการมีสมรรถภาพปอดผิดปกติกับความผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับ*

สรุป: *การศึกษานี้พบว่า มากกว่าร้อยละ 50 ของผู้ป่วยเด็กธาลัสซีเมียชนิดรุนแรงที่ไม่มีอาการนอนกรนมีความผิดปกติของการแลกเปลี่ยนก๊าซขณะหลับแบบ desaturation ร่วมด้วย การตรวจพบสมรรถภาพปอดปกติไม่ได้เป็นเครื่องยืนยันว่าผู้ป่วยมีการแลกเปลี่ยนก๊าซในขณะหลับปกติ อย่างไรก็ตาม การศึกษานี้พบว่า มากกว่าร้อยละ 50 ของผู้ป่วยที่มีสมรรถภาพปอดผิดปกติมีภาวะ desaturation ในขณะหลับร่วมด้วย การประเมินประสิทธิภาพของการแลกเปลี่ยนก๊าซขณะหลับอาจมีประโยชน์ในผู้ป่วยกลุ่มนี้*