

Nocturnal hypoxaemia in patients with Eisenmenger syndrome: a cohort study

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ABSTRACT

Objectives: The objective of the study was to find the prevalence of sleep-related disturbances in patients of Eisenmenger syndrome.

Design: Prospective observational study.

Setting: Tertiary care referral centre in North India.

Participants: The study included 25 patients with Eisenmenger syndrome (mean age 25.2±9.6 years, 18 men) and 12 patients with cyanotic congenital heart disease with pulmonary stenosis physiology (mean age 20.5±8.5 years, 8 men) as controls.

Interventions: All the patients underwent an overnight comprehensive polysomnogram study and pulmonary function testing.

Main outcome measure: Oxygen desaturation index, which is the number of oxygen drops per hour.

Results: The patients and controls had significant nocturnal hypoxaemia in the absence of apnoea and hypopnoea. The mean oxygen drop index in Eisenmenger syndrome group was 9.0±6.2 and in the control group was 8.0±5.9 ($p=0.63$). The apnoea–hypopnoea index was 3.37±5.0 in the Eisenmenger syndrome group and was 2.1±3.6 in the control group. Patients with >10 oxygen drops per hour had significantly higher haemoglobin (17.2±1.3% vs 14.4±1.5%, $p<0.001$) than those with oxygen drops less than 10.

Conclusions: Eisenmenger syndrome patients have significant nocturnal hypoxaemia unrelated to hypopnoea and apnoea. Nocturnal desaturation occurred more frequently in patients with greater haemoglobin values.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) develop nocturnal hypoxaemia,^{1 2} particularly during rapid eye movement (REM) sleep. The major cause of REM hypoxaemia is hypoventilation, with additional contribution from alteration in ventilation/perfusion matching and functional residual capacity reduction. Nocturnal hypoxaemia probably contributes to the development of pulmonary hypertension and

ARTICLE SUMMARY

Article focus

- Sleep-related nocturnal hypoxaemia has not been systematically studied in patients of Eisenmenger syndrome.
- This study was undertaken to find the prevalence of sleep-related disturbances in patients with Eisenmenger syndrome.
- Sleep-related disturbances were compared with patients with ventricular septal defect and pulmonary stenosis.

Key messages

- Eisenmenger syndrome patients have significant nocturnal hypoxaemia unrelated to hypopnoea and apnoea.
- Nocturnal desaturation occurred more frequently in patients with greater haemoglobin values.
- Similar sleep-related disturbances were also found in patients with ventricular septal defect and pulmonary stenosis.

Strengths and limitations of this study

- The first ever study reporting sleep parameters in Eisenmenger syndrome.
- This study consisted of a small number of patients, but may be sufficient for the question to be addressed.
- The reasons and consequences of nocturnal hypoxaemia are not addressed in the study.

polycythaemia in COPD and may predispose to cardiac arrhythmias in some patients.^{1 3} Patients with idiopathic pulmonary artery hypertension also have significant nocturnal hypoxaemia, but these episodes are not related to apnoea and hypopnoea.⁴ Sleep-related nocturnal hypoxaemia has not been systematically studied in patients of Eisenmenger syndrome. This study was undertaken to find the prevalence of sleep-related disturbances in patients with Eisenmenger syndrome. Patients with cyanosis but without pulmonary arterial hypertension were included as controls.

METHODS

The study included 25 patients (18 men) with an unequivocal diagnosis of Eisenmenger syndrome. Mean age was 25.2 ± 9.6 years (range 13–49 years), there were 18 men and 7 women. The control group consisted of 12 patients (8 men) with ventricular septal defect with pulmonary stenosis (VSD PS) physiology (mean age 20.5 ± 8.5 years). The Eisenmenger syndrome group predominantly included patients with large ventricular septal defect (19 patients (76%)). Three patients each had large atrial septal defect and patent ductus arteriosus. The 'VSD PS' group included patients of Tetralogy of Fallot (6), tricuspid atresia VSD PS (3), VSD pulmonary atresia (1), single ventricle PS (1) and double outlet right ventricle VSD PS (1). Patients with significant pulmonary parenchymal disease were excluded. An informed consent was obtained in all patients. The study is approved by the Institute Ethics Committee.

Patients were queried about sleep disturbances like insomnia, frequent nocturnal awakening, nightmares and daytime somnolence using a predeveloped questionnaire. Haemoglobin and haematocrit were measured in all the patients. Oxygen saturation by pulse oximetry (SpO_2) at rest and after a 6 min walk test was measured. Spirometry and measurement of diffusion capacity of the lungs using carbon monoxide (DLCO) were evaluated, as per standard guidelines.⁵

An overnight polysomnography was performed initially using *Judex system* and later using *Embla system* in accordance with the recommendations of the American Thoracic Society.⁶ Polysomnography included EEG, electro-oculogram, electromyogram, oronasal flow, respiratory effort and pulse oximetry recordings. An episode of apnoea was defined as the cessation of airflow lasting at least 10 s. If persistent respiratory effort was present, the apnoea was defined as obstructive apnoea. A hypopnoea was defined as a reduction in airflow by 50% for at least 10 s. An oxygen drop was defined as a fall in SpO_2 of at least 5% lasting for 9 or more seconds. Oxygen desaturation index (ODI) is the number of episodes of oxygen desaturations per hour.

In Eisenmenger syndrome patients, the correlation of ODI as a continuous variable with other variables like haemoglobin, haematocrit, resting and waking SpO_2 levels, arterial blood gas, spirometry values, diffusion capacity, apnoea and hypopnoea, and the sleep efficiency were assessed. The Eisenmenger syndrome patients were arbitrarily divided into two subgroups based on the ODI; patients having $\text{ODI} \leq 10$ and those with $\text{ODI} > 10$. The baseline characteristics and sleep study parameters were compared between the high and low ODI subgroups.

Statistical analysis

The patients of Eisenmenger syndrome and control group were compared using the Mann-Whitney test. The Mann-Whitney test was also used to compare the two subsets of Eisenmenger syndrome patients. The ODI was

related with other variables using Pearson's coefficient. Data are presented as mean \pm SD, and $p < 0.05$ were considered to be significant.

RESULTS

We studied 25 patients of Eisenmenger syndrome and 12 patients with VSD PS physiology as controls. Baseline characteristics of the patients and controls are shown in [table 1](#). Eisenmenger syndrome patients were significantly less cyanosed and had a lower haematocrit level than patients of control group. A higher proportion of Eisenmenger syndrome patients had sleep disturbances compared with patients with VSD PS physiology, though the difference was not statistically significant. The majority of Eisenmenger syndrome patients were mildly symptomatic as evident from the 6 min walk distance and mean baseline saturations. Twenty of the 25 patients were in WHO class II. Eight of the 25 Eisenmenger syndrome patients were receiving sildenafil and 2 patients received bosentan. Nine patients were receiving iron supplementation and none had phlebotomy. However, the iron status of the patients was not systematically studied. None of the patients were receiving supplemental oxygen therapy. Both the groups of patients had a mixed obstructive and restrictive pattern of respiratory abnormality. In Eisenmenger syndrome, obstructive pattern predominantly affected small airways (mean forced expiratory flow (FEF)_(25–75) $40.1 \pm 21.5\%$ of predicted values) with a mild restrictive pattern (total lung capacity (TLC) $72.2 \pm 10.8\%$ of predicted values).

Sleep architecture was normal in all patients. Total sleep time was 388.1 ± 122.9 min in Eisenmenger syndrome patients, compared with 386.2 ± 108.5 min in the control group, with a $>90\%$ sleep efficiency in both the groups. The proportion of REM sleep was also comparable between the two groups. The mean ODI in Eisenmenger syndrome was 9.0 ± 6.2 and in VSD with pulmonary stenosis group was 8.0 ± 5.9 ($p=0.63$). In both the groups, most of the oxygen drops occurred in the absence of apnoea/hypopnoea. The apnoea–hypopnoea index (AHI) was 3.37 ± 5.0 in the Eisenmenger syndrome group and 2.1 ± 3.6 in VSD with pulmonary stenosis group ($p=0.72$).

Among patients with Eisenmenger syndrome, a significant correlation existed between ODI and haematocrit values (spearman correlation coefficient $r=0.78$; $p < 0.001$; [figure 1](#)). ODI did not correlate with age of the patient ($r=-0.05$; $p=0.79$), SpO_2 levels at rest ($r=0.10$; $p=0.62$), 6-min walk distance ($r=-0.33$; $p=0.19$), total sleep time ($r=-0.04$; $p=0.83$) sleep efficiency ($r=0.17$; $p=0.42$) and apnoea/hypopnoea index ($r=0.26$; $p=0.22$; [figure 1](#)). More ODI's occurred during REM sleep than NREM sleep. There was no significant correlation between pulmonary function test variables and ODI. Similar results were seen when the entire study population's ODI was correlated with different parameters. Patients complaining of sleep disturbances had a significantly greater ODI

Table 1 Baseline characteristics, pulmonary function test and sleep study parameters of patients and controls

Variable	Eisenmenger syndrome (n=25)	CCHD with decreased PBF (n=12)	p Value
Age (years)	25.2±9.6	20.5±8.5	0.13
Males	18 (72%)	8 (66.7%)	1.0
Sleep disturbance	13 (52%)	6 (50%)	NS
Haemoglobin (gm/dl)	15.5±1.9	17.5±2.9	0.04
Resting SpO ₂ (%)	87.7±5.1	82.9±5.9	0.02
6 min distance (m)	469.6±108.8	434.3±77.8	0.15
6 min walk SpO ₂ (%)	78.4±7.5	73.8±6.9	0.11
Pulmonary function tests (values % predicted)			
FEV1	62.5±19.8	57.5±17.7	0.65
FEV1/FVC	91.5±21.9	85.0±20.2	0.90
FEF _(25–75)	40.1±21.5	58.5±36.1	0.37
TLC	72.2±10.8	80.0±11.3	0.25
DLCO	70.6±4.9	75.3±2.6	0.06
Polysomnogram variables			
Total sleep time (min)	388.1±122.9	386.2±108.5	0.46
Sleep efficiency (%)	94.6±6.1	96.7±3.3	0.49
REM sleep (%)	16.0±10.5	18.2±12.0	0.74
Apnoea–hypopnoea index	3.4±5.0	2.2±3.6	0.72
Oxygen drop index	9.0±6.2	8.0±5.9	0.63
Mean SpO ₂ during sleep (%)	84.7±5.8	78.1±5.8	0.004
Lowest SpO ₂ during sleep (%)	77.4±8.1	70.7±8.8	0.03

All values mean±SD or number (%).

CCHD, cyanotic congenital heart disease; DLCO, diffusion capacity with carbon monoxide; FEV1, forced expiratory volume in 1 s; FEF_(25–75), forced expiratory flow between 25% and 75% of the vital capacity; FVC, forced vital capacity; PBF, pulmonary blood flow; SpO₂, oxygen saturation by pulse oximetry; TLC, total lung capacity.

(10.6±5.9) as compared with patients without history of sleep disturbances (6.6±5.6, *p* 0.04).

Subgroup analysis

Ten of the Eisenmenger syndrome patients (40%) had >10 oxygen drops per hour. Patients with an ODI>10 had significantly higher haematocrit values as shown in table 2. These patients also had a tendency towards lower baseline SpO₂ levels (*P*–NS). Sleep symptoms and sleep parameters (ie, total sleep time, sleep efficiency, percentage of REM sleep and AHI) were not statistically different between the two groups. Pulmonary function test parameters were also not significantly different between the two groups.

DISCUSSION

Significant nocturnal hypoxaemia occurs in Eisenmenger syndrome patients and controls, which is not related to apnoea and hypopnoea. A control group consisting of VSD PS physiology representing patients with cyanosis but without pulmonary hypertension also showed similar nocturnal hypoxaemia. The control group was included mainly to define the contribution of pulmonary hypertension and basal cyanosis in the causation of nocturnal hypoxaemia. Nocturnal hypoxaemia has been well documented in COPD^{1 2} with the majority of episodes occurring during apnoea and hypopnoea. Nocturnal hypoxaemia, apnoea and hypopnoea have also been reported in normal individuals⁷; however,

oxygen saturation in normal individuals usually does not fall below 90%.⁸ It has been shown that in patients with idiopathic pulmonary hypertension also, nocturnal hypoxia occurs independent of apnoea and hypopnoea.⁴

The ODI in Eisenmenger syndrome patients was significantly related to haematocrit values, but not to resting saturation values or 6 min walk distance (figure 1). Patients with an ODI>10 had significantly higher haematocrit values. There was no significant correlation with other variables (table 2). A correlation between haemoglobin level and nocturnal desaturation has also been observed in patients with idiopathic pulmonary hypertension.⁴ Similar associations of nocturnal hypoxaemia with other variables in patients with idiopathic pulmonary hypertension and Eisenmenger syndrome suggest that there may be a related mechanism causing desaturation in both the conditions. In patients of idiopathic pulmonary hypertension an association between nocturnal desaturation and SpO₂ is reported.⁴ In patients with COPD it has been shown that low awake SpO₂ are predictive of more episodes and more severity of nocturnal desaturation.⁹

The lack of correlation between resting saturation and nocturnal hypoxaemia in the present study may be due to relatively narrow saturation range seen in the study population or less number of patients. The fact that the ODI in Eisenmenger syndrome are related to haematocrit but not to resting saturation is difficult to explain. Oxygen saturation and haemoglobin in Eisenmenger

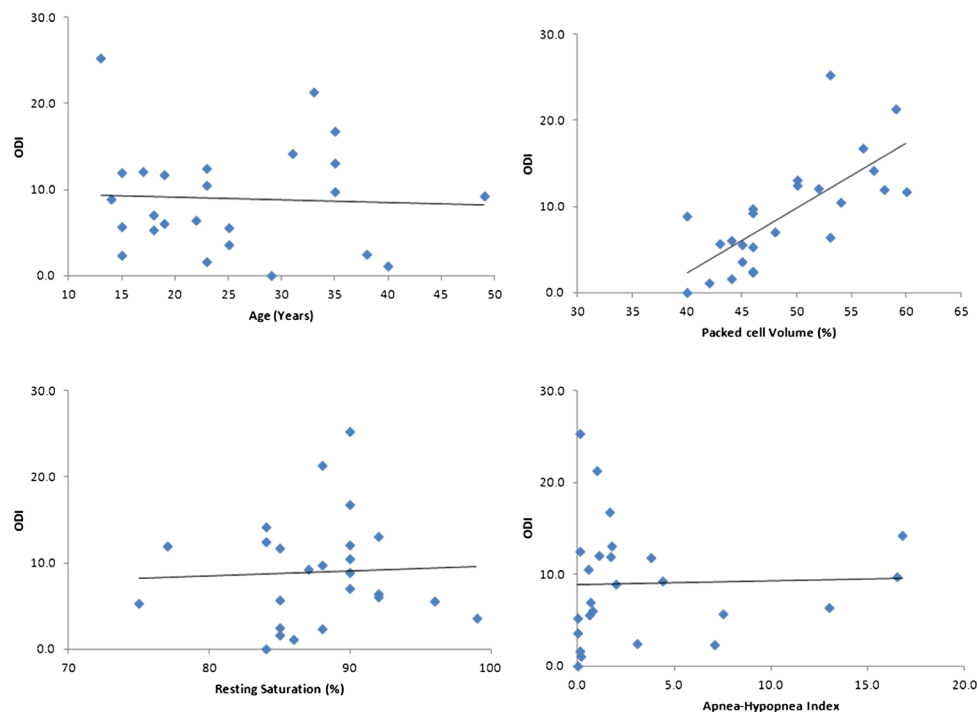


Figure 1 Correlation of ODI (oxygen drop index) with the age of the patient, packed cell volume, resting saturation and apnoea-hypopnoea index is shown.

syndrome patients is a complex interplay of intracardiac shunting, pulmonary vascular disease, disease-specific treatment and iron deficiency. The present study included patients with diverse iron status, disease-specific therapies and in different stages of pulmonary vascular disease. Broberg *et al*¹⁰ suggested that if there are no deficiencies, there is usually a linear relationship between haematocrit and resting oxygen saturation in Eisenmenger syndrome patients. However, even in their study only 21 of the 65 patients had optimal

haemoglobin and no correlation was found between oxygen saturation and haemoglobin for all patients.

Patients who complained of sleep disturbances like, insomnia, nocturnal awakening, nightmares and daytime somnolence had greater oxygen drops in our study. An increased number of oxygen drops in REM sleep was observed as compared with NREM sleep, an observation also reported in COPD patients.¹¹ However, the percentage of REM sleep was not increased in these patients. This is probably an extension of the ordinary

Table 2 Comparison between subgroups of Eisenmenger syndrome patients

Variable	ODI \geq 10 (n=10)	ODI<10 (n=15)	p Value
Age (years)	24.4 \pm 8.5	25.7 \pm 10.5	0.8
Haemoglobin (gm/dl)	17.2 \pm 1.3	14.4 \pm 1.5	0.001
Resting SpO ₂ (%)	87.0 \pm 4.5	88.1 \pm 5.6	0.67
6 min distance (m)	461.7 \pm 82.6	475.2 \pm 128.1	0.31
6 min walk SpO ₂ (%)	76.5 \pm 8.8	80.3 \pm 5.7	0.38
Pulmonary function tests (values % predicted)			
FEV1	68.3 \pm 15.2	58.1 \pm 22.7	0.44
FEV1/FVC	91.5 \pm 10.6	91.5 \pm 28.5	0.22
FEF ₍₂₅₋₇₅₎	70.3 \pm 11.1	91.5 \pm 28.5	0.22
TLC	70.3 \pm 11.1	75.0 \pm 14.1	0.56
DLCO	74.0 \pm 1.7	65.5 \pm 2.1	0.08
Polysomnogram variables			
Total sleep time (min)	403.2 \pm 111.7	378.0 \pm 131.2	0.74
Sleep efficiency (%)	95.3 \pm 4.3	94.1 \pm 7.1	0.89
Apnoea-hypopnoea index	2.9 \pm 5.0	3.7 \pm 5.2	0.82

All values mean \pm SD.

DLCO, diffusion capacity with carbon monoxide; FEF₍₂₅₋₇₅₎, forced expiratory flow between 25% and 75% of the vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ODI, oxygen drop index; SpO₂, oxygen saturation by pulse oximetry; TLC, total lung capacity.

predisposition of respiratory decompensation to take place during REM sleep as compared with the more stable NREM sleep.

Abnormalities of ventilatory function in Eisenmenger syndrome are well known.¹² There is a mild degree of mixed obstructive and restrictive patterns along with a small decrease in DLCO. The decreased TLC and forced vital capacity may be due to cardiac enlargement or to defective pulmonary growth secondary to reduced growth of the thoracic cavity.¹³ Eisenmenger syndrome patients were found to have a mild decrease in TLC and DLCO, but a significantly lower forced expiratory volume (in 1 s) and FEF₂₅₋₇₅ (FEF between 25% and 75% of the vital capacity) has also been reported.¹⁴ The mechanism of reduction in DLCO is not exactly known in Eisenmenger syndrome. It has been shown that DLCO is inversely related to pulmonary vascular resistance in patients with left to right intracardiac shunts.¹⁵ A low DLCO in patients with intracardiac septal defects has been proposed to be due to thickening of the alveolar-capillary membrane.

Desaturation in patients with Eisenmenger syndrome is the result of right-to-left shunting and pulmonary vascular disease with V/Q mismatching. The mechanisms of nocturnal desaturations are not clear. Worsening pulmonary artery haemodynamic changes and increasing right-to-left shunt during sleep may be the major mechanism. However, control group that included patients with cyanosis without pulmonary hypertension also showed similar nocturnal hypoxaemia. Hence, nocturnal desaturation episodes could be an exaggeration of the 'normal' small fall in PaO₂ seen during sleep even in healthy individuals.⁷⁻⁸ A fall of the same magnitude in PaO₂ would lead to significant desaturation in patients with baseline hypoxia, since they are in the steeper part of the oxygen dissociation curve. The predominant obstructive pattern of respiratory abnormality affecting the smaller airways may also result in a ventilation perfusion mismatch and nocturnal hypoxaemia, in which case prophylactic bronchodilators before sleep may help minimise such nocturnal desaturation. Sandoval *et al*¹⁶ showed that patients with Eisenmenger syndrome had a significant decrease in PaO₂ and SpO₂ when they changed position from sitting to the supine position. The decrease was corrected by nasal O₂. They suggested that ventilation perfusion mismatch or a gaseous diffusion abnormality rather than an increase in true right-to-left shunt is responsible for this finding.

The significance of nocturnal desaturation in Eisenmenger syndrome is not clear. Nocturnal desaturation can potentially worsen pulmonary vascular disease and can lead to polycythaemia. Nocturnal hypoxaemia can also lead to cardiac arrhythmias and sudden death, which is one of the commonest modes of death in Eisenmenger syndrome.¹⁷ In patients with COPD, nocturnal hypoxia has been shown to produce secondary polycythaemia and pulmonary hypertension.³ In the present study, patients of Eisenmenger syndrome with a

greater number of oxygen drops had significantly increased haematocrit and haemoglobin levels. However, no arrhythmias were seen in any patient.

In clinical practice, management of Eisenmenger syndrome patients with very low resting saturations is challenging as they often have iron deficiency, which is a marker of poor prognosis.¹⁸ Optimisation of haemoglobin in such patients leads to symptoms of hyperviscosity as the optimal haemoglobin levels are very high. Initiation or escalation of disease-targeting therapy is shown to improve oxygen saturation.¹⁹ Nocturnal oxygen supplementation could be a useful supplementary therapy. The two reported small studies of oxygen therapy in Eisenmenger syndrome included varied group of patients and the end points were not uniform.²⁰⁻²¹ However, 40% supplemental oxygen administered at home is shown to improve saturation and reduce erythrocytosis in a cohort of cyanotic adult patients including Eisenmenger syndrome.²² The utility of nocturnal oxygen therapy in selected subgroup of Eisenmenger syndrome patients, especially those with higher haematocrit values needs to be further studied in randomised controlled trials.

This study consisted of a small number of patients and therefore had limited statistical power to study the reasons and consequences of nocturnal hypoxaemia. Another limitation is the inclusion of patients with patent ductus arteriosus and Eisenmenger syndrome, where upper limb saturation may not reflect the true desaturation. However, only one of the patients showed differential cyanosis and in this patient, the lower limb saturation was also monitored. Further studies are required to ascertain its cause and consequences. Correlation of resting and nocturnal hypoxaemia with invasive haemodynamics would have helped in analysing the contribution of pulmonary vascular changes in its causation. Further, we did not repeat polysomnography after 100% oxygen inhalation which may have helped to evaluate the size of the shunt in these patients.

CONCLUSIONS

Patients with Eisenmenger syndrome have a significant nocturnal hypoxaemia that is not related to apnoea and hypopnoea. The episodes of nocturnal desaturation occurred more frequently in patients with higher haematocrit values.

Contributors SR wrote the protocol, was involved in the analysis and interpretation of the data and wrote the manuscript. RJ initiated the study, guided the analysis and interpretation of the data and critically modified the manuscript. NB and AS collected the data and critically evaluated the manuscript for its intellectual content. MK did the statistical analysis. GS, MB and RG were involved in designing and interpreting the sleep study protocols. GS, MB, SSK, AS, VKB and RG critically evaluated the manuscript and added critical content. RJ is the guarantor. All authors read and approved the final manuscript.

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