Polysomnographic Markers in Children With Cystic Fibrosis Lung Disease

Shruti M. Paranjape, MD[a], Brian M. McGinley, MD[b], Andrew T. Braun, MD[c], Hartmut Schneider, MD, PhD[c]

abstract

BACKGROUND AND OBJECTIVES: Children with cystic fibrosis (CF) often report poor sleep, increased daytime sleepiness, and fatigue. The purpose of this study was to identify respiratory patterns over the spectrum of disease severity in children with CF. The overall hypothesis for the current study is that children with CF compared with snoring control subjects demonstrate gas exchange abnormalities and increased respiratory loads during sleep that are not reported or recognized by conventional polysomnography (PSG).

METHODS: Analysis of breathing patterns and gas exchange on PSG was performed in children with CF and healthy controls matched by age and BMI. For all CF and control subjects, the indication for PSG was evaluation for obstructive sleep apnea based on a history of snoring.

RESULTS: Children with CF, compared with age- and BMI-matched snoring controls, demonstrated lower oxyhemoglobin saturation (95% ± 1.6% vs 98% ± 0.6%, P = .005), higher respiratory rate (19.5 ± 4.9 vs 16.5 ± 1.2 breaths per minute, P = .03), and a higher proportion of inspiratory flow limitation (44.1% ± 24.7% vs 12.1% ± 13.5%, P = .007) during non–rapid eye movement sleep. The respiratory disturbance index did not differ between CF and snoring control groups (1.5 ± 2.7 vs 0.6 ± 0.6 events per hour, P = .11).

CONCLUSIONS: Children with CF exhibited abnormalities in gas exchange and increased respiratory load during sleep compared with normal age- and BMI-matched snoring controls. Because these abnormalities were independent of weight and lung function, sleep state may serve as an opportunity for early detection of breathing abnormalities and possibly CF lung disease progression.

WHAT'S KNOWN ON THIS SUBJECT: Children with cystic fibrosis demonstrate gas exchange abnormalities and increased respiratory loads during sleep independent of lung function, age, and BMI. Assessment of breathing patterns during sleep provides an opportunity for detection of early lung disease progression.

WHAT THIS STUDY ADDS: Children with cystic fibrosis demonstrated increased respiratory loads and gas exchange abnormalities during sleep compared with controls. Based on these findings, sleep assessment in this patient population can identify markers for the early detection of lung disease progression.

[a]*Eudowood Division of Pediatric Respiratory Sciences, and* [c]*Sleep Disorders Center, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; and* [b]*Division of Pediatric Pulmonary, Sleep Medicine, and Cystic Fibrosis, University of Utah, Salt Lake City, Utah*

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Address correspondence to Shruti M. Paranjape, MD, Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University, 200 N Wolfe St, Baltimore, MD 21287. E-mail: sparanj1@jhmi.edu

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In cystic fibrosis (CF), diminished or absent chloride channel function results in dehydrated, viscid secretions and mucus plugging in the lungs that leads to inflammation, chronic infection, progressive small-airway obstruction, bronchiectasis, and the eventual development of hypoxemia, hypercapnia, and respiratory failure. Recently, sleep in CF has been increasingly recognized as a vulnerable state.[1] Whereas individuals with advanced lung disease often exhibit marked disturbances in gas exchange and breathing pattern during sleep, both of which are considered to contribute to lung disease progression,[1,2] the effect of sleep on gas exchange and breathing patterns with milder CF lung disease remains unclear.

The current clinical standard for determining abnormalities in breathing patterns and gas exchange during sleep is a nocturnal study using polysomnography (PSG). Previous studies using PSG focused on children and adults with advanced CF lung disease and demonstrated gas exchange abnormalities, with limited information on sleep and breathing patterns.[3,4] In general, abnormalities in breathing patterns have centered on the assessment of sleep apnea disease severity. Studies in children with CF lung disease[4–6] revealed conflicting results, with some showing an increase in sleep apnea severity[5] while others did not.[7,8] Based on these studies, it is possible that indices describing sleep disordered breathing do not account for important perturbations in breathing patterns and gas exchange,[9] particularly in children with CF lung disease.

We and others have described sensitive markers of abnormalities in breathing patterns that are not routinely included in the analysis of traditional polysomnographic measures. These include the prevalence of inspiratory flow limitation (IFL),[10,11] determination of respiratory rate,[10,12] and measurement of inspiratory duty cycle.[10,13] The aim of the current study was to use these measures to assess gas exchange and breathing patterns in children with CF matched by age and BMI to snoring controls undergoing evaluation for obstructive sleep apnea (OSA). We hypothesized that children with CF compared with snoring controls would exhibit breathing pattern alterations and gas exchange abnormalities not reflected by conventional polysomnographic markers of sleep apnea disease severity.

METHODS

Subjects and Study Design

We reviewed PSG in a total of 43 subjects, 19 with CF and 24 controls, who had undergone clinical sleep evaluation at a tertiary pediatric care center for a history of snoring and sleep disruption with concern for possible OSA. Of the 24 control subjects, 7 were excluded because we could not identify sufficient duration of the nasal pressure signal owing to dislodgement of the nasal cannula or mouth breathing, which prevented obtaining an accurate airflow signal for the detection of IFL. Of the 19 CF subjects, 6 were excluded on the basis of (1) incomplete pulmonary function test (PFT) data for subjects <6 years of age (n = 3) and (2) inaccurate conversion of airflow signals from the PSG tracing for the detection of IFL (n = 3).

Of the remaining 13 CF subjects and 17 controls, 10 pairs were matched by age. According to review of clinical records, none of the subjects had undergone adenotonsillectomy before PSG. Children with CF were not being treated for pulmonary exacerbation at the time of PSG. Many of the control subjects were referred to a tertiary center only for the sleep study, which limited the availability of clinical data, including history of other existing respiratory conditions, prescribed therapies, physical examination of the upper airway, or pulmonary function assessment. This retrospective analysis was reviewed and approved by the Johns Hopkins University Institutional Review Board (NA_00073417).

Polysomnography

Overnight sleep studies were recorded digitally on specialized stationary workstations or portable units (REM-Logic v1.1, Med-care, Boca Raton, FL). Physiologic signals included right and left electrooculogram, submental electromyogram, electrocardiogram, and EEG (C_4M_1, O_1M_2, and F_4M_1). Respiratory effort via thoracoabdominal strain gauge and continuous pulse oximetry were measured. Alterations in systemic CO_2 were monitored by transcutaneous probe ($tcCO_2$), and alterations in arterial oxygen by oxyhemoglobin saturation (SaO_2) with standard pulse oximeters. SaO_2 and $tcCO_2$ were quantified separately by the duration and magnitude of episodic changes during sleep. Mean SaO_2 and $tcCO_2$ for the total sleep period and the percentage of total sleep time spent with hypoxia (SaO_2 <90%) and hypercapnia ($tcCO_2$ >50 mm Hg) served as key markers of blood gas disturbances.[14]

Sleep and Respiratory Events

Standard PSG scoring techniques were used to stage sleep, arousals, and respiratory events.[15] The respiratory disturbance index (RDI) was calculated for obstructive and central respiratory events per hour of sleep separately for each individual for the entire night. Apnea and hypopnea indices were calculated separately as events per hour of sleep for each individual during periods of non–rapid eye movement (NREM) and rapid eye movement (REM) sleep.

Breathing Pattern Analysis

The nasal cannula signal was used to assess the respiratory pattern and

prevalence of IFL as previously described[10] during periods of quiet wakefulness, NREM sleep, and REM sleep. Airflow analysis included measurement of respiratory rate, duration of inspiration, and duration of the entire respiratory cycle. We used a custom computer program that randomly generated three 3-minute samples per hour of sleep. IFL was identified as previously described[13,16,17] by visual inspection of airflow tracings during defined periods of stable NREM sleep in the absence of arousal artifacts (Fig 1). In brief, IFL was defined when inspiratory airflow showed the following characteristics: flattened contour with an early inspiratory flow maximum (VI_{max}), high-frequency oscillation, and prolonged inspiratory time.[13] IFL was quantified as a percentage of the flow-limited breaths relative to the total number of breaths in the 3-minute samples during NREM sleep.[10]

Statistical Considerations

Data are reported as median ± SD unless otherwise specified. Demographic and clinical characteristics were summarized using medians and ranges. Analyses were performed using Student *t* tests. All reported *P* values are 2-sided, and significance was set at $P < .05$.

RESULTS

Study Population

Of the sample of 43 children with CF and snoring controls, we identified 10 pairs matched by age to compare PSG indices in NREM and REM sleep. Ten age-matched children with CF (7 boys, 3 girls) and 10 snoring control subjects (5 boys, 5 girls) (Table 1) were eligible for PSG analysis. In these pairs, 6 subjects (4 CF, 2 snoring controls) completed sleep studies of <360 minutes. The apnea hypopnea index and SaO_2 of these 6 subjects were similar to those of the respective groups as a whole.

Median age for both groups was 9.6 ± 3.6 years. Median BMI was 17.5 ± 1.9 kg/m^2 for the CF group and 19.1 ± 2.8 kg/m^2 for the snoring control group ($P = .16$). Median BMI *z*-score was 0.07 ± 0.92 for the CF group and 0.53 ± 0.96 for the snoring control group ($P = .08$) (Table 1). Pulmonary function data were available only for the CF group (median predicted forced expiratory volume in 1 second [FEV_1] 87% ± 25.7% [range 36% to 115%]). Predicted FEV_1 was <50% for 1 CF subject, between 50% and 80% for 4, and >80% for 5.

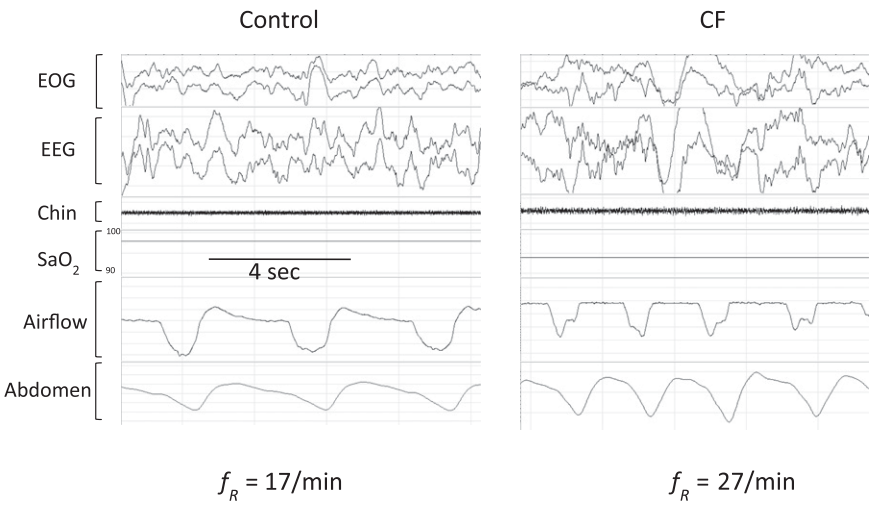

FIGURE 1
Representative PSG tracings in control and CF subjects. Representative PSG tracings from two 7-year-old subjects depict breathing patterns and rates during NREM sleep. The control subject shows SaO_2 97%, normal respiratory rate, and rounded airflow tracing. The CF subject shows SaO_2 95%, a sawtooth tracing indicative of inspiratory flow limitation, and tachypnea.

Comparison of Standard PSG Data

In children with CF compared with age- and BMI-matched snoring controls, there was no difference in total sleep time, sleep efficiency, or the proportions of NREM and REM sleep (Table 2). RDI did not differ in children with CF compared with snoring controls (1.5 ± 2.7 vs 0.6 ± 0.6 events per hour, $P = .11$), and did not indicate clinically significant OSA in either group. There were no differences between the 2 groups in apnea or hypopnea indices during NREM or REM sleep.

Gas Exchange Parameters During Sleep

The SaO_2 nadir was lower in children with CF compared with age- and BMI-matched snoring controls (91% ± 3.7% vs 94% ± 1.6%, $P = .03$). Although average SaO_2 was similar in children with CF and snoring controls during wakefulness (97% ± 2.1% vs 98% ± 0.7%, $P = .1$), it was lower in children with CF during both NREM sleep (95% ± 1.6% vs 98% ± 0.5%, $P = .005$) and REM sleep (96% ± 1.7% vs 98% ± 0.6%, $P = .05$). There were no differences in mean CO_2 measurements during wakefulness, NREM sleep, or REM sleep or in peak end tidal CO_2 ($ETCO_2$) levels in children with CF compared with healthy controls (Table 2).

Respiratory Pattern During Sleep

Children with CF exhibited higher respiratory rates during NREM sleep (19.5 ± 4.9 vs 16.5 ± 1.2 breaths per minute, $P = .03$) but not during either REM sleep (20.1 ± 2.4 vs 17.3 ± 5.8 breaths per minute, $P = .28$) or quiet wakefulness (22.4 ± 3.5 vs 19.5 ± 4.8 breaths per minute, $P = .17$) (Table 3). There was no difference in the inspiratory duty cycle between the CF and snoring control groups

TABLE 1 Demographic and Anthropometric Data in CF and Control Subjects Matched by Age and BMI

Characteristic	CF	Control	*P*
n	10	10	
Male gender, %	70	50	
Age, y	9.6 ± 3.6	9.6 ± 3.6	
BMI, kg/m^2	17.5 ± 1.9	19.1 ± 2.8	.16
BMI, *z*-score	0.07 ± 0.92	0.53 ± 0.96	.08
FEV_1, % of predicted	87 ± 25.7	—	

Values are expressed as median ± SD. *P* values are derived from Student *t* test.

during wakefulness, NREM sleep, or REM sleep (Table 3).

Inspiratory Flow Limitation During NREM Sleep

The prevalence of IFL during stable NREM sleep in children with CF was ~4-fold higher (Table 3) than in age- and BMI-matched snoring controls (44.1% ± 24.7% vs 12.1% ± 13.5%, $P = .007$).

DISCUSSION

The major findings of our study were that children with CF compared with snoring controls exhibited lower SaO_2 during sleep, independently of age, BMI, and lung function, that was not apparent during wakefulness. Moreover, children with CF demonstrated a higher respiratory rate and proportion of IFL during NREM sleep compared with snoring controls, indicating that children with CF also have increased respiratory loads during sleep.

Previous work has established that children and adults with CF, particularly those with advanced lung disease, exhibit sleep disruption, increased arousal frequency, and gas exchange abnormalities during sleep.[2] However, the correlation between pulmonary function and the onset of sleep-related hypoxemia in CF is modest, and the most sensitive predictor of nocturnal hypoxemia is daytime hypoxemia.[18] Some studies show that OSA is prevalent in infants and young children with CF.[5] OSA in older children and adults with CF can be related to increased upper-airway resistance from adenotonsillar hypertrophy and other associated conditions such as nasal polyposis and chronic pansinusitis.[1,7] In our study, children and adolescents with CF did not meet clinical PSG criteria for a diagnosis of OSA. Nevertheless, children with CF showed a higher respiratory rate and lower SaO_2 during NREM and REM sleep that was not apparent during wakefulness. Thus, sleep state may serve as a diagnostic window for early detection of CF lung disease progression.

Whereas mean SaO_2 was similar between groups during wakefulness, we observed significant SaO_2 reductions during NREM and REM sleep. Even though lower SaO_2 may be related to chronic lung and lower-airway disease, the similar SaO_2 values during wakefulness between the 2 groups suggests that children with CF may recruit compensatory mechanisms to defend impairments in lung function and maintain adequate ventilation. In contrast, the lower SaO_2 during sleep suggests that compensatory mechanisms are inadequate because of a loss of volitional efforts to maintain ventilation, such as upright posture and increased respiratory effort and rate. Alternatively, sleep may aggravate hypoventilation, which arises from rapid shallow breathing or inspiratory flow limitation, as previously shown.[1,2,10,19] In our study, we demonstrate an increase in respiratory rate during NREM and REM sleep and the proportion of IFL during NREM sleep, which represents the major proportion of sleep. Regardless of the mechanism, it appears that both NREM and REM

TABLE 2 Standard PSG Data in CF and Control Subjects Matched by Age and BMI

Category	CF	Control	*P*
Sleep architecture			
TST, min	371 ± 103	392 ± 50	.35
Sleep efficiency, %	89.2 ± 24.3	83.3 ± 10.1	.99
NREM, % of TST			
Stage 1	0.7 ± 2.9	0.5 ± 1.7	.29
Stage 2	49.8 ± 8.5	55.5 ± 10.0	.18
Stage 3	25.7 ± 15.4	27.7 ± 9.1	.71
REM, % of TST	19.9 ± 9.6	18.8 ± 3.5	.54
Airway obstruction			
RDI, events/h	1.5 ± 2.7	0.6 ± 0.6	.11
Apnea index, events/h			
NREM	0.0 ± 0.6	0.1 ± 0.5	.80
REM	1.0 ± 1.8	1.0 ± 1.1	.51
Hypopnea index, events/h			
NREM	0.4 ± 2.5	0.0 ± 0.1	.06
REM	1.0 ± 2.2	0.0 ± 0.5	.13
Gas exchange			
Mean SaO_2, %			
Wake	97 ± 2.1	98 ± 0.7	.10
NREM	95 ± 1.6	98 ± 0.6	.005
REM	96 ± 1.7	98 ± 0.6	.05
SaO_2 nadir, %	91 ± 3.7	94 ± 1.6	.03
Mean CO_2, mm Hg			
Wake	40.1 ± 1.8	42.7 ± 4.1	.91
NREM	41.6 ± 2.0	43.9 ± 4.2	.99
REM	41.9 ± 2.7	43.6 ± 4.0	.88
Peak $ETCO_2$, mm Hg	49 ± 4.7	49 ± 4.3	.97

Values are expressed as median ± SD. TST, total sleep time. *P* values are derived from Student *t* test.

TABLE 3 Breathing Pattern Analysis in CF and Control Subjects Matched by Age and BMI

Pattern	CF	Control	*P*
Respiratory rate, *f*			
Wake	22.4 ± 3.5	19.5 ± 4.8	.17
NREM	19.5 ± 4.9	16.5 ± 1.2	.03
REM	20.1 ± 2.4	17.3 ± 5.8	.28
NREM IFL, %	44.1 ± 24.7	12.1 ± 13.5	.007
IFL >30%, %	70	20	
Heart rate, bpm			
Wake	90.3 ± 17.8	88.1 ± 11.5	.35
NREM	80.5 ± 13.7	77.5 ± 8.8	.50
Inspiratory duty cycle, T_i/T_{tot}			
Wake	0.43 ± 0.05	0.40 ± 0.02	.11
NREM	0.43 ± 0.06	0.39 ± 0.03	.22

Values are expressed as median ± SD. bpm, beats per minute; T_i, inspiratory time; T_{tot}, total respiratory cycle time. *P* values are derived from Student *t* test.

sleep are associated with worsening SaO_2.

An unexpected finding was the markedly higher rate of IFL during NREM sleep in children with CF compared with snoring controls, while both groups demonstrated similar RDIs. We were unable to quantify the amount of IFL during REM sleep primarily because many CF and control subjects did not have a sufficient number of stable periods without arousals. Moreover, demonstration of IFL in REM sleep requires esophageal pressure measurement, which was not part of the clinical PSG protocol. Children are known to demonstrate partial upper airway obstruction in both REM and NREM sleep.[10,20] In this study, we quantified the proportion of IFL only during NREM sleep because NREM sleep constituted a significant proportion of the night's sleep during which breaths could be characterized without arousals or awakenings.

Although we anticipated some degree of IFL based on the history of snoring in both groups, we expected a lower rate in the CF population because of the slightly lower BMI in these children (Table 1). IFL in children is known to be associated with adenotonsillar hypertrophy, severe obesity, abnormalities of mandibular or maxillary structure, and increased nasal resistance.[10,11] Although tonsillar hypertrophy and obesity were not noted in our study population, it is possible that the CF group had either some degree of mandibular or maxillary narrowing or increased upper-airway resistance related to nasal polyposis or chronic sinus disease that contributed to the increase in IFL. Alternatively, increases in intrapulmonary airway resistance may have increased respiratory effort and markedly lowered inspiratory tracheal pressure swings, since IFL occurs when tracheal pressure falls below a threshold known to collapse the upper airway.[10] Regardless of the mechanism, IFL is known to further increase respiratory effort and inspiratory loads.[10,21] In our study, based on the findings of increased IFL and respiratory rate, sleep in children with CF, which included children with normal lung function, was associated with markedly increased respiratory loads that may have contributed to lower SaO_2 during NREM and REM sleep.

In our study, $ETCO_2$ values were comparable in children with CF with mild to severe lung disease and snoring controls, although the study groups were not large or homogeneous enough to demonstrate differences. Elevations of CO_2 during sleep are known to induce an increase in respiratory rate to a greater extent than hypoxemia. $ETCO_2$ is known to be underestimated in the setting of both chronic lung disease and tachypnea, and was likely underestimated in the CF group.[2] For this reason, $tcCO_2$ measurements are preferred, but reliable and reproducible measurements were likely not obtained or reported as part of the clinical PSG protocol or interpretation.

This study has several strengths. First, we included comparisons of children with CF to a control group matched by age and BMI, which is often lacking in case series studies. Second, we compared wakefulness to sleep in both groups, which allowed us to use each group as its own control. Third, the assessment of sleep disordered breathing was more sensitive compared with conventional methods, since IFL was classified using the unfiltered airflow signal from the nasal cannula with a novel method to assess upper-airway obstruction as previously published.[13]

Limitations of our study include the small sample size because of the use of data from existing sleep studies. A further limitation of the study was the retrospective review of symptoms leading to clinical assessment by PSG. The CF group could not be completely characterized with respect to lung disease severity because not all subjects had available PFTs with small-airway disease parameters, lung volume measurements, diffusion capacity, or chest imaging studies that coincided with the timing of the PSG. In addition to limited clinical historical data, we did not have lung function data for the snoring controls, but we believe it was reasonable to assume normal lung function in this group.

Although we included snoring controls and excluded individuals with a documented history of sleep apnea, it is possible that the clinical record did not accurately reflect all of the symptoms and findings that led to the sleep study evaluation. Because snoring is a symptom of sleep disordered breathing that is

accompanied by increased respiratory effort, systemic inflammation, and sleep pattern alterations,[9,22–25] the snoring control group does not represent a group of healthy children,[26] though some studies have described IFL of ≤30% in healthy individuals.[27] Snoring and sleep disordered breathing are rarely seen in healthy, normal-weight children and are more prevalent in children with obesity and adenotonsillar hypertrophy.[28] None of these conditions was present in our CF population. Nevertheless, we speculate that differences in IFL, respiratory rate, and gas exchange in children with CF compared with a healthy nonsnoring group may be more prominent than the findings reported in this study.

There are several important clinical implications of this study. First, in children with mild lung disease, the evaluation of sleep provides a unique diagnostic opportunity to reveal potential ventilatory compromise that is not exhibited during wakefulness. Thus, sleep-related disturbances in breathing patterns may serve as an early marker for disease progression. Second, assessment of sleep disordered breathing in children with chronic lung diseases should include measurement of IFL and respiratory rate. Because IFL is known to affect growth, development,[29,30] neurocognitive function,[31] and school performance[30] in children with OSA, our findings of increased respiratory rate and increased IFL during sleep in children with CF may contribute further to increased caloric expenditure and declines in growth, nutritional status, and development in a population already at risk for hastened lung disease progression.

CONCLUSIONS

We conclude that children with mild CF lung disease exhibit abnormalities in gas exchange and increased respiratory loads during sleep compared with age- and BMI-matched controls with snoring. Because these abnormalities were independent of weight and lung function, sleep state may serve as an opportunity for early detection of breathing abnormalities and possibly CF lung disease progression. We conclude that sleep state may serve as a diagnostic window for early detection of CF lung disease progression and that sleep, even in mild CF lung disease, is associated with increased respiratory loads.

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ABBREVIATIONS

CF: cystic fibrosis
$ETCO_2$: end tidal CO_2
FEV_1: forced expiratory volume in 1 second
IFL: inspiratory flow limitation
NREM: non–rapid eye movement
OSA: obstructive sleep apnea
PFT: pulmonary function test
PSG: polysomnography
RDI: respiratory disturbance index
REM: rapid eye movement
SaO_2: oxyhemoglobin saturation
$tcCO_2$: transcutaneous CO_2
VI_{max}: inspiratory flow maximum

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