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Predictive value of respiratory parameters in patients with obstructive sleep apnea and chronic heart failure with preserved ejection fraction

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Abstract

Aim. To study individual functional parameters of respiration in different phases of sleep in patients with obstructive sleep apnea (OSA) and chronic heart failure with preserved ejection fraction (HFpEF) and to assess their effect on the clinical course of the disease.

Methods. The study included 86 men with OSA [with an apnea-hypopnea index (AHI) ≥15 per hour]. Upon inclusion in the study, all patients underwent a polysomnographic study and echocardiography, the level of brain natriuretic peptide (NT-proBNP) was determined, a six-minute walk test was performed. After 12 months of prospective observation, the patients were divided into 2 groups according to the clinical course of chronic heart failure: with unfavorable (n=33) and favorable (n=53) clinical course. The prognostic significance of the studied parameters of respiration to the course of the disease was assessed by using logistic and linear regression.

Results. A significant role of the following respiratory parameters as predictors of chronic heart failure progression was established: obstructive apnea-hypopnea index for the entire night sleep [odds ratio (OR) 1.04, p=0.002] and in the phase of rapid eye movement sleep (REM) (OR 1.24, p=0.001); the index of respiratory disorders for the entire sleep period (OR 1.06, p=0.044) and in REM sleep phase (OR 1.25, p=0.003). For hospital readmission, the predictive role was determined for obstructive apnea/hypopnea index for REM phase (OR 1.07, p=0.044) and index of respiratory disorders for REM phase (OR 1.13, p=0.040).

Conclusion. The prognostic value of the obstructive apnea-hypopnea index and the index of respiratory disorders for the entire night sleep and in the phase of REM sleep was revealed for patients with OSA and chronic heart failure with preserved ejection fraction, which allows considering these parameters as independent predictors of an unfavorable clinical course in this group of patients.

Keywords: chronic heart failure with preserved ejection fraction (HFpEF), obstructive sleep apnea, rapid eye movement sleep, apnea-hypopnea index.

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Background. Obstructive sleep apnea syndrome (OSAS) is characterized by a complex of specific respiratory disorders during sleep, which triggers secondary negative cardiovascular and neuroendocrine mechanisms that contribute to abdominal obesity and cardiovascular complications. At present, data from major clinically controlled prospective studies demonstrated the relationship of OSAS with arterial hypertension, cardiac arrhythmias, and conduction abnormalities, as well as increased sudden cardiac death risk at night [1,2].

The OSAS problem is urgent because of its particularly widespread prevalence; according to various authors, its detection rate reaches 5%–7% in

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the adult population [3,4]. There are no accurate data on the epidemiology of OSAS in the Russian Federation, but considering the high prevalence of the main risk factors for this syndrome (overweight, smoking, and thyroid pathology), its rather high prevalence in the Russian population can be predicted.

Key links in the OSAS pathogenesis include the overload of the right heart compartment due to a periodic increase in intra-abdominal pressure during apnea with pulmonary hypertension formation in the presence of intermittent nocturnal hypoxemia with subsequent hyperactivation of the sympathetic nervous and renin-angiotensin-aldosterone systems, the development of endothelial dysfunction and hypoxic vasoconstriction of small pulmonary arteries, and the activation of the N-terminal pro-brain natriuretic peptide (NT-proBNP) [5, 6]. Apparently, these factors initiate the emergence and progression of global right ventricular dysfunction and pulmonary hypertension with the formation of chronic cor pulmonale at a certain stage.

The mechanism of dysfunction formation of the left heart compartments in OSAS is mainly mediated by secondary arterial hypertension with the formation of myocardial hypertrophy of the left heart compartments and diastolic dysfunction resulting in chronic heart failure (CHF) with preserved ejection fraction (CHFpEF). Thus, as OSAS and its characteristic cascade of neurohumoral pathogenetic mechanisms progress, CHFpEF is most possible to be formed at a certain stage with elements of diastolic dysfunction of both right and left heart compartments with corresponding clinical manifestations [7].

The presence of OSAS can be considered an important comorbid background in a significant number of CHF patients, based on the fact that breathing disorders during sleep in these patients are not the only cause of CHF formation. According to different authors, breathing disorders during sleep occur in 50%–80% of cases with heart failure, whereas the prevalence of OSAS in CHF patients is approximately 18%, which significantly exceeds the general population indicators [8].

Specific patterns of pathological respiration characteristic of CHF patients include central sleep apnea, which is pathophysiologically based on Cheyne–Stokes respiration [9]. There are many indications associating increased cardiovascular risk and unfavorable CHF clinical course with central sleep apnea onset [10].

However, elements of central apnea are often described in patients with severe OSAS, which is combined in these patients with typical obstructive episodes. According to published research results, the adverse clinical course and mortality of CHF patients in the presence of central sleep apnea correlated with such electrophysiological parameters of the polysomnographic study including the apnea/hypopnea index (AHI), the central apnea index, the number of arousals per h, and the percentage superficial stages of sleep to total sleep time. However, these works discuss CHF with a reduced EF and pronounced clinical CHF presentation, namely, the functional class (FC) 3–4 according to the classification of the New York Heart Association (NYHA) [11]. Studies of the sleep structure and different breathing patterns involving CHFpEF patients are few, and the results presented in the publications are contradictory.

The most accurate method for diagnosing OSAS is polysomnography, which not only identifies pathological respiratory events but also allows correlation between true sleep duration and structure. Thus, because of a specific polysomnographic presentation, the rapid eye movement (REM) sleep phase can be identified and distinguished from the rest of the sleep period, which is the non-REM (NREM) sleep phase. Researchers' particular interest has always been associated with REM sleep, which is characterized by the suppression of other motor activities, decrease of skeletal muscle tone, and generation of cardiac and respiratory arrhythmias accompanied by the emergence of low-amplitude desynchronized activity on the electroencephalogram. As a result of such study, the main quantitative indicator of respiratory disorders, AHI, is assessed, and arousals are also possible to register, which are associated with respiratory efforts that are considered when calculating the respiratory distress index (RDI).

The literature presents data on an increase in the respiratory disorder frequency in the REM sleep phase, as well as their special prognostic significance in terms of cardiovascular complication development [12, 13]. This is associated with a decrease in the tone of most muscles, as well as additional hyperactivation of the sympathetic nervous system, which creates circumstances for the aggravation of respiratory disorders and negative reactions from the cardiovascular system. Several researchers believe on the fact that an increase in pulmonary artery pressure during obstructive apnea development during the REM phase of sleep, regardless of the degree of arterial hypoxemia, has been proven [14].

The prognostic role of pathological breathing patterns in different phases of nocturnal sleep in patients with OSAS and CHFpEF has not been sufficiently studied. The practical significance of further research is determined by the possibility of more accurate risk stratifications in this pa-

tient cohort and the development of personalized approaches to therapy with a more aggressive and early therapeutic strategy in the high-risk group.

The study aimed to analyze individual functional parameters of respiration in different phases of sleep in patients with OSAS and CHFpEF and to assess their impact on the disease clinical course.

Materials and methods. The study protocol was approved by the local ethics committee of the Novosibirsk Clinical Hospital "RZhD-Medicine" (protocol no. 28 dated 04/16/2018). All patients gave written informed consent to participate in the study. The study participants were men who met the following inclusion criteria:

1) moderate and severe OSAS (with AHI ≥ 15/h),

2) arterial hypertension, including in patients with stabilized blood pressure (BP) in the course of antihypertensive drug therapy, and

3) abdominal obesity with waist circumference of ≥ 92 cm and body mass index (BMI) ≥ 30 kg/m^2.

Exclusion criteria:

1) primary pulmonary hypertension;

2) history of pulmonary artery thromboembolism;

3) severe bronchial asthma and severe chronic obstructive pulmonary disease;

4) valvular heart apparatus lesions (insufficiency of the mitral, tricuspid, or aortic valve of degree 2 or higher);

5) hypertrophic and dilated cardiomyopathy;

6) ischemic heart disease;

7) chronic atrial fibrillation;

8) CHF with reduced and intermediate EF (EF < 50%);

9) thyroid gland pathology, severe renal and/or hepatic failure (glomerular filtration rate of lower than 30 mL/min/m^2 according to the Chronic Kidney Disease Epidemiology Collaboration formula);

8) refusal to participate in the study.

To diagnose OSAS, all patients underwent a polysomnographic study of nocturnal sleep using the Somnolab 2PSG diagnostic system (Weinemann, Germany). The severity of obstructive breathing disorders during sleep was assessed by AHI. The study included patients with moderate (15 ≤ AHI < 30/h) and severe (AHI ≥ 30/h) OSAS. The average nocturnal saturation level (SpO_2av.), desaturation index, central sleep apnea index, and RDI were also evaluated by assessing these parameters for the entire sleep period and selectively in the REM sleep phase. A 6-min walk test was performed on all patients enrolled. The blood serum NT-proBNP level *in vitro* was determined by enzyme-linked immunosorbent assay using NTproBNP-IFA-BEST reagents (Vektor-Best, Russia) on a Multiskan FC analyzer (China).

The study included 86 men with moderate and severe OSAS (AHI ≥ 15/h) and mean age of 54 ± 1.5 [31.0; 78.0] years. Abdominal obesity (waist circumference > 92 cm) was diagnosed in all patients enrolled in the study, with BMI exceeding 30 kg/m^2 in all of them; all patients had arterial hypertension, but at the time of study inclusion, the patients achieved target BP levels using the most suitable antihypertensive drug therapy. In accordance with NYHA, CHF FC I was diagnosed in 33.7% of patients (n = 29) and CHF FC II in 39.5% (n = 34), and in other cases (n = 23), the 6-min walk test distance was >550 m. At the same time, the NT-proBNP level in all cases exceeded the above 125 pg/mL reference value.

After 12 months of prospective follow-up, the patients were retrospectively divided into two groups depending on the CHF course. Groups 1 (n = 33) and 2 (n = 53) included patients with unfavorable and favorable CHF courses, respectively. The criteria for the unfavorable CHF course include the development of new CHF cases or progression according to the 6-min walk test (with the transition to a more severe class by NYHA) and the development of clinically significant cardiac arrhythmias during the follow-up period (12 months).

Echocardiography was performed in all patients based on the standard protocol using an EPIQ device (Philips Ultrasound, Inc., USA).

Patient groups were comparable in terms of comorbid pathology and risk factors (Table 1).

The parameters of breathing disorders in the nocturnal sleep period were studied using polysomnography, including obstructive apnea/hypopnea index for the entire sleep period (AHIobs.), AHIobs. in REM sleep phase (AHIobs.REM), central apnea/hypopnea index, RDI for the entire sleep period and REM sleep, SpO_2av., and desaturation indices for the entire sleep period and REM sleep phase.

All calculations were performed using the R software package, version 4.0.2. Logistic and linear regressions were used to study the relationship of predictors with dichotomous outcomes and assess the association of predictors with continuous outcomes, respectively. The uncorrected models were used as well as models corrected for age and BMI. Regression analysis results are presented as β-ratios for continuous outcomes and odds ratios (OR) for dichotomous outcomes. The critical p-value significance level for all analysis procedures was 0.05.

Results. The groups of patients at the inclusion stage were comparable according to the main structural and functional echocardiographic parameters, such as cardiac chamber size and volume, left ventricular EF, fractional right ventricle area change, work index of the right ventricular myocardium,

Table 1. Clinical and demographic characteristics of the patients examined

Indicator	Group 1 (n = 33)	Group 2 (n = 53)	p-value
Age, years	52 [33; 71]	50 [31; 78]	0.717
Body mass index, kg/m^2	36.1 [30.1; 74.8]	36.8 [30.06; 77.2]	0.268
CHF FC I (NYHA), n (%) CHF FC II (NYHA), n (%)	8 (24.2) 15 (45.5)	21 (39.6) 19 (35.8)	0.142 0.069
NT-proBNP, pg/mL	338 [168; 678]	278 [177; 815]	0.024
6-min walk test, m	416 [318; 634]	527 [318; 640]	0.014
SBPav., mmHg DBPav., mmHg	132 [128; 138] 88 [75; 94]	134 [128; 136] 88 [78; 95]	0.376 0.431
COPD, n (%)	9 (27.3)	13 (24.5)	0.345
Smoking, n (%)	12 (36.4)	15 (28.3)	0.877
Dyslipidemia, n (%)	17 (51.5)	23 (43.4)	0.453
Diabetes mellitus, n (%)	6 (18.2)	9 (17.0)	0.120

Note: CHF, chronic heart failure; FC, functional class; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; SADav., average daily systolic blood pressure; DBPav., average daily diastolic blood pressure; COPD, chronic obstructive pulmonary disease.

Table 2. Average values of the parameters under study depending on the progression of chronic heart failure (according to the 6-min walk test)

Parameters studied	β-coefficient, 95% CI, uncorrected p	β-coefficient, 95% CI, p corrected for age and BMI
Age	−0.01 (from −0.90 to 0.88, p = 0.974)	−0.06 (from −0.92 to 0.80, p = 0.889)
BMI	−1.36 (from −2.37 to −0.36, p = 0.009)	−1.37 (from −2.38 to −0.35, p = 0.009)
AHIobs.	−1.16 (from −1.51 to −0.81, p < 0.001)	−1.11 (from −1.49 to −0.74, p < 0.001)
REM sleep AHIobs.	−1.15 (from −1.48 to −0.82, p < 0.001)	−1.11 (from −1.47 to −0.75, p < 0.001)
Central apnea/hypopnea index	−1.79 (from −2.62 to −0.96, p = 0.068)	−1.72 (from −2.54 to −0.91, p < 0.001)
RDI	−1.50 (from −1.93 to −1.08, p < 0.001)	−1.46 (from −1.90 to −1.01, p < 0.001)
REM sleep RDI	−1.31 (from −1.73 to −0.89, p < 0.001)	−1.25 (from −1.68 to −0.81, p < 0.001)
SpO_2av.	3.31 (from 0.95 to 5.68, p = 0.071)	2.71 (from 0.29 to 5.12, p = 0.028)
REM sleep DI	−1.21 (from −1.67 to −0.75, p < 0.001)	−1.13 (from −1.65 to −0.61, p < 0.001)

Note: CI, confidence interval; BMI, body mass index; AHIobs., obstructive apnea/hypopnea index for the entire sleep period; RDI, respiratory distress index; SpO_2av., average night saturation level; DI, desaturation index; REM, rapid eye movement.

systolic pressure in the right ventricle, and anterior wall thickness of the right ventricle.

According to the regression analysis results, a significant role of the breathing parameters (AHIobs., AHIobs.REM, RDI, and RDI in the REM sleep phase) was established as CHF progression predictors according to the 6-min walk test, which were predictors of an unfavorable CHF course. Meanwhile, the SpO_2av. level and central apnea severity indicators did not reveal significant correlations with CHF clinical course (Table 2).

The logistic regression analysis revealed a significant role of the respiratory parameters as predictors of CHF progression, assessed by the transition to a more severe NYHA class (Table 3), namely, AHIobs., AHIobs.REM, RDI, RDI REM, and DI in REM sleep phase, which were predictors of unfavorable CHF course. Meanwhile, the SpO_2av. level and the central AHI did not reveal any significant correlations with CHF clinical course.

When analyzing repeated hospitalizations for cardiovascular diseases and their relationship with the parameters under study, the predictive value was established significantly only for the AHIobs. REM and RDI in the REM sleep phase. No significant associations with repeated hospitalizations were found in the rest of the parameters (Table 4).

Discussion. The prognostic role of the hyperactivation phenomenon as an additional diagnostic criterion for respiratory distress during nocturnal sleep is consistently congruent with the classic pathogenetic model of the cardiovascular continuum of CHF development, reflecting the role of hypersympathicotonia as one of the ma-

Table 3. Average values of the parameters under study depending on the presence or absence of chronic heart failure progression (according to the transition to a more severe class by NYHA)

Parameters studied	No progression	Progression	OR (95% CI, *p*)	OR (95% CI, *p*), analysis corrected for age and BMI
Age, years	51.3 (10.1)	51.6 (8.8)	1.00 (0.96–1.05. p=0.861)	—
BMI, kg/m^2	37.1 (7.3)	39.6 (9.3)	1.04 (0.98–1.11. p=0.177)	—
AHIabs., per h	33.7 (18.3)	48.2 (19.3)	1.04 (1.02–1.07. p=0.002)	1.04 (1.01–1.07. p=0.004)
AHIobs. in REM sleep, per h	33.3 (18.5)	49.6 (20.0)	1.24 (1.02–1.07. p=0.001)	1.14 (1.02–1.07. p=0.002)
Central apnea/hypopnea index, per h	13.9 (8.9)	18.3 (9.4)	1.05 (1.00–1.11. p=0.068)	1.05 (1.00–1.11. p=0.074)
RDI, per h	10.0 (7.2)	12.5 (5.1)	1.06 (0.99–1.14. p=0.044)	1.06 (0.99–1.14. p=0.098)
RDI in REM sleep, per h	33.8 (15.4)	44.9 (14.7)	1.25 (1.02–1.08. p=0.003)	1.35 (1.01–1.08. p=0.005)
DI, per h	17.2 (9.2)	19.4 (9.4)	1.03 (0.98–1.08. p=0.290)	1.02 (0.97–1.07. p=0.404)
SpO_2av., %	91.9 (4.0)	91.7 (2.4)	0.99 (0.87–1.13. p=0.858)	1.01 (0.89–1.18. p=0.871)
DI in REM sleep, per h	35.8 (14.1)	49.5 (15.9)	1.06 (1.03–1.10. p <0.001)	1.06 (1.03–1.11. p=0.001)

Note: NYHA, New York Heart Association; OR, odds ratio; CI, confidence interval; BMI, body mass index; AHIobs., obstructive apnea/hypopnea index for the entire sleep period; RDI, respiratory distress index; DI, desaturation index; SpO_2av., average night saturation level; REM, rapid eye movement.

jor factors of cardiovascular risk. In this regard, such an indicator as RDI, which also considers arousal as a polysomnographic phenomenon that reflects a characteristic transition to a more superficial stage of sleep at the time of apnea, in addition to actual cessation of respiratory activity, may have additional diagnostic and prognostic significance, as demonstrated in this study. At the same time, this parameter probably not only reflects the respiratory distress degree in OSAS but also serves to a certain extent as an indicator of autonomic instability in general, which increases its prognostic role.

The differentiated assessment of respiratory parameters in different sleep phases is worth mentioning as a separate point. The neurohumoral shift aspects noted in the REM sleep phase, with a characteristic imbalance of the autonomic nervous system toward the prevalence of the sympathetic component and an increase in catecholamine concentration, followed by the corresponding hemodynamic changes (increased heart rate and BP), create additional circumstances for the implementation of cardiovascular risks in this sleep phase. The increase in the frequency of acute coronary events and strokes in the predawn time, when the contribution of REM sleep to the structural sleep cycle is maximal, has long been known in practical medicine.

However, there are data on the aggravation of obstructive respiratory distress during sleep with pronounced forms of OSAS in the REM sleep phase due to an obvious decrease in muscle tone [14]. At a certain extent, this can explain the additional prognostic value revealed when assessing the studied parameters of respiration in the REM sleep phase (AHI and RDI in this phase).

The lack of correlations between the CHF clinical course and parameters characterizing the degree of nocturnal hypoxemia, namely, the SpO_2av. and desaturation index levels, can be considered to some extent unexpectedly. In relation to the nocturnal hypoxemia degree and SpO_2av., the most convincing data were previously obtained with regard to their prognostic value. Thus, in one of the largest studies on this problem [15] (10,701 patients with a 5-year follow-up), a significant correlation was revealed in the SpO_2av. level with the frequency of sudden cardiac death in CHF patients.

In this study, the strongest predictors of sudden cardiac death were age over 60 years (OR 5.53), AHI > 20 (OR 1.60), mean overnight saturation lower than 93% (OR 2.93), and minimal overnight saturation lower than 78% (OR 2.60; all *p*-values were lower than 0.0001). At the same time, this study included patients with severe structural myocardial pathology (ischemic heart disease and cardiomyopathies), and many of them had CHF with reduced EF, which did not affect the study results. In a cohort of more intact patients with less pronounced structural changes and preserved EF, the prognostic value of the nocturnal hypoxemia level will probably be less pronounced, where the first positions belong to indicators that directly characterize disorders in breathing dynamics in OSAS, namely, AHI and RDI, which has been demonstrated.

The probable pathogenetic mechanism of the diastolic dysfunction occurrence with an outcome of CHFpEF consists of gradual secondary arterial

Table 4. Average values of the parameters under study, depending on the presence and absence of repeated hospitalizations for cardiovascular diseases

Parameters studied	No repeated hospitalizations	Repeated hospitalizations	OR (95% CI, *p*)	OR (95% CI, *p*), analysis corrected for age and BMI
Age, years	51.1 (9.7)	52.0 (9.5)	1.01 (0.96–1.06. p=0.679)	—
BMI, kg/m^2	38.1 (7.2)	37.8 (10.1)	1.00 (0.93–1.05. p=0.880)	—
AHIabs., per h	37.7 (19.1)	42.8 (21.4)	1.01 (0.99–1.04. p=0.268)	1.02 (0.99–1.04. p=0.199)
AHIobs. in REM sleep, per h	38.1 (19.7)	47.6 (22.3)	1.07 (0.99–1.03. p=0.044)	1.08 (0.99–1.04. p=0.016)
Central apnea/hypopnea index, per h	15.2 (9.7)	16.3 (8.5)	1.01 (0.96–1.06. p=0.594)	1.01 (0.97–1.07. p=0.554)
RDI, per h	10.3 (6.7)	12.3 (6.4)	1.07 (0.98–1.12. p=0.212)	1.08 (0.98–1.13. p=0.184)
RDI in REM sleep, per h	37.9 (16.0)	38.2 (16.4)	1.13 (0.97–1.03. p=0.040)	1.10 (0.97–1.03. p=0.046)
DI, per h	16.8 (9.0)	20.8 (9.4)	1.05 (1.00–1.10. p=0.071)	1.05 (1.00–1.11. p=0.050)
SpO_2av., %	92.1 (3.0)	91.2 (4.2)	0.93 (0.81–1.06. p=0.248)	0.92 (0.79–1.05. p=0.212)
DI in REM sleep, per h	40.2 (15.6)	43.0 (17.6)	1.01 (0.98–1.04. p=0.463)	1.01 (0.98–1.05. p=0.361)

Note. The values of the parameters indicated are presented as mean values, with mean error in brackets. OR, odds ratio; CI, confidence interval; BMI, body mass index; AHIobs., obstructive apnea/hypopnea index for the entire sleep period; RDI, respiratory distress index; DI, desaturation index; SpO_2av., average night saturation level; REM, rapid eye movement.

hypertension development for the left heart compartment and chronic pulmonary hypertension for the right heart compartment. According to the published works on this problem, a direct relationship was recorded between AHI and arterial hypertension degree in OSAS [5].

The literature also presents direct correlation indications between AHI and pulmonary hypertension severity in severe OSAS, and some authors consider it proven that the pressure in the pulmonary artery increases during obstructive sleep apnea development during the REM sleep phase, regardless of the arterial hypoxemia degree [5]. The data obtained in the study are consistent with the high prognostic role of RDI during the REM sleep phase, which is superior in prognostic value to all other parameters studied.

When analyzing central sleep breathing distress in the study, correlations with the clinical CHF course did not reach a significant level. The evidence base for central sleep apnea, which main respiratory pattern is Cheyne–Stokes respiration, is limited mainly to the cohort of CHF patients and those with decreased EF [7]. Apparently, both the prevalence of this type of respiratory distress and its pathogenetic role in the CHFpEF patient category are less significant, which is consistent with the available literature data [7,9].

To clarify the prognostic role of individual respiration indicators during nocturnal sleep and to study the pathogenesis of cardiovascular complications in OSAS in more detail, it seems promising to evaluate these parameters in dynamics with a longer management of this patient cohort.

The results obtained enable us to evaluate the study markers as independent predictors of an unfavorable clinical course of the disease and to use them in the future to stratify the clinical risk and determine therapeutic management in these patients.

CONCLUSIONS

1. For patients with OSAS and CHFpEF, the breathing parameters during nocturnal sleep, namely, general AHIobs. index, REM sleep AHI, general RDI, and RDI in REM sleep, have prognostic significance.

2. These parameters characterizing the severity of OSAS can be considered independent predictors of unfavorable clinical course in this group of patients.

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