Russian Journal of Cardiology 2023;28(S2):5334
doi:10.15829/1560-4071-2023-5334
https://russjcardiol.elpub.ru

LITERATURE REVIEWS
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)
ISSN 2782-2257 (online)

The problem of cross risk of arterial hypertension progression, obstructive sleep apnea syndrome and COVID-19

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This review considers the risk factors for arterial hypertension (AH) progression, obstructive sleep apnea syndrome (OSAS) and novel coronavirus infection (COVID-19) as potential variables for the prognostic models of estimating the probability of destabilization of the mentioned conditions. The most published studies consider AH and OSAS as the risk factors influencing the course of COVID-19, while moderate and mild COVID-19 can be destabilizing factor regarding to AH and OSAS. In addition, COVID-19, AH and OSAS are interrelated with sleep quality. The worsening of sleep quality often can be both a consequence of these diseases and a factor aggravating their course, and also can cause the increased vulnerability to acute diseases. An increased body mass index is a universal risk factor for many diseases and clinical conditions, and the monitoring of body mass increases the degree of the control of the diseases associated with obesity. In addition, the worsening of sleep quality can be both a consequence of any of above-mentioned conditions and a factor aggravating their course. Also, a promising direction for improving prognostic models is the analysis of autonomic dysfunction in patients.

Keywords: COVID-19, arterial hypertension, obstructive apnea sleep syndrome, prognosis estimation.

Relationships and Activities: none.

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Received: 13.01.2023
Revision Received: 08.02.2023
Accepted: 26.04.2023

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For citation: Popov K. A., Bulaeva Yu. V., Ermasova S. A., Shvarts Yu. G. The problem of cross risk of arterial hypertension progression, obstructive sleep apnea syndrome and COVID-19. *Russian Journal of Cardiology*. 2023;28(2S):5334. doi:10.15829/1560-4071-2023-5334. EDN UMEFOX

Key messages

- An association between COVID-19, hypertensive disease and obstructive apnea sleep syndrome as well as the mechanisms of mutual worsening between them exist.
- Potential predictors of adverse outcomes are proposed; a comprehensive approach estimating prognosis of course of chronic diseases during and after COVID-19 is needed.
- Additional study of COVID-19 as a potential risk factor for decompensation and more severe course of arterial hypertension and obstructive apnea sleep syndrome as well as respiratory disorders during sleep is required.

Novel coronavirus infection (COVID-19) is associated with cardiovascular complications in the acute and long-term periods. In addition, COVID-19 often provokes the worsening of the course of already existing cardiovascular system (CVS) diseases. At the same time, arterial hypertension (AH), cardiovascular diseases (CVDs), obesity, diabetes and others are the risk factors (RFs) of more severe course of COVID-19. Among hospitalized COVID-19 patients, ~40% have at least one chronic disease. The proportion of comorbid patients in the cases ended with a lethal outcome is over 70%. According to data obtained by Gold MS, et al., AH was more common in patients with severe course of COVID-19 (47,65%) and in lethal cases (47,90%) [1]. According to ACTIV registry, most hospitalized COVID-19 patients have chronic diseases among which the CVDs prevail [2]. It also should be noted that severe and critical complications of COVID-19 are significantly more common in patients with obstructive sleep apnea syndrome (OSAS). It is also known that OSAS is one of the RFs of AH development [3], which adversely affects the course and control of AH and other CVDs [4]. We may judge of the incidence of OSAS in patients with COVID-19 using just indirect signs because this issue is not covered in the literature found according to the specified criteria. In general, we may suppose that there are bidirectional and mutually aggravating interrelationships between CVDs, including AH, and COVID-19 [5], and obesity, autonomic imbalance, changes in the renin-angiotensin-aldosterone system (RAAS) and hypoxia can be the connecting links between OSAS, HD and COVID-19. Taking into account a high incidence of polymorbidity in patients with COVID-19 as well as a distinct mutual aggravation, a complex approach to assess the prognosis of the course of chronic diseases during and after COVID-19 is required. The review is aimed to analyze the published data concerning the interrelations and possible mechanisms of mutual aggravation between hypertensive disease, OSAS and COVID-19.

Methodology of study

We systematically searched the PubMed, Google Scholar, Web of Science databases from 2000 to 2022 in accordance with the following keywords: "arterial hypertension", "obstructive sleep apnea", "COVID-19", "risk assessment", "outcome predictors", "risk factors", "comorbidity". We selected 48 publications concerning the possible mechanisms of mutual aggravation between the mentioned diseases as well as the assessment of the possible predictors of adverse outcomes. The type of study was not a selection criterion. Apart from RFs of severe COVID-19 course, the present review discusses characteristics such as the quality of night sleep, body mass index (BMI), and the state of the autonomic nervous system (ANS). They are considered as potential predictors of the destabilization of AH and OSAS against the background of COVID-19 pandemic. We found a limited number of studies considering COVID-19 as a potential RF of the decompensation and more severe course of AH as well as respiratory disorders during sleep. That is why the use of meta-analysis techniques was impossible. Based on the literature data, it is possible to make just preliminary conclusions and to propose hypotheses on the problem under consideration.

Role of OSAS and AH in the prognosis of COVID-19

OSAS is characterized by recurrent partial or complete obstruction of the airways during sleep, leading to shortness of breath, desaturation and arousals from sleep. A high incidence of OSAS is associated with the increased incidence of AH, obesity, depression, gastroesophageal reflux disease, diabetes mellitus, hypercholesterolemia, asthma [6]. OSAS is also associated with the increased risk of CVDs [4]. Many conditions associated with OSAS coincide with the RFs of severe course and adverse outcome in COVID-19 [7]. Some authors identify the additional predictors of the presence of OSAS for example, the hypertonic load time index [8] that emphasizes an interrelationship between OSAS and the state of CVS. Several pathophysiological mechanisms contribute to the interrelationships between OSAS and vascular risk, including neurohormonal dysregulation, endothelial dysfunction and inflammation [9]. The latter are also typical of the acute course and consequences of COVID-19. CPAP therapy, in turn, decreases arterial pressure (AP) but there were no proves that it decreases the risk of CVDs and serious cardiovascular events. At the same time, the decrease of body weight improves the indicators of AP and lipids in blood against the background of OSAS, whereas the addition of CPAP showed no significant improvement in the indicators of AP or lipids in blood [10].

According to the results of the studies, CPAP may independently affect the level of AP. There are two basic mechanisms of the increase in AP in OSAS, which can be prevented by CPAP. Periodic sympathetic activation accompanied by vasoconstriction caused by the repeated episodes of desaturation and hypoxia, is one of the key mechanisms responsible for the increase in AP in OSAS [11]. Another possible mechanism explaining pathophysiology of AH in OSAS, is the activation of RAAS. The release of renin is associated with the increase in the sympa-

thetic nervous system activity and the loss of sodium due to increased nocturnal diuresis provoked by an increase in the concentration of natriuretic peptide in response to excessive negative intrathoracic pressure during apnea [12].

Thus, a number of the studies have shown the interrelationship between AH, OSAS and COVID-19. However, the issue of the independent effect of confirmed OSAS and AH on the forecast of COVID-19 remains disputable. Besides, at the time of writing the review, the most published studies were focused on the factors affecting the course of COVID-19. The characteristics of the COVID-19 course, which could be the prognostic criteria for the AH and OSAS destabilization, are still under discussion as hypotheses. Meanwhile, the loss of the control of AH due to COVID-19 is often observed in inpatients [13], and can be a serious RF of CVD development, affecting the patients` quality and duration of life.

Decrease of sleep quality in the prognosis of the AH and OSAS destabilization against the background of COVID-19

OSAS is closely interrelated with the quality of sleep. At the same time, sleep quality is one of the basic factors in the control of AH and normal functioning of all body systems. The meta-analysis results showed that people with sleep deficiency had higher values of average systolic and diastolic AP. According to questionnaires, it was also shown that patients with AH had statistically significant decrease in sleep quality [14].

A lot of empirical data of sleep disorders against the background of COVID-19 pandemic have been accumulated. Many hypotheses of the potential mechanisms of these disorders were proposed. A number of authors believe that psychological health is the determining RF of insomnia development in COVID-19 because the results of the studies show correlation between development of depression, anxiety disorders and sleep disorders [15]. But the decrease in the level of physical activity and number of social contacts because of the pandemic limitations or the disease can be themselves the independent RFs for the development of psychological disorders [16]. The exact mechanisms of the direct influence of SARS-CoV-2 on sleep quality are not found. However, the long-term persistent sleep disorders can be considered as the manifestations of post-COVID syndrome following the disease [17]. It should be noted that post-COVID syndrome can be caused by both cerebral disorders due to vascular lesions [18] and the cerebral lesions due to direct influence of COVID-19 virus [19] or indirect mechanism through the formation of immune complexes [20]. In turn, sleep quality can affect the prognosis of the COVID-19 course as well as destabilization of chronic diseases such as AH and OSAS. An open randomized clinical trial which investigated the use of melatonin in addition to basic therapy of COVID-19, has showed more than 2% higher blood saturation in the affected group compared to the control group [17]. Obviously, it is possible to improve the course of this virus infection by normalizing sleep that indirectly confirms the negative role of sleep disorders in COVID-19. Thus, COVID-19 leads to sleep worsening which can be caused by indirect or direct influence of infectious process.

BMI as an independent predictor of adverse outcomes of AH, OSAS and COVID-19

Mutual influence of AH, obesity, COVID-19 and OSAS may look obvious but the identification of the independent predictors of adverse outcomes is possible only within large studies with an appropriate design. Using single-factor analysis, the CORONADO research revealed several characteristics associated with the risk of death on the 7th day of hospitalization for COVID-19. They included age, AH, micro- and macrovascular diabetic complications and concomitant diseases: heart failure and OSAS. But multiply factor analysis revealed no statistically significant independent relationship between severe course of COVID-19 and age, gender, the glucose level control, hypertension or the use of AH and diabetes basic therapy, including RAAS blockers. Only BMI was independently related to a primary outcome. Dyspnea, lymphopenia and increased levels of aspartate aminotransferase and C-reactive protein at admission to hospital were also independent prognostic factors of severe course of COVID-19 [21]. The evidences of the influence of obesity on the course of infectious diseases are not new. For example, during H1N1 pandemic, obesity was independently associated with higher risk of hospitalization, severe course and adverse outcome of influenza. In COVID-19, obesity is also serious independent RF of adverse outcome and severe course. In addition, obesity is associated with decreased immune response to vaccination that can potentially make these patients more susceptible to infection [22]. Obesity is associated with metabolic syndrome (MS) but some authors express doubt whether it is possible to use parameters such as glycemic profile and insulin resistance to build prognostic models for assessing the risk of COVID-19 severity [23].

The role of obesity in the occurrence of AH and its resistant form is well-known. There is an opinion that obesity and MS are the predisposing factors of post-COVID syndrome [24]. Starting from the pandemic, a lot of studies investigated relationship between cardiometabolic syndrome and COVID-19 have been published. Most studies stated such RFs

of severe COVID-19 as CVD, insulin resistance, MS, type 2 diabetes mellitus and increased BMI [25]. Along with this, the risk of cardiac and vascular complications in the nearest months after acute COVID-19 is equally increased in both obese and non-obese individuals [26].

Obesity is also a key factor for OSAS development. In patients with normal BMI, a 10% increase in weight is associated with a sixfold increase in the risk of OSAS [27]. And conversely, a 10% weight loss results in 26% decrease in the apnea-hypopnea index. Like in the case of hypertension, the relationship between obesity and OSAS is mutually increasing. One of the explanations for this interrelationship can be the association of obesity with chronic subclinical inflammation, the "unifying" role of which was mentioned above. Inflammation predisposes people to OSAS, and OSAS itself is a pro-inflammatory process [28]; consequently, an excessive body weight is a common RF for many diseases and clinical conditions, and the control of body weight increases the degree of the control for diseases associated with obesity.

Apart from clinical and pathophysiological features, obesity creates additional difficulties in managing this group of patients: features of intubation, the need for higher positive pressure during CPAP therapy, problems of transportation and performing a number of diagnostic procedures. All these difficulties may also affect the prognosis because they lead to the delay in diagnostics, require more advanced skills of personnel and potentially increase the risk of a variety of complications.

Significance of the phenomenon of mute hypoxia for an adequate clinical assessment of the patient's condition

One more universal pathogenetic factor in many diseases including OSAS and COVID-19 is hypoxia. Both diseases can have a mutually aggravating effect in particular due to the induction of hypoxia. And hypoxia does not always have obvious clinical manifestations. It is known that AP rising can be a reaction to hypoxia. Mute hypoxia in patients with SARS-CoV-2 infection is diagnosed using a pulse oximeter, blood gas level in and six-minute walk test. Mute hypoxia itself is not a RF for more severe course of COVID-19 or an adverse outcome. Nevertheless, the absence of specific complaints during desaturation and the registration of only raised blood pressure or routine diagnosis of a hypertensive crisis can lead to incorrect clinical assessment of the patient's condition and untimely assistance. The causes of mute hypoxia in patients with COVID-19 have not been clear so far. The existing data indicate a probable lesion of the central nervous system and also the probable absence of hypoxic vasoconstriction in these patients [29]. The compensation of CVS hypoxemia is crucial for maintaining oxygen delivery to tissues. The compensatory reserve of cardiovascular system for hypoxemia is more likely to determine the clinical outcomes in COVID-19 than the degree of hypoxia itself [30].

There are some contradictions on this issue. On the one hand, hypoxemia and altered hemodynamics in OSAS against the background of AH may contribute to the increased coagulopathy in COVID-19 and accordingly worsen the prognosis [31]. On the other hand, according to the results of the existing studies there are no data confirming a significant effect of mute hypoxia on the prognosis of the course of a main disease. And there are no unambiguous data on an increase in the risks of an unfavorable COVID-19 prognosis in the presence of a compensated chronic disease, in particular AH, as mentioned above. At the same time, severe form of COVID-19 is associated with polymorbidity. The cause of this seeming contradiction is probably explained as follows. The prevalence of AH and OSAS in patients with COVID-19 can be caused by the common predictors of the development of these diseases. Thus, the prognosis of COVID-19, OSAS and AH can be determined not so much by mutual effect of the diseases as the collection of the common predisposing factors: obesity, chronic inflammation, physical inactivity, stress and others.

Benefits of CPAP therapy in the era of COVID-19

When considering the role of hypoxia in mutual aggravation of OSAS, AH and COVID-19, it is impossible not to note the value of CPAP. The results of the CORONADO research showed that the patients required CPAP for the OSAS treatment, have a higher risk of death from COVID-19 [21]. Probably, this is caused by more severe course of OSAS and combined pathology typical of such patients. According to the data of the RECOVERY-RS research, the use of CPAP in patients with severe hypoxemia in COVID-19 significantly decreases the risks of tracheal intubation and death compared to oxygenation with moistened oxygen through nasal cannulas or a mask [32]. Miller MA, et al. performed a systematic review of the studies concerned with CPAP therapy and COVID-19. They noted that the most prevalent RFs of lethal outcome were common to COVID-19 and OSAS. These RFs include elderly age, hypertension, CVDs, pulmonary diseases and diabetes mellitus. The authors also pay special attention to obesity as a prevalent RF, common to many diseases [7]. This review served as a starting point for a qualitative meta-analysis of 13 cohort studies where Hu M, et al. showed that OSAS was independently associated with a significantly increased risk of death among patients with COVID-19 [33].

There is no enough data yet based on which it would be possible to unambiguously determine the recommendations for the use of CPAP in the combination of OSAS and COVID-19. At the same time, the use of CPAP as non-invasive mechanical lung ventilation seems promising in such comorbid patients.

Autonomic imbalance as a predictor of clinical outcome in combined pathology

One of general causes of the development and worsening of the discussed conditions can be also the changes in the ANS. Obesity and AH naturally determine a number of specificities in the ANS regulation. And the ANS plays an important role in the regulation of the whole body homeostasis including immune system, CVS and coagulation system [34, 35]. Considering the role of autonomic dysfunction in morbidity and mortality from COVID-19 [36], it is suggested to use the monitoring of the vagal tone in patients with COVID-19 as a prognostic marker of COVID-19 disease course [37].

Sleep fragmentation and chronic intermittent hypoxia in OSAS may cause an inflammatory reaction and sympathetic activation [38]. Besides, it is important to note that OSAS manifests in particular in the fluctuations of the ANS tone and disturbance of sleep architecture, and is accompanied by the increased negative intrathoracic pressure which directly affects cardiac function including the heart rate variability (HRV) [39].

The HRV analysis is a reliable non-invasive instrument reflecting the autonomic tone. When analyzing HRV, patients with severe COVID-19 course demonstrated significantly lower values of SDNN ($P<0,001$) and SDANN ($P<0,001$) and higher values of LF/HF than patients with mild course. HRV correlates with COVID-19 disease severity. Patients with severe COVID-19 disease course have more pronounced disorders of HRV, which demonstrate a linear correlation with the N-terminal pro-brain natriuretic peptide, D-dimer and immune function. The data of HRV measurement can be used as a non-invasive predictor of the time to virus elimination as well as a clinical outcome as this is showed in the study of Pan Y, et al. [40]. An underlying mechanism of these changes is still not completely known. The design of the mentioned study did not take into account the presence or absence of chronic CVDs, whereas the autonomic cardiac rhythm regulation significantly differs between patients with COVID-19 and without concomitant cardiovascular pathology and patients having both AH and COVID-19. Another study showed that patients with both COVID-19 and AH have higher sympathetic tone compared to patients with COVID-19 and without concomitant CVDs [41]. According to the design of the study performed by Skazkina VV, et al., severe course of COVID-19 was a criterion of exclusion. Thus, the results can be interpreted only regarding patients with mild and moderate COVID-19. Despite quite significant results, the data of all mentioned studies are obtained on a limited patient sampling and require confirmation on large samples with using more perfect design. In addition, the HRV values would be advisable to combine with other clinical predictors for the complex assessment of the disease status and for prognostic evaluation.

Value of RAAS and its blockers in combination of AH, OSAS and COVID-19

Along with autonomic dysfunction, patients with AH have a disturbed regulation of RAAS, that is also observed in patients with OSAS and COVID-19. Angiotensin-converting enzyme 2 (ACE2) receptors are mainly expressed in the CVS organs, and ACE2 was identified as a receptor for the entry of SARS-CoV-2 [42]. Both in patients with OSAS and with AH and obesity, an increased expression of ACE2 receptors is observed that would favor the viral invasion [43]. The cardiac complications in COVID-19 include myocarditis, acute coronary syndrome, heart failure and arrhythmias [44]. OSAS can potentiate the severity of these complications that obviously increases the risk of adverse outcomes.

However, there is some uncertainty in this regard. It is known that the ACE2 expression is more pronounced in patients with CVDs [45]. At the beginning of the pandemic, the different authors made an assumption that the ACE inhibitors may negatively affect the prognosis in patients with CVDs and AH. However, later this assumption has been disproved by a series of studies. By 2022 no reliable data has appeared, confirming that the ACE inhibitors cause the increase in ACE 2 receptors in the human tissues [46] or otherwise affect the COVID-19 course and outcomes [47].

In this context, it seems interesting that a meta-analysis performed by Gold MS, et al., revealed no statistically significant relationship between CVDs and mortality in COVID-19 [35].

It should be noted that all given results are obtained on relatively small samples therefore, there is a need in further large studies to prove or disprove an interrelationship between the condition of RAAS, CVDs, AH, OSAS and COVID-19.

Features of post-COVID syndrome and probability of destabilization of AH and OSAS

One of the most discussed topics is post-COVID syndrome and/or long-COVID. Currently, there is no common opinion whether to consider these two terms as synonyms or different clinical conditions. This makes a literature review on the given issue difficult because the criteria of determination of

post-COVID syndrome and the endpoints vary from study to study. Most authors agree on two criteria: 1) the symptoms last >4 weeks in the absence of any other potential causes; 2) the symptoms develop or persist after acute confirmed or probable COVID-19. Thus, patients with post-COVID syndrome are united by persistence or occurrence of the symptoms after COVID-19 [48]. At the same time, it remains unclear whether to consider the persistence of symptoms such as increased fatigue, shortness of breath, sleep disturbance, blood pressure fluctuations that have arisen or intensified after infection, as post-COVID syndrome or decompensation of the mentioned diseases. Moreover, the effect of the presence and character of post-COVID syndrome on the probability of AH and OSAS destabilization remains poorly studied. There is no much literature concerning direct physiological impact of COVID-19 on sleep but it highlights the negative synergy between the immune response to COVID-19, including prolonged, and the pro-inflammatory condition caused by OSAS. Obviously, post-COVID syndrome is of the greatest interest precisely regarding to the prognosis of the course of existing chronic diseases, after the acute period of COVID-19 has passed.

Conclusion

Thus, the literature data analysis dedicated to the problem of cross risk of AH, OSAS and COVID-19, in general confirmed bidirectional mutually aggravating interrelationships between these conditions. Most studies consider AH and other chronic diseases as RFs of more severe COVID-19 but only a limited number of researchers studied COVID-19 and post-COVID period as a destabilization factor of AH and OSAS.

It should be noted that at the time of writing the review, the studies based on the multiply factor models established no a reliable relationship between the presence of compensated AH and OSAS and unfavorable COVID-19 prognosis, despite a significantly higher incidence of these conditions in patients with COVID-19 than in the general population.

Also, there were no reliable confirmations of the hypotheses of the association between any methods for the treatment of AH and OSAS with higher/lower risk of infection or more severe/mild course and outcome of COVID-19 disease.

At the same time, we may consider established that obesity is a significant independent RF of both unfavorable prognosis of COVID-19 and the presence of AH and OSAS and their unfavorable course. In obesity there are the "mechanisms-candidates" that can negatively affect the development of these diseases. Besides, obesity can complicate the management of patients and indirectly affect the prognosis of this group of patients.

We can also assume that COVID-19 and its consequences may negatively affect the characteristics of AH and OSAS due to numerous pathogenic factors including hypoxia and aggravating of autonomic imbalance. In this regard, the diagnostics of autonomic dysfunction in patients after COVID-19 aimed to determine the probability of post-COVID syndrome development and AH destabilization, seems perspective. In turn, the study of sleep quality seems perspective regarding to the building of multifactorial prognostic models for both long-term COVID-19 outcomes and the clinical course of AH.

Relationships and Activities: none.

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