DOI 10.1007/s10517-022-05393-7

Bulletin of Experimental Biology and Medicine, Vol. 172, No. 3, January, 2022

EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Mechanisms of the Effects of Short-Term Inhalations of Xe and O_2 Gas Mixture in the Rehabilitation of Post-COVID Ventilation Failure

V. V. Udut[1,3], S. A. Naumov[1], E. V. Udut[1,2], S. S. Naumov[2], D. N. Evtushenko[3], O. N. Chumakova[1], and G. N. Zyuz'kov[1]

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 172, No. 9, pp. 362-366, September, 2021
Original article submitted July 12, 2021

The article presents a theoretical rationale and a clinical case of relief of post-COVID ventilation failure by inhalation of Xe and O_2 gas mixture. Pneumonitis of coronavirus etiology transforms saturated phospholipids of surfactant into a solid-ordered phase, which disrupts surface tension, alveolar pneumatization, and alveolar-capillary gas exchange. Using molecular modeling (B3LYP/lanl2dz; GAUSSIAN09), we demonstrated that Xe atom due to the van der Waals dispersion interaction increases the distance between the phospholipid acyl chains providing a phase transition from the solid-ordered to liquid phase and restored the surface-active monolayer surfactant film. A clinical case confirmed that short-term inhalations of the Xe and O_2 gas mixture relieved manifestations of ventilation insufficiency and increased SpO_2 and pneumatization of the terminal parts of the lungs.

Key Words: *post-COVID complications; Xe; pulmonary surfactant; dipalmitoylphosphatidylcholine; molecular electrostatic potential*

Respiratory failure is a key component in the pathogenesis of SARS-CoV-2 infectious lesion to the terminal compartments of the lungs at the level of the alveolar-capillary border with the involvement of the microvasculature [12]. This is confirmed by the results of instrumental and clinical examinations and laboratory tests: ground-glass opacity with varying degrees of involvement of pulmonary fields on CT [13]; reduced SpO_2 in arterial blood up to the values indicating the need for both ventilation and O_2 support [8]; hemostasis system disturbances and, in particular, appearance of high D-dimer values confirming the thrombotic processes and compensatory enhancement of fibrinolysis; increased ferritin and other proinflammatory characteristics of the blood [6,7].

The above non-specific, but determining the course of the disease, manifestations of the infectious disease persist during convalescence, which can last up to 3 months or more, depending on the severity of organ damage in the acute period [15]. Such a long recovery period is explained by damage to the terminal parts of the lungs with areas of atelectasis that violated the alveolar architectonics and the air—blood barrier, where the inflammatory component, which provides increased transudation of plasma and cellular blood components in the acute period, is inhibited by the presence of microvascular block thrombosis and loss of functional activity of pulmonary surfactant. Dam-

[1]E. D. Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia; [2]Siberian State Medical University, Ministry of Health of the Russian Federation, Tomsk, Russia; [3]National Research Tomsk State University, Tomsk, Russia. ***Address for correspondence:*** udutv@mail.ru. V. V. Udut

age to the alveolar-vascular region of the lungs often leads to respiratory failure, a decrease in the partial pressure of blood O_2, and can cause fibrosis [1].

Therefore, patients recovering from the disease have various symptom complexes directly or indirectly associated with respiratory failure: depression, anxiety, sleep disorders, weakness, headache, shortness of breath, cough, etc. and requiring rehabilitation measures [5,9,14,15].

According to Regulations of the Ministry of Health of the Russian Federation, the main components of post-COVID rehabilitation are breathing exercises, physiotherapy, and drug therapy aimed at restoring lung function [2]. The technology of short-term inhalation with a Xe and O_2 gas mixture can be applied as a therapeutic option, at least in relation to depression, anxiety, sleep disorders, shortness of breath, cough, pain syndromes, *etc*. [3,4]. The possibility of using inhalations Xe and O_2 gas mixtures is also confirmed by the data on the use of hyperpolarized xenon (^{129}Xe isotope) in the form of inhalations in magnetic resonance imaging of the lungs to assess their ventilation, microstructure and gas exchange [10]. These data led us to an assumption that short-term inhalations of the Xe and O_2 mixture can be effective in the therapy of post-COVID complications.

Our aim was theoretical substantiation and clinical demonstration of the effectiveness of short-term inhalations of Xe and O_2 gas mixture in the therapy of respiratory failure and associated stress disorders.

MATERIALS AND METHODS

Molecular modeling was performed using Gaussian 09 software (computing cluster SKIF, Tomsk State University) with the density functional theory method (DFT method) with a hybrid functional B3LYP and a basic set of functions lanl2dz adjusted for elements of 1-6 groups of the D. M. Mendeleev periodic table. The calculation results were visualized using the GaussView 5.0.8 software package.

The short-term inhalations of Xe and O_2 gas mixture (70 and 30%, respectively) were performed daily for five days on the SAKI (stationary) apparatus for xenon inhalation produced by Biology Gas Service Scientific Corporation. Xenon (KseMed) produced by Akela-N Company was used [3,4].

The patient signed informed consent for the procedures and disclosure of the medical history facts and results of the therapy.

RESULTS

The pulmonary surfactant plays the key role in pneumatization of the lungs at the alveolar level (the level of air-capillary exchange). Surfactant phospholipids form a monolayer at the air-fluid interface, which provides a significant decrease in surface tension necessary to stabilize the lungs during the final phase of expiration [11].

Since half of the surface-active phospholipids consists of saturated species represented mainly by dipalmitoylphosphatidylcholine (DPPC) containing residues of palmitic (hexadecanoic) acid, the molecules of unbranched long-chain saturated hydrocarbons $C_{16}H_{34}$ were used as the model system.

A well-known characteristic feature of aggregation of phospholipids into a solid-ordered phase is a significant decrease in their lateral mobility determining surface tension. Therefore, in the system simulating such a (solid-ordered) phase, first of all, geometry optimization was carried out in order to determine the minimum distance by which hydrocarbon molecules can be brought together, and this distance was about 6.7 Å. The maps of the distribution of molecular electrostatic potential (MEP) show that a common region of negative MEP (red isolines) is formed between hydrocarbon molecules, which explains their low lateral mobility in the solid-ordered phase (Fig. 1, *a*).

Introduction of the Xe atom with a bulky 54-electron shell that is easily polarized due to the van der Waals dispersion interaction into this model system leads to the appearance of a region of positive MEP surrounded by two regions of negative MEP of acyl (hydrocarbon) chains (Fig. 1, *b*). Thus, the appearance of a Xe atom nearly doubles the distance between hydrocarbons; the change in Gibbs energy (ΔG) is -23.96 kJ/mol, which indicates the possibility of a spontaneous process, which is endothermic, because the change in enthalpy (ΔH) is 8 kJ/mol.

At the second stage of interaction (ΔG= -36.51 kJ/mol; ΔH=-5.9 kJ/mol) Xe is released and the acyl chains of phospholipids acquire individual lateral mobility (due to the solid-ordered to liquid phase transition) with the recovery of the surface-active surfactant film, and the liberated Xe atom immediately enters the recycle of interaction with acyl chains of phospholipids in the solid-ordered phase. This recycling will take place as long as there are aggregates of the solid-ordered surfactant phase. The released Xe atom will interact only with the acyl chains of phospholipids of the solid-ordered phase of the surfactant, but not with the molecules of the monolayer of a normally functioning surfactant, since ΔG for such a process is greater than zero (Fig. 1, *c*).

These findings suggest that inhalation of Xe due to restoration of the surface tension of the surfactant, should increase pneumatization of the terminal parts of the lungs and reduce the manifestations of respiratory failure.

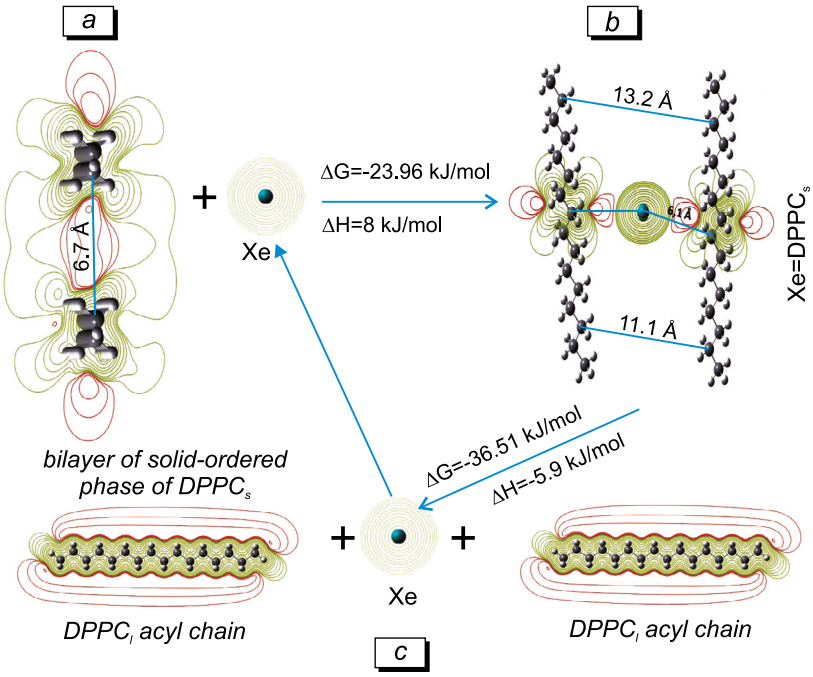

Fig. 1. Processes occurring in the system simulating the interaction of the xenon atom (Xe) with acyl chains of DPPC. *a*) Interaction of Xe with a bilayer of a solid-ordered phase of $DPPC_s$; *b*) intermediate complex Xe with two acyl chains of $DPPC_s$ (Xe-$DPPC_s$); *c*) disintegration of the intermediate complex with the formation of individual acyl chains of $DPPC_l$ and free Xe.

To confirm the targeted action of Xe in restoring functional activity of surfactant in case of its inflammatory damage, we present clinical observation illustrating the effectiveness of short-term inhalation of Xe and O_2 gas mixture in relieving respiratory failure and associated stress disorders in a patient recovering from coronavirus infection.

Patient A., 48 years, complained of weakness, fatigue, shortness of breath at rest, anxiety, and depressed mood. The medical history says that the patient has been ill for 30 days and has been staying in a hospital for 17 days. Discharge diagnosis: Primary: J12.8, severe viral bilateral polysegmental pneumonia. Respiratory failure 2-3, complication: U07.1. coronavirus infection caused by SARS-CoV-2 virus, virus identified. According to MSCT data, the lesion of the lung parenchyma of the ground-glass type occupied 45% (Fig. 2, *a*). On examination: respiratory rate (RR) at rest is 30 per minute; blood oxygen saturation (SpO_2) is 91%; HR is 94 bpm. Psychometry: moderate depression; moderate anxiety.

In order to correct these complaints, the patient was offered a technology for relieving stress disorders and a series of short-term inhalations of Xe and O_2

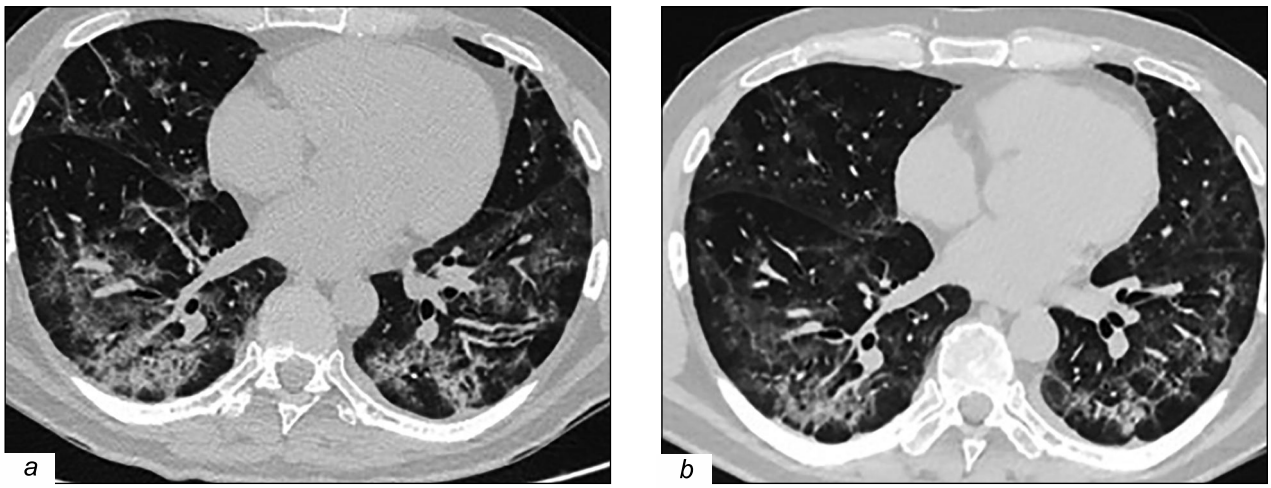

Fig. 2. MSCT before (*a*) and after (*b*) the course of Xe and O_2 inhalations.

TABLE 1. Dynamics of HR, SpO_2, and RR during Inhalations of Xe and O_2 Mixture

Parameter	Session 1		Session 2		Session 3		Session 4		Session 5	
	before	after	before	after	before	after	before	after	before	after
HR, bpm	88	84	87	84	77	77	83	82	76	78
SpO_2, %	91	98	92	97	96	97	96	98	97	98
RR, per minute	30	20	28	22	18	19	18	17	19	15

with a mixture (with the patient's consent). During inhalation, patient's condition was monitored by subjective (dizziness, euphoria, and parasthesia) and objective parameters (SpO_2, HR, RR, and nystagmus). The effects of short-term inhalation of the Xe and O_2 mixture were assessed by the dynamics of SpO_2, HR, and RR (Table 1) and results of MSCT performed at the end of the inhalation course (Fig. 2, *b*). We observed a relief of respiratory failure and a pronounced decrease in focal ground-glass lesions in the lung tissue. Along with the registered relief of respiratory failure, a significant improvement in patient's condition was noted: a decrease in depression, anxiety, an improvement in the quality of sleep.

Thus, the proposed mechanism of action of Xe in restoring the monolayer of the surface-active film of the pulmonary surfactant is confirmed in the clinic, where short-term inhalations of the Xe and O_2 mixture provide prompt relief of post-COVID respiratory failure.

REFERENCES

1. Vinokurov AS, Zyuzya YuR, Yudin AL. Evolution of follow up ct signs in patients with COVID-19 in early stage. Luch. Diagnost. Ter. 2020;11(2):76-88. doi: 10.22328/2079-5343-2020-11-2-76-88. Russian.
2. Temporary Guidelines. Prevention, Diagnosis, and Treatment of New Coronavirus Infection (COVID-19). Ver. 11, May 2021 [URL: https://edu-rosminzdrav.ru.com/profilaktika-diagnostika-i-lechenie-covid-19/]. Russian.
3. A Method for the Correction of Acute and Chronic Stress Disorders Based on Inhalation of Therapeutic Doses of Medical Xenon Brand KseMed. Medical technology. Federal Service for Surveillance in Healthcare Approval No. FS 2010/227 from June 17, 2010. Russian.
4. The Use of Oxygen-Xenon Mixture for Pain and Pain Syndromes. Federal Service for Surveillance in Healthcare Approval No. FS 2010/123 from April 2, 2010. Russian.
5. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, Ellis H, Goodall D, Gough M, Lewis S, Norman J, Papadopoulou T, Roscoe D, Sherwood D, Turner P, Walker T, Mistlin A, Phillip R, Nicol AM, Bennett AN, Bahadur S. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br. J. Sports Med. 2020;54(16):949-959. doi: 10.1136/bjsports-2020-102596
6. Carubbi F, Salvati L, Alunno A, Maggi F, Borghi E, Mariani R, Mai F, Paoloni M, Ferri C, Desideri G, Cicogna S, Grassi D. Ferritin is associated with the severity of lung involvement but not with worse prognosis in patients with COVID-19: data from two Italian COVID-19 units. Sci. Rep. 2021;11(1):4863. doi: 10.1038/s41598-021-83831-8
7. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int. J. Lab. Hematol. 2020;42(Suppl, 1):11-18. doi: 10.1111/ijlh.13229
8. Gautret P, Million M, Jarrot PA, Camoin-Jau L, Colson P, Fenollar F, Leone M, La Scola B, Devaux C, Gaubert JY, Mege JL, Vitte J, Melenotte C, Rolain JM, Parola P, Lagier JC, Brouqui P, Raoult D. Natural history of COVID-19 and therapeutic options. Expert Rev. Clin. Immunol. 2020;16(12):1159-1184. doi: 10.1080/1744666X.2021.1847640
9. Hao F, Tan W, Jiang L, Zhang L, Zhao X, Zou Y, Hu Y, Luo X, Jiang X, McIntyre RS, Tran B, Sun J, Zhang Z, Ho R, Ho C, Tam W. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain Behav. Immun. 2020;87:100-106. doi: 10.1016/j.bbi.2020.04.069
10. Li H, Zhao X, Wang Y, Lou X, Chen S, Deng H, Shi L, Xie J, Tang D, Zhao J, Bouchard LS, Xia L, Zhou X. Damaged lung gas exchange function of discharged COVID-19 patients detected by hyperpolarized 129Xe MRI. Sci. Adv. 2021;7(1):eabc8180. doi: 10.1126/sciadv.abc8180
11. Pérez-Gil J. Structure of pulmonary surfactant membranes and films: The role of proteins and lipid-protein interactions. Biochim. Biophys. Acta. 2008;1778(7-8):1676-1695. doi: 10.1016/j.bbamem.2008.05.003
12. Rybakova MG, Karev VE, Kuznetsova IA. Anatomical pathology of novel coronavirus (COVID-19) infection. First impressions. Arkh. Patol. 2020;82(5):5-15. doi: 10.17116/patol2020820515
13. Ufuk F, Savaş R. Chest CT features of the novel coronavirus disease (COVID-19). Turk. J. Med. Sci. 2020;50(4):664-678. doi: 10.3906/sag-2004-331
14. Vaes AW, Machado FVC, Meys R, Delbressine JM, Goertz YMJ, Van Herck M, Houben-Wilke S, Franssen FME, Vijlbrief H, Spies Y, Van 't Hul AJ, Burtin C, Janssen DJA, Spruit M.A. Care dependency in non-hospitalized patients with COVID-19. J. Clin. Med. 2020;9(9):2946. doi: 10.3390/jcm9092946
15. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. doi: 10.1016/j.eclinm.2020.100463