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Chemical kinetics of the development of coronaviral infection in the human body: Critical conditions, toxicity mechanisms, "thermoheliox", and "thermovaccination"

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ABSTRACT

Kinetic modeling of the behavior of complex chemical and biochemical systems is an effective approach to study of the mechanisms of the process. A kinetic model of coronaviral infection development with a description of the dynamic behavior of the main variables, including the concentration of viral particles, affected cells, and pathogenic microflora, is proposed. Changes in the concentration of hydrogen ions in the lungs and the pH -dependence of carbonic anhydrase activity (a key breathing enzyme) are critical. A significant result is the demonstration of an acute bifurcation transition that determines life or system collapse. This transition is connected with exponential growth of concentrations of the process participants and with functioning of the key enzyme carbonic anhydrase in development of toxic effects. Physical and chemical interpretations of the therapeutic effects of the body temperature rise and the potential therapeutic effect of "thermoheliox" (respiration with a thermolized mixture of helium and oxygen) are given. The phenomenon of "thermovaccination" is predicted, which involves stimulation of the immune response by "thermoheliox".

1. Introduction

In the most recent decade, many studies have appeared on the topic of modeling viral growth dynamics in the organism with consideration of the production of pathogenic microflora and the response of the human immune system [1–10]. C. Beauchemin and A. Handel presented a review of the mathematical models of influenza development dynamics inside the organism with and without consideration of the immune response [8]. For example, the authors modified the simplest model of influenza virus infection with the addition of equations for the delay of virus production (6–8 h), the induction of interferon to inhibit virus replication in an infected cell, and the treatment process [9]. Most mathematical models describe the incubation period, the period of viral growth, the inclusion of the body's immune system and the treatment of infection, but do not consider the causes of system collapse, i.e., the molecular causes of death associated with the development of the disease. Mathematical models do not include disorders of the acid-alkaline balance (pH), which plays an important role in the functioning of the respiratory tract and metabolism [10,11]. The increase in carbon dioxide and the accumulation of acidic metabolites lead to a decrease in pH in the lesion zone and a decrease in the catalytic activity of carbonic anhydrase, which corresponds to respiratory acidosis [12].

Infection of a living organism by viral particles with the development of clinical symptoms that potentially lead to collapse (death) of the body is a complex, dynamic process. The most important parameters determining the process dynamics are the concentration of the infecting agent or virus, the concentration of pathogenic microflora symbiotrophically developing on the affected cells of the body, and the physical conditions of the process development, such as the temperature and pH of the medium.

Currently, the etiology of acute coronavirus infection is becoming clearer [13,14]. The disease development process involves several

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stages:

- The initial stage includes infection and growth of viral concentration. This incubation period can occur without visible clinical changes. Therefore, in the case of a powerful immune system in the body, the virus does not continue to develop. In the second case, the immune system cannot cope with the virus, and viral penetration into the host cells initiates an exponential increase in the concentration of viral particles and the transition from the mild to the severe form of the disease.
- The next stage is destruction of the host cells by the virus and accumulation of dead cells.
- Under intensive aerobic conditions, necrotic biochemical processes of oxidation take place in dead cells, including lipid peroxidation, release of organic acids of the tricarboxylic acid cycle, ATP (adenosine triphosphate) hydrolysis with formation of phosphoric acid and other acidogenic processes.
- Local acidification of the lesion zone occurs.
- All enzymes with the imidazole group of histidine (pK_a7.0) in the active center, particularly the key enzymes of carbonic anhydrase and plasmin in the plasminogenic fibrinolytic complex, stop working in the lesion zone. The protonation of them blocks catalytic activity by reducing the pH (increasing the concentration of hydrogen ions). The lesion zone stops releasing CO_2 into the gas phase and accumulates bicarbonate.
- Microvessels are clogged in the lesion zone. Thrombus formation means that the plasmin-plasminogenic system that continuously dissolves fibrin clots and blood clots in the body is locally "turned off". Disabling the plasmin-plasminogenic system has the same effect as the "shutdown" of carbonic anhydrase. The active center of the plasmin contains an imidazole group of histidine, the protonation of which reversibly blocks the activity of plasmin in the lesion zone. Plasmine stops hydrolyzing fibrin clots, and thus a blood clot occurs.

To create conditions for the suppression of viral infection and management of the treatment process, it is necessary to build and analyze kinetic models that describe the dynamics of the pathological process.

2. Materials and methods

The kinetic model is based on the kinetic equations describing the growth and evolution of microbial and viral populations [15,16]. The ODE (ordinary differential equation) system was integrated using a specially developed program (in Delphi Community Edition). The solution of the kinetic model allows us to visualize the dynamic responses of all variables and study the behavior of the system as the parameters are varied.

3. Results and discussions

Kinetic model. In this paper, we propose a mathematical model that describes the dynamics of viral infection growth, the formation of pathogenic microflora and the pH changes in the lesion zone. The kinetic model of the process is proposed below, and parametric analysis is performed. The model is based on the kinetic equations presented in previous work [15,16] on the growth and evolution of microbial and viral populations.

The development of the pathology can be represented by the following scheme:

$N \rightarrow 2N$ the viral replication stage;

$C \xrightarrow{N} P$ the stage of cell destruction by viral particles with formation of destruction products P, which is a substrate for growth of pathogenic microflora M.

$M \xrightarrow{\mu(P)} 2M$ the stage of reproduction (growth) of pathogenic microflora on the products of cell destruction

The basic system of equations can be represented as

$$\frac{dN}{dt} = k_1 N - \alpha(T)N, \qquad t = 0, \quad N = N_0, \tag{1}$$

where N is the concentration of viral infection; k_1 is a specific rate of virus replication in the body; $\alpha(T)$ is a parameter characterizing the rate of virus destruction due to temperature inactivation, immune response, etc.; N_0 is the initial infecting viral concentration.

As the virus penetrates into the body's cells, especially lung cells, it multiplies and destroys the infected cells. The destruction product (P) is metabolically destroyed cells, which are a favorable medium for the growth of pathogenic microorganisms (M). The products (P) are in fact dead cells, which act as a substrate for the growth of pathogenic microflora.

$$\frac{dP}{dt} = k_2 N, \qquad t = 0, \quad P = P_0 = 0, \tag{2}$$

$$\frac{dM}{dt} = \mu(P)M - \beta(T)M, \qquad t = 0, \quad M = M_0. \tag{3}$$

The specific rate of the growth of microorganisms $\mu(P)$ depends on the concentration of the "destroyed" cells P and can be presented by Mono's equation:

$$\mu([P]) = \frac{\mu_m P(t)}{K_p + P(t)}, \tag{4}$$

where μ_m is a maximum specific growth rate. K_p is the pathogen affinity for substrate P and $\beta(T)$ is a parameter characterizing the thermal death of microorganisms.

Under conditions of limited aeration and in zones of weak air exchange, pathogenic microflora, e.g., pneumococci, are optional anaerobes that use an anaerobic mechanism of ATP synthesis producing organic acids. This is the path to local mild acidosis and to collapse (death) of the body.

It is known that a pH value of 7.15 in the blood system is critical. The body's metabolism cannot function sustainably if the pH value is below 7.15 in the blood system because many enzymes contain the imidazole group of histidine as a component of the active center with pK_a 7.0–7.2, depending on the protein structure [17]. Protonation of the imidazole group leads to complete loss of the catalytic activity of the enzyme.

The key enzyme for the functioning of the respiratory system is carbonic anhydrase, which performs the reaction $HCO_3^- \rightarrow CO_2 + OH^-$ of carbon dioxide transfer from the liquid to gas phase in the form of gaseous carbon dioxide. Blocking the activity of carbonic anhydrase (pK_a7.0) is a complete respiratory stop.

It can be assumed that under conditions of significant lung damage by the pathogenic microflora, the shift in the pH in the lungs by 0.2–0.3 units is the main factor in respiratory system collapse.

Within the model under consideration, the dynamics of pH change in the lesion zone can be described by the equation:

$$\frac{dH^+}{dt} = \gamma\left(H_0^+ - H^+\right) + \delta M + \omega \cdot P - v_c, \qquad t = 0, \quad H^+ = H_0^+, \tag{5}$$

where it is assumed that the proton production rate is proportional to the concentration of pathogenic microflora. The coefficient δ characterizes the productivity of microorganisms in the proton emission and the buffer properties of the blood system. The member $\gamma(H_0^+ - H^+)$ describes an open system by protons, where H_0^+ is the concentration of protons entering into the lesion zone, H^+ is the "average" concentration in the lesion area, γ is the mass transfer coefficient. v_c is the rate of enzymatic reaction of carbonic anhydrase, i.e., the rate of production of hydroxyl ions by the reaction catalyzed by carbonic anhydrase. Considering the

dependence of the rate of carbonic anhydrase on pH, the rate equation can be represented as follows

$$v_c = \frac{V_m \left[HCO_3^-\right]}{(1 + H^+/K_a)\left(K_m + \left[HCO_3^-\right]\right)} = \frac{A}{1 + H^+/K_a}. \quad (6)$$

Under conditions of a constant bicarbonate concentration (a relatively small region of process development), the constant multiplier in equation (6) is combined by constant A.

The solution of the system of equations (1)–(6) allows to obtain a kinetic description of the observed phenomenon of pathology development due to infection of the organism by coronavirus. One of the process scenarios is presented in Fig. 1. The integration of equations (1)–(6) was performed with the following parameter values: $k_1 = 2{\cdot}10^{-2}$ h^{-1}, $k_2 = 10^{-2}$ h^{-1}, $\alpha = \omega = 5{\cdot}10^{-3}$ h^{-1}, $\beta = 10^{-3}$ h^{-1}, $\gamma = 0.1$ h^{-1}, $\delta = 10^{-2}$ h^{-1}, $\mu_m = 2.5{\cdot}10^{-2}$ mol/(L·h), $K_a = 10^{-7.2}$ mol/L, $K_p = 10^{-3}$ mol/L, $A = 5$ mol/(L·h), $N(0) = 10^{-3}$ mmol/L, $P(0) = 0$, $M(0) = 10^{-3}$ mmol/L, and $H^+(0) = H_0^+ = 10^{-7.4}$ mol/L.

The obtained solution qualitatively describes the phenomenon of infection and disease development:

1. Incubation period during which practically no signs of the disease are observed. From Fig. 1 (dashed line) it is observed that with the parameters given above this period lasts 150 h (approximately 6.5 days).
2. At the end of the incubation period (induction period), rapid symbiotrophic growth of the virus concentration and pathogenic microflora concentration with significant accumulation of virus and microorganisms is observed.
3. In primary periods of pathology development (the incubation period and initial period of active growth of the virus and pathogenic microflora concentrations), the pH value in the lesion zone is in the range 7.4–7.2. In the absence of treatment and a purposeful effect on the system behavior, bifurcation growth and pH blocking of carbonic anhydrase activity are observed. As a consequence, complete respiratory failure occurs. With the given parameters (listed above), the model predicts that respiratory arrest should be observed on the 15th–16th day after infection. The collapse has a bifurcated character, and the transition point is clearly identified graphically (see Fig. 1). The bifurcation point is a fundamentally important characteristic of the process and is the point of "no return", i.e., the time of death of the body. When passing through this point, the release of CO_2 from the liquid phase to the gas phase is stopped. Uncontrolled growth occurs in the bicarbonate concentration in the blood, i.e., complete blocking of breathing occurs.

It is of interest to study the influence of parameter variations on the system behavior to identify the most sensitive elements and methods of process control. Let us consider several important cases.

Virus destruction (immune response). The most sensitive parameter defining the system behavior is the characteristic of the rate of viral destruction (α parameter). Under natural conditions, the destruction process is based on activation of the immune system to produce antibodies against viral proteins. Within the studied model, a highly convenient parameter characterizing the main feature of the process is τ_{cr}, which is the time at which the system can exist before collapse (lifetime after infection). The integration of the equation system and computational procedures allow visualization of this time. The lifetime is the time before the bifurcation transition of hydrogen ion concentration (break point and experimentally rapid growth of H^+ (see Fig. 1). The dependence of τ_{cr} on α parameter is observed using methods of mathematical experiments. Fig. 2 shows the dependence of H^+ on time with various α values and the observed dependence of τ_{cr} on α.

The critical point is the point $\alpha = k_1$, at which the growth rate of the viral concentration in the body becomes equal to zero. This is the condition of complete recovery.

Antibiotics (suppression of pathogenic microflora growth). The growth rate of pathogenic flora (equation (4)) has a significant impact on the development of the infectious process. In therapy, this process is regulated by the introduction of antibiotics that suppress the growth of microorganisms to varying degrees.

The results of a mathematical experiment on the influence of the μ_m and K_p parameters on the system lifetime are presented in Fig. 3. A decrease in the rate of growth of microorganisms (decrease in μ_m and increase in K_p) has a favorable effect on the lifetime (time before bifurcation transition, i.e., before the pH jump).

Key role of carbonic anhydrase. The carbonic anhydrase enzyme plays a crucial role in the respiratory mechanism. The enzyme "discharges" the biochemically formed bicarbonate ion in the form of gaseous CO_2 and a hydroxyl ion. Under normal physiological conditions (pH~7.4), this reaction is practically irreversible (a system is open by CO_2). The catalytic activity of carbonic anhydrase is controlled by an ionogenic group with pK$_a$7 (see equation (6)).

The shift in pH (even a notably small shift) in an acidic medium (decrease in pH) reduces the catalytic activity of the enzyme while decreasing the rate of production of OH^- ions [12]. The process is self-accelerating, leading to bifurcation of the pH jump.

Fig. 4 shows the dependence of τ_{cr} on the catalytic activity of carbonic anhydrase A. It is observed that the lifetime (τ_{cr}) can be significantly increased by increasing the catalytic activity of the enzyme. Carbonic anhydrase contains a Zn^{2+} ion in the active center [18], which

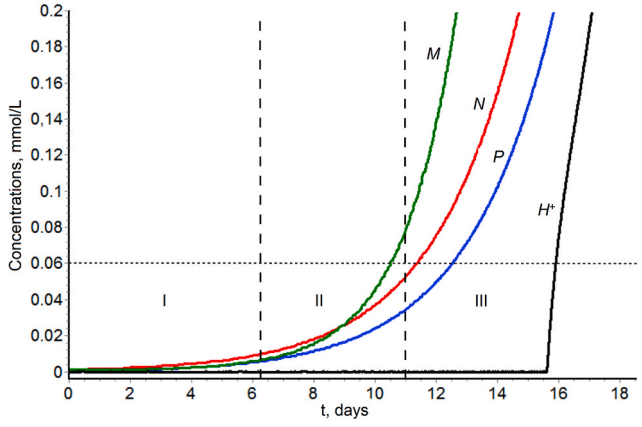

Fig. 1. Dynamics of change in the concentrations of a virus (N), "destroyed" cells (P), pathogenic microflora (M), and hydrogen ions (H^+) at viral infection ($\omega = 0$). I) incubation period of the virus; II) mild form of the disease; III) severe form of the disease and collapse.

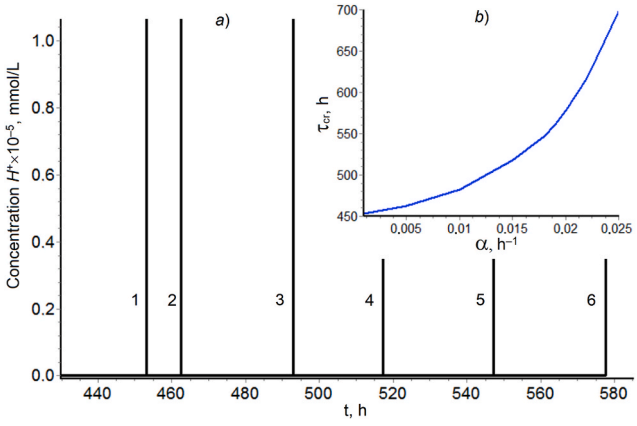

Fig. 2. Dependencies of hydrogen ion concentration on time (a) at $\omega = 0$ and variation in the rate of viral destruction α: 1) 10^{-3} h^{-1}; 2) $5{\cdot}10^{-3}$ h^{-1}; 3) $1.2{\cdot}10^{-2}$ h^{-1}; 4) $1.5{\cdot}10^{-2}$ h^{-1}; 5) $1.8{\cdot}10^{-2}$ h^{-1}; 6) $2{\cdot}10^{-2}$ h^{-1} and the dependence of τ_{cr} on α (b).

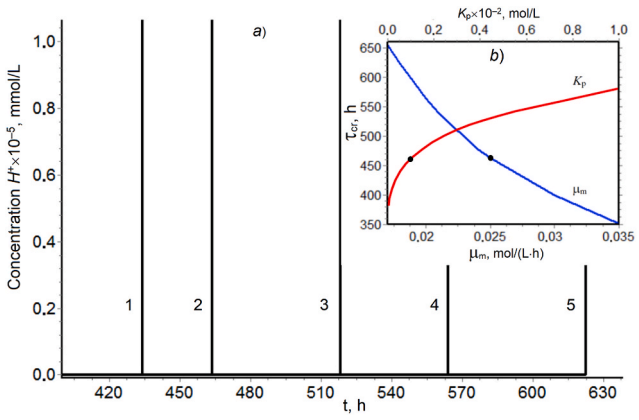

Fig. 3. Dynamics of the change in concentration H^+ (*a*) at $\omega = 0$ and different values of the maximum rate of growth of microorganisms μ_m: 1) 0.027 mol/(L·h); 2) 0.025 mol/(L·h); 3) 0.022 mol/(L·h); 4) 0.02 mol/(L·h); 5) 0.018 mol/(L·h) and dependence of τ_{cr} on the parameters μ_m and K_p (b). Points denote the values of parameters μ_m and K_p, used in plotting of Fig. 1.

means that the patient's metabolism must be saturated with Zn^{2+} ions for the effective treatment of viral damage. Ion Zn^{2+} of carbonic anhydrase plays the role of electrophilic agent, which is a key element of the active center of the enzyme.

Inhibition of necrotic processes, antioxidants. Under conditions of deep aeration, e.g., when using artificial lung ventilation devices, the oxidation processes with the formation of acids develop in the affected cells with broken membranes. Excess oxygen can trigger the development of acidogenic processes. Within the discussed model, this process is presented by the term ωP in equation (5).

We analyzed the influence of the ω parameter on the system behavior, and the dependence of bifurcation point (τ_{cr}) on ω was also studied. A decrease in the acid production rate by dead cells influences τ_{cr} significantly, and this dependence is nearly linear. It can be expected that the use of antioxidants is a positive factor in the treatment of coronavirus infection.

Therapeutic effect of high temperature. The natural process of disease development is associated with an increase in body temperature. The inflammatory response is initiated by a large complex of biochemical reactions, including the synthesis of inflammation mediators of the prostaglandin type [19,20], synthesis of heat shock proteins, and activation of the immune system.

The increase in temperature first affects the increase in the rate of thermal death of microorganisms and viruses. It is known that as the temperature increases the concentration of microorganisms and viruses decreases exponentially as a result of thermal death:

$$N(t) = N_t \exp(-k_N \Delta t),$$
$$M(t) = M_t \exp(-k_M \Delta t),$$

where N_t and M_t are the concentrations of pathogens at the moment of time t, Δt is the time of exposure at increased temperature, and k_N and k_M are the kinetic characteristics of thermal death (see, for example, Figure 7.33 and 7.34 of the textbook by J.E. Bailey, D.F. Ollis, Biochemical engineering fundamentals, McGraw-Hill, New York, 1986) [21].

A more detailed analysis of the data presented in these figures shows that the dependence of the kinetic parameters of thermal death $k_N(t)$ and $k_M(t)$ is subordinate to the classical Arrhenius equation:

$$k_N(t) = k_{N0} \exp\left(-\Delta H_N^* / (RT)\right),$$
$$k_M(t) = k_{M0} \exp\left(-\Delta H_M^* / (RT)\right),$$

where ΔH_N^* and ΔH_M^* are the activation energies of the thermal death of viruses and microorganisms, respectively.

Microorganisms, including pathogens, are highly sensitive to temperature increases. Thus, the rate of death of *Escherichia coli* at a transition from 54 °C to 60 °C increases by 14.3 times. The rate of death of *Staphylococcus aureus* increases by almost 5 times with an increase in temperature from 53 °C to 57 °C. From the data presented in Ref. [21], we can estimate that $\Delta H_M^* = 100$ kcal/mol (thermal death of *S. aureus*) and $\Delta H_M^* = 118$ kcal/mol (thermal death of *E. coli*). If we assume that the thermal death of viruses is determined by the thermal degradation of capsule proteins, it can be accepted that $\Delta H_N^* = 40 - 50$ kcal/mol.

Within the discussed model, it appears possible to consider the effects of direct inactivation of viruses and pathogenic microorganisms at the transition from the "normal" temperature of 36 °C to the temperature of the inflammatory process, 41°C. It is well known that an increase in temperature to 40–42 °C is an important factor in the development of inflammatory process [20]. If the activation energy of thermal destruction of viruses is conditionally taken to be equal to 40 kcal/mol, then the transition from normal temperature to inflammation temperature increases the parameter α by 2.8 times. Calculations show that in this case, the bifurcation point of collapse shifts from 360 h to 420 h. At an activation energy of 50 kcal/mol, the parameter α increases by 3.5 times and the collapse shifts to 440 h. Thus, the patient gets significant additional time to fight the disease. In any case, an increase in temperature leads to thermoinactivation of the virus and an increasing the patient's life time.

The structure of equation (1) is essential. The exponential growth of the virus concentration is only possible at $k_1 > \alpha$. Within the basic parameters of the model ($k_1 = 2{\cdot}10^{-2}$ h^{-1}, $\alpha = 5{\cdot}10^{-3}$ h^{-1}), the increase of α by more than 4 times ($\alpha = 2{\cdot}10^{-2}$ h^{-1})) leads to a complete stop of virus infection development (full therapeutic effect). The performed calculations illustrate and explain the therapeutic effect of the increasing temperature (Fig. 5).

Within the kinetic model, it is possible to estimate the time period of temperature increase (Δt_{ther}), necessary for the therapeutic effect Δt_{ther}

$$\Delta t_{ther} = \frac{\ln(M_0/M)}{\gamma_{36}} \exp\left[\frac{\Delta H_M^*}{R}\left(\frac{1}{T_{36}} - \frac{1}{T_{41}}\right)\right],$$

where M_0/M is the depth of lung cleanse from the microbiological pathogen, γ_{36} is the kinetic parameter of thermal death ($5{\cdot}10^{-3}$ h^{-1}), ΔH_M^* is the activation energy of the thermal death of the microorganism, and T_{36} and T_{41} are the patient's temperature in normal conditions and with the increase in temperature, respectively. Estimates show that the depth of inactivation of the microorganism at 10 times (M_0/M) = 10 will be achieved in 34 h; at 100 times, in 65 h.

Therapeutic effect of "thermoheliox". The use of "thermoheliox",

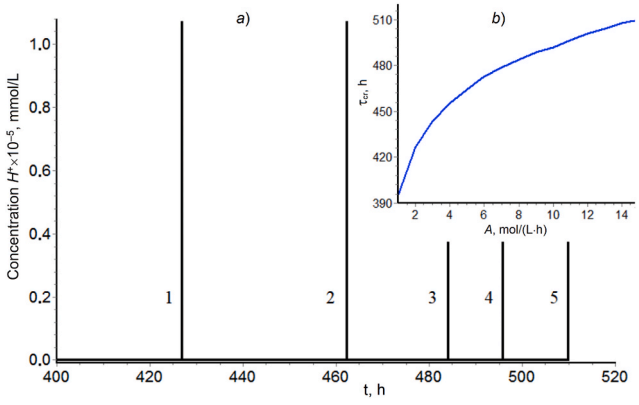

Fig. 4. Dynamics of the shift in the bifurcation transition point of concentration H^+ (*a*) at $\omega = 0$ and variation in the carbonic anhydrase rate *A*: 1) 2 mol/(L·h); 2) 5 mol/(L·h); 3) 8 mol/(L·h); 4) 11 mol/(L·h); 5) 15 mol/(L·h) and dependence of τ_{cr} on the catalytic activity rate of carbonic anhydrase *A* (*b*).

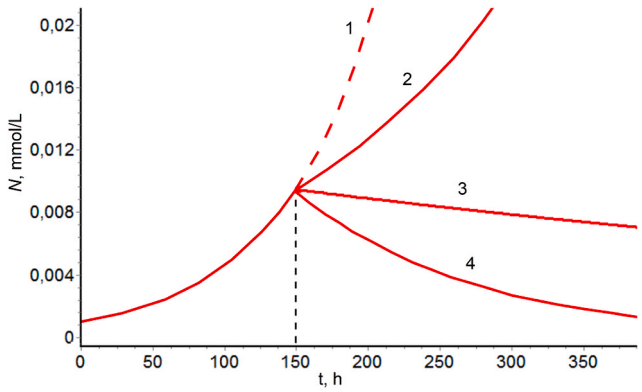

Fig. 5. Dynamics of viral growth: dashed line 1) $\alpha = 0$. Changes in the dynamic picture with an increase in the thermoinactivating processes at $\omega = 0$: solid lines 2) $\alpha = 5{\cdot}10^{-3}$ h^{-1}; 3) $\alpha = 7.5{\cdot}10^{-3}$ h^{-1}; 4) $\alpha = 10^{-2}$ h^{-1}.

which is a thermolized mixture of helium and oxygen, appears to be the most promising therapeutic means of suppressing viral growth. The essence of the approach is to influence the patient's respiratory system with a "thermoheliox" at relatively high temperatures. The therapeutic procedure consists of supplementing the patient's breathing with a helium-oxygen mixture (80–60% helium, 20–40% oxygen) at gas-mixture temperatures of 50–90 °C.

The methodology of using a thermolized mixture of helium and oxygen has a detailed scientific justification and has found highly effective application in the treatment of pathologies of the respiratory system, ischemic stroke [22–24]. "Thermoheliox" is also used for treatment of pregnant pathologies (A.A. Panin et al., unpublished data). The successful therapeutic application of the method was reported for more than 2500 patients in the pulmonology and neurology departments of D. D. Pletnev City Clinical Hospital [22–24]. A.A. Panin developed a unique medical device that allows regulation of the composition and temperature of the helium-oxygen mixture and drug delivery to the lungs [25]. The available experimental experience and practice (use in saunas for breathing air at up to 100 °C) demonstrate that a thermolized mixture of oxygen and nitrogen is practically harmless to the human body within 20–30 min of exposure. Safety of using of breathing air heated to high temperatures is confirmed by centuries of experience with saunas. This is also confirmed by clinical experience [22–24].

A thermolized mixture of helium and oxygen behaves in a similar way. Helium, with its high diffusion capacity, drains well, bypasses all body tissues, and significantly improves microcirculation in all organs and tissues. "Thermoheliox" significantly improves oxygen delivery, reduces airway resistance, improves the ventilation-perfusion ratio through the alveolar-capillary membrane of the lungs and normalizes the acid-alkaline state. "Thermoheliox" is much more effective than a mixture of oxygen and helium at room temperature. Mammalian and human cells use specialized protection mechanisms against temporary overheating (heat-shock proteins). At the same time, the virus is effectively destroyed by denaturation of proteins and nucleic acids. For example, the flu virus at 50–60 °C "lives" for a few minutes, the HIV virus is inactivated by a factor of 100 at 56 °C for 30 min, the hepatitis virus loses its activity at 100 °C for 2 min, and foot-and-mouth disease virus is destroyed at 50–60 °C in 5–10 min [21,26].

The principle of instability of viruses to increased temperatures is the basis for the seasonal nature of viral infections transmitted by airborne means. It is of interest to analyze the influence of "thermoheliox" within the discussed model of the development of the virus-microbial lesion. If we take the activation energy of viral thermodestruction as 50 kcal/mol, a 30-min exposure of the lesion at 60 °C of the medium can reduce its concentration by several times (Fig. 6). Subsequent exposures lead to a dramatic reduction.

It is possible to estimate the dependence of the destruction degree of the pathogenic virus on temperature (N/N_0) at a 30-min respiratory exposure.

$$\frac{N}{N_0} = \exp\left(-\alpha(T_{36})\Delta t_{\exp} \cdot \exp\left[-\frac{\Delta H_M^*}{R}\left(\frac{1}{T_w} - \frac{1}{T_{36}}\right)\right]\right).$$

In this work, T_w is the "working" temperature of the affected medium. When "thermoheliox" is used, the gas mixture enters the respiratory system with the nominal temperature T_n and usually has a gas-mixture temperature that is 10–20° lower at the outlet. In this equation, $\alpha(T_{36})$ is the kinetic parameter at normal body temperature (in this case, $5{\cdot}10^{-3}$ h^{-1}), and $\Delta t_{\exp}$ is the breathing time of an exposure (usually 0.5 h). From the equation, it follows that at a "working" temperature of 50 °C, $N/N_0 = 0.91$; at 60 °C, $N/N_0 = 0.41$; at 65 °C, $N/N_0 = 0.056$, i.e., at 50 °C, "thermoheliox" destroys only approximately 10%.

"Thermovaccination" as the stimulation of the immune response by "thermoheliox". One of the expected effects of using "thermoheliox" at increased temperature (70–90 °C) is thermoinactivation (thermal destruction) of viral particles, which means the appearance of destroyed viral particles that are unable to multiply protein-nucleic associates in the patient's blood. In this case, the higher the temperature of heliox is during the exposure, the more effective the destruction of viruses, and consequently, the higher the concentration of particles. Inactivated viral and protein components of the virus in the blood are natural vaccines. The body must synthesize antibodies according to a standard immune response procedure. A natural "thermovaccination" process occurs, and this is the natural protection of the body.

Considering the processes of thermodegradation of the virus N, the formation of antigen fragments a and the growth of antibodies J, the system of equations (1)–(6) can be modified in the following form (variables in this system of equations reflect the concentrations of an agent in the lesion zone or the amount of this agent in the body):

$$\begin{aligned} &\frac{dN}{dt} = k_1 N - \alpha(T)N - \xi N{\cdot}J, \quad t = 0, \quad N = N_0, \\ &\frac{da}{dt} = \alpha(T)N, \quad t = 0, \quad a = 0, \\ &\frac{dJ}{dt} = \sigma{\cdot}a, \quad t = 0, \quad J = 0. \end{aligned} \tag{7}$$

The σ parameter corresponds to approximately three days of "maturation" of the immune response ($\sigma \sim 0.015$ h^{-1}). It is assumed that antigen a is formed by inactivation and destruction of the viral particles. The process of "maturation" of the immune system with the formation of antibodies and the rate of "killing" of the virus and its removal from the system are linearly dependent on the concentration of antibodies J and the virus concentration ($-\xi N{\cdot}J$ term). It is qualitatively observed that at certain values of parameters α(T), σ and ξ in equation dN/dt, the

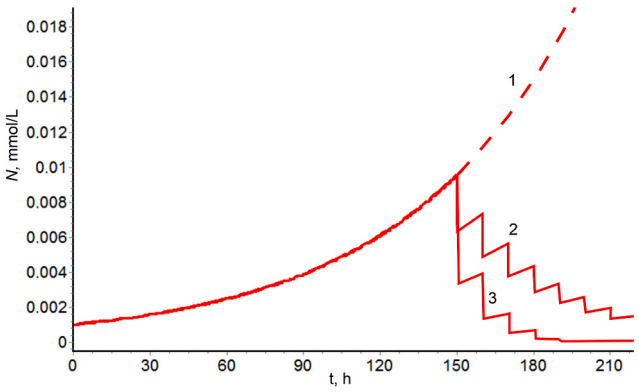

Fig. 6. Dynamics of the change in concentration of a virus (N) at $\omega = 0$: 1) accumulation of a virus in absence of therapeutic procedure (dotted line); 2) at periodic exposure by "thermoheliox", $T_w = 55$ °C; 3) $T_w = 60$°C.

negative terms exceed k_1 and the virus is killed.

Integration of the system of equations (2)–(7) leads to solutions in which the virus concentration grows exponentially, reaches a maximum and falls to zero. Computing calculations were performed at $\xi = 0.03$ h^{-1}, $\sigma = 0.015$ h^{-1}, $a(0) = J(0) = 0$, and the values of the parameters given above.

Fig. 7 shows the results of the calculation for a case in which the immune response is not sufficiently intense and the collapse (bifurcation point) occurs before the immune response gains full power. The treatment assumes complete destruction of the virus ($N = 0$), reaching a constant level for the number of affected cells (P) and a high level of antibodies (J). It is observed that the collapse (H^+ curve) occurs significantly earlier than the system is able to cope with the viral infection. To achieve a positive result, it is necessary to increase the power of the immune response. Within the model, this means that it is necessary to first increase the antigen concentration (parameter $\alpha(T)$) and possibly the efficiency of antibody synthesis.

The increased temperature in the development of acute inflammatory processes appears to have at least two consequences:

1) Increased temperature is a physical factor contributing to the thermal destruction of proteins and inactivation of the virus.
2) Appearance of inactivated viral particles and viral proteins in the blood is a classical factor of immune response development and synthesis of specific antibodies. In the framework of traditional immunization methods, the creation of a vaccine is based on the introduction of "weakened" and inactivated viral particles or their proteins into the body.

Of interest is the impact of the rate of thermal inactivation of the virus (α(T) parameter), the rate of "maturation" of the immune response (σ parameter) and the rate of virus destruction (ξ parameter) on the intensity of the immune response. Fig. 8 shows the results of calculation of the level of antibodies J and the amount of virus N with variation in the parameter α(T).

The results of the calculations with variation of parameter σ (the characteristic rate, the activation time of the immune system and antibody synthesis) are presented in Fig. 9, which shows that the higher the activation rate of the immune system is, the faster the virus is destroyed.

More significant effects are to be expected when using "thermoheliox", which is a breathing mixture of oxygen and helium with increased temperature (55–90 °C). Fig. 10 shows the results of calculations when the system of exposure with increasing the temperature from 50 to 90 °C is included in the mechanism of pathology development.

Estimations show that with the transition from 36 °C to 60 °C, α(T) increases by 10–15 times. Considering the relative multiplicity of lung treatment with "thermoheliox" (30 min, at an external temperature range of 70–90 °C), this process is presented in Fig. 10 by a jump in antigen concentration. It is observed that this result leads to a dramatic

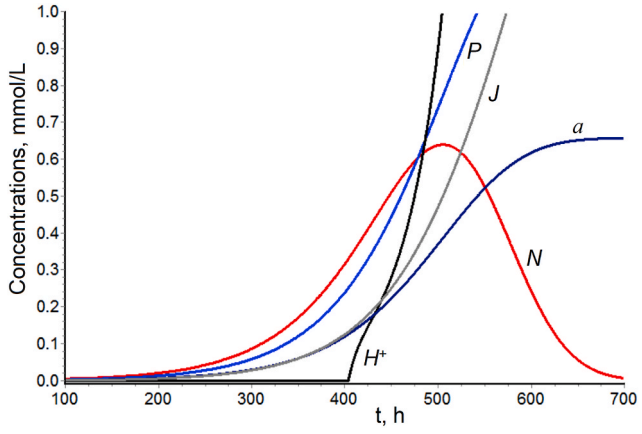

Fig. 7. Kinetics of immune response: accumulation of antigen a and antibodies J and the kinetic change in the amount of virus N and the product of cell destruction P in the case of a low-intensity immune response. The values of the parameters are given above.

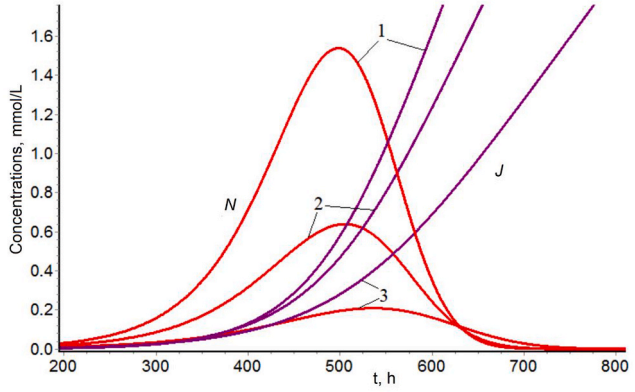

Fig. 8. Changes in the concentrations of virus N and antibodies J on time and variation in the rate of virus destruction due to thermal inactivation α(T): 1) $3{\cdot}10^{-3}$ h^{-1}; 2) $5{\cdot}10^{-3}$ h^{-1}; 3) $8{\cdot}10^{-3}$ h^{-1}.

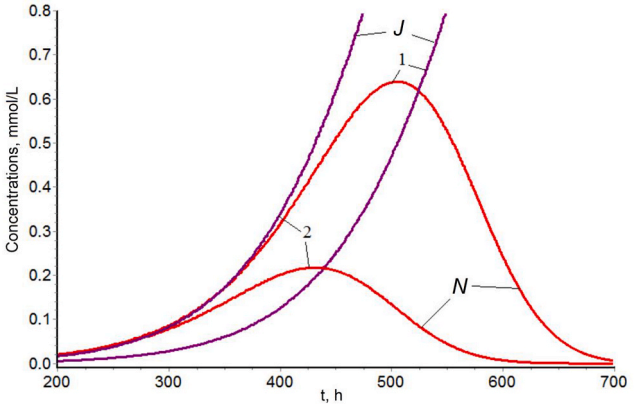

Fig. 9. Dynamics of changes in the concentrations of virus N and antibodies J with variation in the activation rate of the immune system σ: 1) 0.015 h^{-1}; 2) 0.045 h^{-1}.

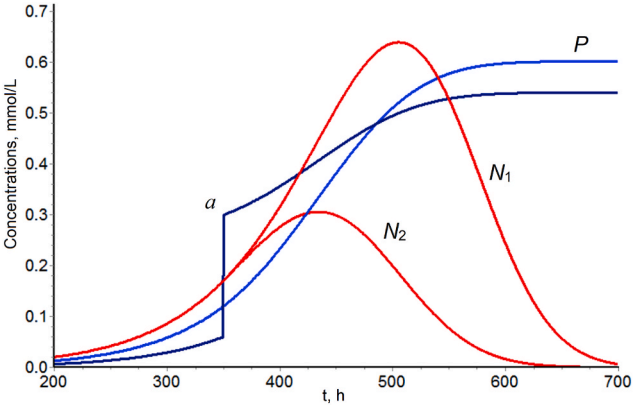

Fig. 10. Effect of "thermoheliox" on the development of the immune response (jump in antigen concentration (a)) and on the dynamics of virus destruction (N_2) and reaching a constant level for the number of affected cells (P) ("thermovaccination" on the 15th day of infection). For comparison, the dynamics of the change in virus concentration (N_1) without the thermal effect of "thermoheliox" (same curve N as in Fig. 7) are given.

increase in the rate of accumulation of *J* antibodies and a significant increase in the rate of elimination of the virus.

Theoretical analysis of the kinetic behavior of an organism infected with a coronavirus predicts significant activation of the immune response with increased temperature (therapeutic effect of temperature rise) under the thermal effect of a high-temperature (60–90 °C) respiratory mixture of oxygen and helium. The molecular basis of stimulation is the thermodestruction of viral particles with an increase in the concentration of destructured proteins, which act as an antigen for the synthesis of specific antibodies.

4. Conclusions

The considered kinetic model describes the main features of acute viral infection in the human body, the dynamics of antibody accumulation, and the immune response. The model creates a basis for the use of "thermoheliox" in treatment of patients affected by coronavirus and allows us to chart a way to create a new method of fighting viral lesions. Additionally, the model allows prediction the behavior of the system when the virus is destroyed and when the growth of pathogenic microflora is suppressed by antibiotics. The key role of carbonic anhydrase as an enzyme that "frees" lungs from CO_2 is analyzed in detail. The possibilities of inhibition of the acid-genic processes of antioxidants and the therapeutic effects of high temperature are considered.

This work describes the general regularities of stimulation of the immune system by "thermoheliox". Application of this method to each individual patient has personal features. It is important to control the general state of the body and blood oxygenation because it is necessary to achieve 97–99% the oxygenation of the patient's blood. To achieve these values at patient inhalation, it is necessary to individually set more or less oxygen content in heliox during a single procedure. The oxygen level in the helium-oxygen respiratory mixture should not be overly high. It is methodologically advisable to apply this method of vaccination for patients in the initial stage of infection and for patients with medium disease severity at repeated exposure with use of "thermoheliox" with temperatures in the range of 80–90 °C for 15–20 min with a rest period of 20–40 min. The work is carried out with clinicians who treat patients with coronavirus infection. They have achieved outstanding clinical results. The method of thermovaccination by "thermoheliox" may also be applicable for other respiratory viral infections. At least the kinetic model predicts such type of effects.

These recommendations have been used to treat patients affected by coronavirus. Clinical testing of "thermoheliox" as a new therapeutic approach against the coronavirus infection was conducted at N.V. Sklifosovsky Research Institute of Emergency Medicine in Moscow. Patients with lung lesions of 50–80% are brought to the clinic. Clinical procedures have been performed on dozens of patients. All patients have been cured. As a rule, the patient is exempt from coronavirus on day 2–3 of treatment (PCR test is negative). On day 3–4, the patient accumulates a full set of specific antibodies (IgG and IgM).

The principal advantages of "thermoheliox" stimulation of natural vaccination are the universality of the approach and its applicability to various viruses and pathogens.

CRediT authorship contribution statement

Sergey D. Varfolomeev: Conceptualization, Methodology, Supervision, Writing - original draft, preparation. **Alexander A. Panin:** Resources, Data curation, Validation, Writing - review & editing. **Valeriy I. Bykov:** Methodology, Validation. **Svetlana B. Tsybenova:** Software, Visualization, Writing - review & editing. **Alexander G. Chuchalin:** Conceptualization, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2020.109209.

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