Journal of Communicable Diseases
Volume 55, Issue 3 - 2023, Pg. No. 83-89
Peer Reviewed & Open Access Journal

Research Article

Role, Impact, and Effect of Angiotensin-converting Enzyme 2 (ACE2) in Patients with COVID-19 under High-altitude Conditions

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DOI: https://doi.org/10.24321/0019.5138.202343

I N F O

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How to cite this article:
Alymkulov A, Tagaev T, Vityala Y. Role, Impact, and Effect of Angiotensin-converting Enzyme 2 (ACE2) in Patients with COVID-19 under High-altitude Conditions. J Commun Dis. 2023;55(3):83-89.

Date of Submission: 2023-08-25
Date of Acceptance: 2023-10-05

A B S T R A C T

Background: A number of studies on the mechanisms of the positive effect of angiotensin (Ang) converting enzyme type 2 (ACE2) on the general condition of patients with coronavirus disease (COVID-19) reflect its direct correlation with the ACE2 concentration. This study investigated how the high-altitude factor affects angiotensin regulatory systems in patients with COVID-19 in susceptible populations.

Materials and Methods: A prospective cohort study of 335 patients with COVID-19 and concomitant arterial hypertension determined general clinical, immunological, and other parameters of health status. Group I included 135 patients of both genders with moderate COVID-19 caused by SARS-CoV-2 and moderate arterial hypertension (AH) who refused anti-hypertensive drugs. Losartan was given to 200 patients of both genders with a laboratory-confirmed mild SARS-CoV-2 infection and moderate AH in Group II.

Results: Comparing Group II to Group I, the general condition parameters were found to be noticeably improved in Group II. Additionally, patients in Group II showed positive blood coagulation system dynamics. When comparing Groups I and II, the immune response was seen to be more stable in Group II.

Conclusions: Group I patients with ACE2 deficiency set off a chain of events, most of which had to do with how Ang II affected the body by turning on angiotensin type 1 receptors. Observations made in Group II showed a favourable response to Ang-(1–7) and its effects on angiotensin type 2 receptors, Mas receptors, and the lowering of ACE2 bradykinin, blocking the implementation of the pro-inflammatory action through B1 receptors.

Keywords: COVID-19, Angiotensin-converting Enzyme 2, Arterial Hypertension, Mas Receptors, Angiotensin Type 1 Receptors

Introduction

Coronavirus disease (COVID-19) is a viral disease that affects the respiratory system and can cause serious problems such as kidney failure. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1–8] Additionally, it has been shown that patients with concomitant chronic illnesses had a greater mortality risk during the pandemic.[9]

Angiotensin (Ang) converting enzyme type 2 (ACE2) is expressed on the surface of numerous human cells and shows the affinity of the SARS-CoV-2 S-peptide to this ACE2.[9,10] It has been demonstrated that ACE2 promotes the progression of diseases and avoids the prevention of pulmonary fibrosis by converting Ang II to Ang-(1–7).[11–14] Additionally, bradykinin is prevented from reaching the bradykinin B1 receptor, which neutralises the harmful effects of bradykinin pathways, by ACE2 binding to bradykinin in the lungs.[15,16]

In a German study, the mechanisms of ACE2's effect on the platelet system were identified. The results of the study showed that Mas receptors are found on the surface of platelets. When Ang- (1–7) binds to these receptors, they release prostacyclin and nitric oxide, both of which help prevent blood clots.[17–19]

By binding to ACE2, SARS-CoV-2 limits the amount of ACE2 that enters the cell, which weakens the Ang-(1–7) formation axis and affects Mas receptors while improving the Ang II synthesis axis and affecting angiotensin type 1 receptors (AT1 receptors).[20–22]

It is interesting to note that ACE2 deficiency worsens with age and is more common in males than females,[23] which correlates with gender-specific COVID-19 mortality rates.[24] In particular, we are interested in the association of ACE2 deficiency with arterial hypertension (AH). In the study of Zhong et al., ACE2 deficiency has been associated with exacerbation of AH and cardiac hypertrophy due to the accumulation of Ang II.[25] ACE2 is a gateway for SARS-CoV-2, but the high affinity of the S-peptide for ACE2 indicates a low significance of the amount of ACE2 on the cell surface.[26]

Furthermore, the action of SARS-CoV-2 results in ACE2 deficiency, which increases the imbalance along the angiotensin 1–7 axis (weakening of protective mechanisms) and along the angiotensin 2 axis (increased harmful effect), thereby reducing the reserve of compensatory mechanisms with concomitant AH.[27,28]

The pandemic covered all regions of the planet, including the highlands. The high-altitude factor considered in our study leads to the occurrence of AH in people living in these regions. The highlands are characterised by low atmospheric pressure and low oxygen content in the air, which stimulates compensatory AH.[29] To date, no study has been conducted regarding the features of the action of ACE2 on the body in high-altitude conditions.

The objective of this study was to determine the mechanisms of the influence of the high-altitude factor on the angiotensin regulation systems in patients with COVID-19 in the most vulnerable groups of the population.

Materials and Methods

This is a prospective cohort study of 335 patients with COVID-19, divided into two groups, conducted in the Naryn Regional United Hospital of the Ministry of Health of the Kyrgyz Republic from April 20, 2021, to February 20, 2022. Group I (n = 135) consisted of patients of both genders with a laboratory-confirmed diagnosis of COVID-19 caused by SARS-CoV-2 of moderate severity, with concomitant moderate AH (International Classification of Diseases-10) who refused anti-hypertensive drugs. The average age of participants in this group was 58.42 ± 5.17 years. Group II (n = 200) included patients of both genders with a laboratory-confirmed diagnosis of a coronavirus infection caused by SARS-CoV-2 of moderate severity, with concomitant moderate AH (International Classification of Diseases-10) receiving anti-hypertensive treatment with angiotensin receptor blockers (losartan). The average age of participants in this group was 59.75 ± 4.61 years.

In order to capture the functional impact of ACE2 as a hypotensive enzyme, the blood pressure of participants was recorded with the calculation of pulse pressure, pulse, and blood saturation to assess the general condition; basic clinical tests, inflammatory markers, haemostasis system, interleukin (IL) status, and indicators of oxidative stress were conducted/ analysed. The assessment of the overall dynamics of recovery was carried out according to the parameters of the days of hospital stay.

The obtained data were presented as the mean ± standard deviation. Statistical analysis was performed using Excel (XLSTAT) v2020.1 (Microsoft, Addinsoft, Paris, France). Differences were considered statistically significant at $p < 0.05$. Patients' confidentiality was maintained, and informed consent was collected from all patients prior to the start of the study. This study was approved by the Bioethical Committee of the International Higher School of Medicine, Bishkek, Kyrgyzstan (Protocol No. 24 dated April 18, 2021).

Results

In this study, we found a constant high blood pressure in Group I as compared to Group II with comparative bradycardia. The main parameters remained at the reference values for patients with COVID-19, despite the differences in the days of hospital stay (Table 1).

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202343

Table 1.Parameters of the Functional State of the Studied Groups

Parameters	Group I (N = 135)	Group II (N = 200)	p Value
SBP (mmHg)	144.62 ± 9.12	128.83 ± 12.57	0.31
DBP (mmHg)	78.24 ± 3.15	72.59 ± 2.97	0.192
Pulse blood pressure (mmHg)	66.38 ± 1.97	56.24 ± 1.61	0.001
Heart rate (bpm)	75.21 ± 2.57	83.74 ± 3.24	0.04
Saturation (%)	90.74 ± 4.22	94.27 ± 3.85	0.54
Leukocytes (10^9/l)	4.89 ± 0.026	5.71 ± 0.077	0.001
Lymphocytes (%)	22.45 ± 1.86	31.05 ± 2.94	0.01
Platelets (10^9/l)	214.51 ± 12.44	255.19 ± 16.29	0.05
CRP (mg/l)	11.85 ± 0.71	8.34 ± 0.97	0.004
Number of days of hospital stay	17.3 ± 0.71	13.7 ± 1.53	0.03

All data are expressed as mean ± standard deviation.
*p < 0.05, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CRP: C-reactive protein

In the blood coagulation system, the patients showed varied levels of protocol values for the corresponding diagnosis, but even in this case, higher levels of coagulative activity were noted in Group I relative to Group II (Table 2).

In assessing the IL status and products of lipid peroxidation, the values were found to be located in the reference field for the corresponding clinical conditions of the study groups.

In Group I, the system of pro-inflammatory interleukins had higher values than the system of anti-inflammatory cytokines. This was shown by the fact that the tumour necrosis factor-α (TNF-α)/ IL-10 coefficient was equal to 1.136. In Group II, the TNF-α/ IL-10 coefficient was equal to 0.672, which showed that the two systems had a more balanced effect (Table 3).

Table 2.Parameters of the Blood Coagulation System in the Studied Groups

Parameters	Group I (N = 135)	Group II (N = 200)	p Value
Fibrinogen (g/l)	2.87 ± 0.043	3.11 ± 0.051	0.001
Activated plasma recalcification time (seconds)	41.85 ± 2.21	55.78 ± 3.46	0.001
Activated partial thromboplastin time (seconds)	28.26 ± 0.75	31.76 ± 0.64	0.001
Pro-thrombin index (%)	117.53 ± 2.14	103.71 ± 3.28	0.001
Pro-thrombin time (seconds)	10.56 ± 0.154	12.41 ± 0.293	0.001
Thrombin time (seconds)	12.59 ± 0.42	14.91 ± 0.97	0.020
D-dimer (ng/ml DDU)	172.15 ± 10.57	107.56 ± 15.21	0.001

*p < 0.05
All data are expressed as mean ± standard deviation.

Table 3.Parameters of Oxidative Stress and IL Status in the Studied Groups

Parameters	Group I (N = 135)	Group II (N = 200)	p Value
IL-1β (pg/ml)	2.97 ± 0.086	1.85 ± 0.052	0.001
IL-4 (pg/ml)	1.54 ± 0.067	2.08 ± 0.044	0.001
IL-6 (pg/ml)	3.01 ± 0.039	2.71 ± 0.018	0.001
IL-10 (pg/ml)	3.75 ± 0.063	5.91 ± 0.055	0.001
TNF-α (pg/ml)	4.26 ± 0.073	3.97 ± 0.081	0.008
Coefficient (TNF-α/ IL-10)	1.136 ± 0.028	0.672 ± 0.071	0.001
Lipid hydroperoxides (U/ml)	2.53 ± 0.116	1.33 ± 0.082	0.001
Ketones (U/ml)	1.84 ± 0.061	0.73 ± 0.073	0.001

All data are expressed as mean ± standard deviation.
*p < 0.05, IL-1β: Interleukin 1β, IL-4: Interleukin- 4, IL-6: Interleukin-6, IL-10: Interleukin-10, TNF-α: Tumor necrosis factor-α

ISSN: 0019-5138
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Discussion

Based on the findings, it was seen that the general course of the disease in both groups of patients corresponded to the protocol parameters. However, when comparing the groups with each other, a fascinating paradox was observed, wherein a vast majority of the studied parameters in Group I were worse than those in Group II. The activity and amount of ACE2, specifically its role in splitting Ang II to Ang-(1–7) and Ang I to Ang-(1–9), were linked to the occurrence of AH.[20,30–32] A significant role in the pathogenesis of the acquired differences in the studied groups was performed by the system of excretion, action, and degradation of angiotensin compounds.

Blocking AT1 receptors is one of the main mechanisms due to which Group I did better than Group II. The two primary impacts of SARS-CoV-2 on the angiotensin system are as follows: 1) the presence of an attached viral particle decreases the amount of ACE2 directly; 2) the presence of an attached viral particle starts a chain of reactions that leads to the production of IL-6, which increases the production of ACE2 (Figure 1).[33–35]

ACE2 raises the concentration of Ang II in the body, enhancing its effects. In patients with COVID-19 and concurrent essential AH who did not receive anti-hypertensive therapy, a

decrease in ACE2 concentration and an increase in Ang II concentration resulted in an imbalance between the regulatory and counter-regulatory functions of the angiotensin system (Figure 2).

In Group II, SARS-CoV-2 had a unidirectional effect, namely, it reduced the concentration of ACE2 due to direct consumption during the process of entering the cell. We think that a rise in IL-6, followed by a rise in ACE2 and Ang II, and a blockage of AT1 receptors lead to a further rise in the concentration of ACE2 in order to use Ang II through the AT2 receptors. Losartan helps keep the balance between the regulatory and counter-regulatory angiotensin systems in people with COVID-19 and essential AH who are also taking therapy to treat their high blood pressure (Figure 3).

In addition to its direct counter-regulatory effect, ACE2 shows its positive result through additional mechanisms: 1) by binding to the Mas receptors in the alveolar epithelium, it has an increased anti-inflammatory effect with a smaller number of infiltrations and a decrease in the risk of fibrosis in the lungs in the future; 2) binding to Mas receptors on the surface of platelets stimulates the release of prostacyclin and nitric oxide; the latter has an antithrombotic effect (Figure 4).[18,19,36,37]

Our study reflects indirect confirmation that the above mechanisms played a positive role in patients in Group II since their coagulation system parameters turned out to be better as compared to those in Group I in all phases of thrombosis (Figure 5).

Being expressed on the surface of the ciliated epithelium, ACE2 is involved in the process of neutralising bradykinin, making it possible for the latter to realise its effect by binding to B1 receptors.[15,16] In our study, the levels of cytokines, lipid peroxidation products, and the TNF-α/ IL-10 ratio all show that this mechanism reduces inflammatory activity. When the virus is directly introduced into the cell, it causes inflammation, which triggers the release and concentration of bradykinins in the lung tissue. This leads to persistent inflammation and a higher risk of fibrosis in Group I, where ACE2 activity is blocked, whereas the parameters are much better in Group II, where bradykinin activity is not blocked by ACE2 (Figure 6).

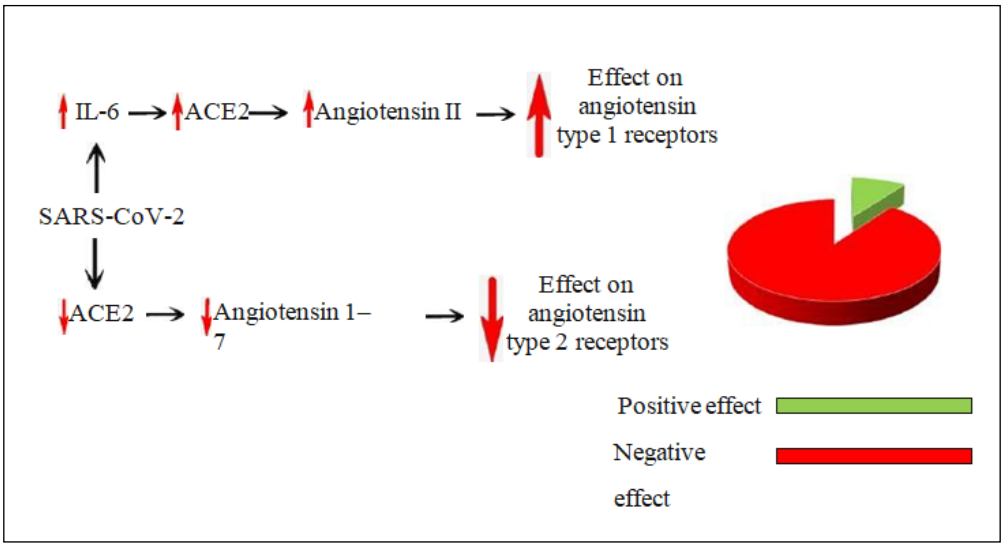

Figure 1.Effect of SARS-CoV-2 on the Angiotensin System

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202343

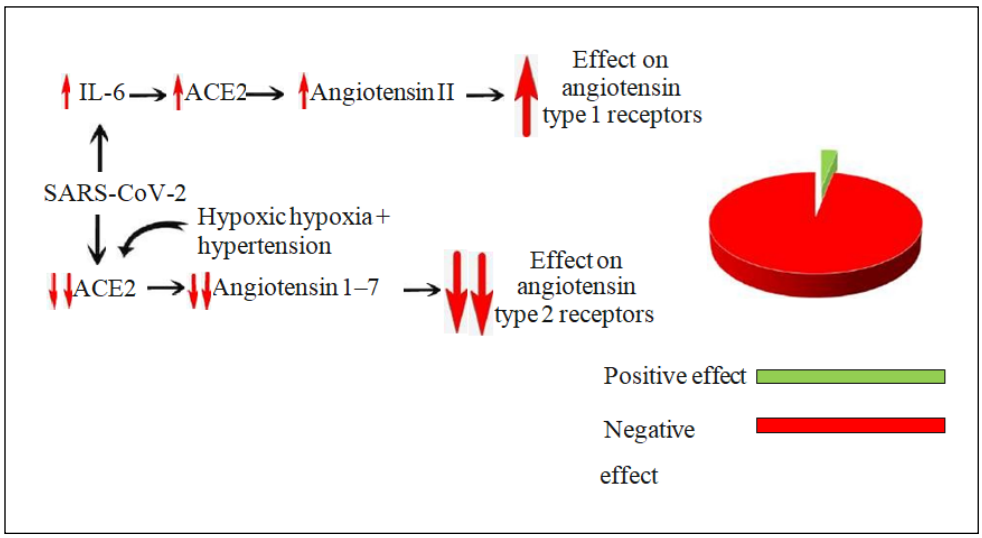

Figure 2.Mechanism of Imbalance of the Regulatory and Counter-regulatory Systems of Angiotensin Compounds in Group I

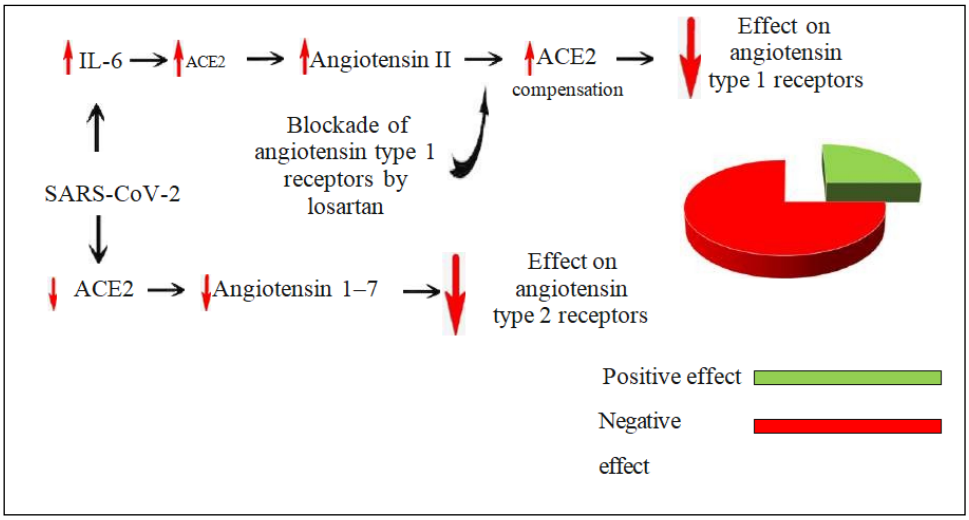

Figure 3.Mechanism of Rebalancing in the Regulatory and Counter-regulatory System of Angiotensin Compounds in Group II

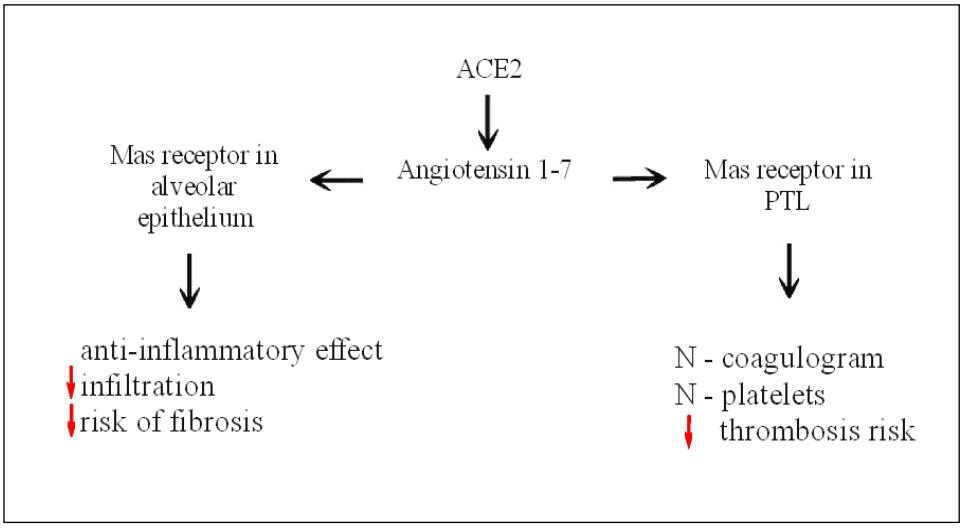

Figure 4.Alternative mechanisms for realizing the positive effect of ACE2

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202343

Conclusion

The axes of the angiotensin mechanisms of regulation and counter-regulation significantly influence the aetiology of the development of inflammation, thrombosis, and respiratory failure. As a result, Group I patients with ACE2 deficiency triggered a cascade of reactions, with a majority of axes linked to the effect of Ang II via activation of AT1 receptors. In Group II, processes were observed that showed positive responses to Ang-(1–7) and its impact on AT2 receptors, Mas receptors, and the reduction of ACE2 bradykinin, preventing the implementation of the pro-inflammatory effect through B1 receptors.

Authors' Contributions

Conception, design of the work, manuscript preparation, and data acquisition: Argen Alymkulov, Tugolbai Tagaev, and Yethindra Vityala. Clinical management: Argen Alymkulov. Manuscript preparation and data acquisition: Argen Alymkulov, Tugolbai Tagaev, and Yethindra Vityala.

Conflict of Interest: None

Source of Funding: None

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ISSN: 0019-5138
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