CLINICAL AND EXPERIMENTAL HYPERTENSION
https://doi.org/10.1080/10641963.2020.1764018

Taylor & Francis
Taylor & Francis Group

Check for updates

Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin–angiotensin system inhibitors

Xian Zhou[a]*, Jingkang Zhu[b]*, and Tao Xu[a]

[a]Department of Critical Care Medicine, Wuhan Fourth Hospital, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [b]Hypertension Laboratory, Fujian Provincial Cardiovascular Disease Institute, Provincial Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China

ABSTRACT

In December 2019, COVID-19 outbroke in Wuhan, China. The current study aimed to explore the clinical characteristics of COVID-19 complicated by hypertension. In this retrospective, single-center study, we recruited 110 discharged patients with COVID-19 at Wuhan Fourth Hospital in Wuhan, China, from January 25 to February 20, 2020. All study cases were grouped according to whether they had a history of hypertension. Then, a subgroup analysis for all hypertensive patients was carried out based on whether to take ACEI or ARB drugs. The mean age of 110 patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) were male patients. The main underlying diseases included hypertension [36 (32.7%)] and diabetes [11 (10.0%)]. Compared with the non-hypertensive group, the lymphocyte count was significantly lower in the hypertensive group (average value, 0.96×10^9/L vs 1.26×10^9/L), and analysis of clinical outcomes showed that the crude mortality rate was higher in the hypertensive group [7/36 (19.4%) vs 2/74 (2.7%)]. Patients treated with ACEI or ARB, compared with the control group, were younger (average age, 58.5 years vs 69.2 years), but there was no statistical difference in the crude cure rate [10/15 (66.7%) vs 15/21 (71.4%)] and the crude mortality rate [2/15 (13.3%) vs 5/21 (23.8%)]. In conclusions, the COVID-19 patients with a history of hypertension had a significantly lower lymphocyte count on admission. The elderly and comorbidities such as hypertension may together constitute risk factors for poor prognosis in patients with COVID-19. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension.

ARTICLE HISTORY
Received 12 April 2020
Revised 27 April 2020
Accepted 27 April 2020

KEYWORDS
Clinical characteristics; coronavirus disease 2019; hypertension; ACEI or ARB

Background

Since December 2019, Wuhan City, Hubei Province has successively discovered multiple cases of patients with pneumonia infected by a novel type of coronavirus. With the spread of the epidemic, other cases in China and abroad have also been found. As of March 21, 2020, a total of 81,054 COVID-19 cases in China have been confirmed.

The new coronavirus belongs to the beta-type coronavirus, which has an envelope and is round or oval, usually polymorphic, and 60–140 nm in diameter. Its genetic characteristics are significantly different from SARSr-CoV and MERSr-CoV. Current research shows that it has more than 85% homology with bat SARS-like coronavirus (bat-SL-CoVZC45). Recently, the International Virus Classification Commission had proposal named the novel coronavirus as "SARS-CoV-2"(1), and the World Health Organization has officially named the novel coronavirus pneumonia as "COVID-19."

At present, it has been confirmed that receptor-binding mechanism in infection of host cells by novel coronavirus is the binding of the coronavirus S protein to the human angiotensin-converting enzyme 2 (ACE2) protein, which involves in the regulation of blood pressure in the human body (2). It is widely present in the lungs, heart, kidneys, and intestines. Additionally, studies had reported that a considerable number of patients with COVID-19 were complicated by underlying diseases such as hypertension and the proportion of patients with hypertension was high. Peng et al. showed that among 138 COVID-19 patients, the proportion of patients with hypertension was the highest (43/138, 31.2%) (3). Huang et al. also found that 15% of patients with COVID-19 had hypertension, ranking second among all comorbidities (4). In addition, there were reports that most of the deaths disclosed during the early stage of the COVID-19 epidemic were complicated by hypertension. However, at present, there were no researches about the clinical characteristics of COVID-19 patients with hypertension and the effects of taking ACEI or ARB drugs on patients' prognosis. Therefore, we selected hypertension as a case–control retrospective study to investigate the clinical characteristics of hypertensive patients exposed to the COVID-19.

Methods

Study design and patient population

This case series was approved by the institutional ethics board of Wuhan Fourth Hospital (KY2020-027-01). All study cases were from confirmed patients with COVID-19 at Wuhan Fourth Hospital discharged from January 25 to February 20, 2020. Wuhan Fourth Hospital is located in Wuhan, Hubei Province, which is one of the first batch of COVID-19

CONTACT Tao Xu dcxutao@163.com Department of Critical Care Medicine, Wuhan Fourth Hospital, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430034, China

*These authors contributed equally to this article.

© 2020 Taylor & Francis

diagnosis and treatment hospitals requisitioned by the Wuhan Municipal Government. All patients included in the study were diagnosed and treated in accordance with the COVID-19 diagnosis and treatment program issued by the Chinese National Health Committee.

The medical records of patients were collected and analyzed by the research team of the Department of Critical Care Medicine, Wuhan Fourth Hospital. The clinical data included demographic data, medical history, underlying comorbidities, symptoms, signs, laboratory findings, treatment measures, and clinical outcomes. All study cases were grouped according to whether they had a history of hypertension. Then, hypertensive patients were further divided into two groups based on whether to take ACEI or ARB.

Statistical analysis

Prism 5 (GraphPad Software, La Jolla, CA, USA) and SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) were used to perform statistical analysis. Means of two groups were tested for the statistical difference using unpaired Student's *t*-test. The distribution of categorical variables was evaluated using Chi-square test. $P < .05$ was considered statistically significant. The association between whether to take ACEI or ARB and prognosis in COVID-19 patients with hypertension was examined by logistic regression analysis performed by SPSS.

Results

Baseline characteristics

The study included 110 patients with COVID-19 who had been discharged. The mean age of all patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) male patients. The most common symptoms at onset of illness were fever [94 (85.5%)], dry cough [71 (64.5%)], fatigue [38 (34.5%)], and dyspnea [25 (22.7%)]. Less common symptoms were pharyngalgia, anorexia, nausea, vomiting, diarrhea, dizziness, headache, and myalgia. Patients with fever were mainly moderate fever [66 (60.0%)]. Common underlying diseases included hypertension [36 (32.7%)], diabetes [11 (10.0%)], and cardiovascular disease [10 (9.1%)] (Table 1).

Table 1. Baseline characteristics of patients diagnosed with COVID-19.

No. of patients	*N* = 110
Age, years, mean (SD)	57.7(14.2)
Sex, *n* (%)	
Female	50(45.5%)
Male	60(54.5%)
Signs and symptoms, *n*(%)	
Fever	94(85.5%)
39°C < T < 40°C	6(5.5%)
38°C < T ≤ 39°C	66(60.0%)
37.3°C ≤ T ≤ 38°C	22(20.0%)
T < 37.3°C	16(14.5%)
Dry cough	71 (64.5%)
Fatigue	38(34.5%)
Dyspnea	25(22.7%)
Pharyngalgia	3(2.7%)
Diarrhea	10(9.1%)
Anorexia	10(9.1%)
Nausea	1(0.9%)
Vomiting	1(0.9%)
Dizziness	2(1.8%)
Headache	1(0.9%)
Myalgia	5(4.5%)
Comorbidities, *n* (%)	
Hypertension	36(32.7%)
Cardiovascular disease	10(9.1%)
Diabetes	11(10.0%)
Cerebrovascular disease	3(2.7%)
Epilepsy	1(0.9%)
COPD	3(2.7%)
Asthma	1(0.9%)
Chronic kidney disease	2(1.8%)
Chronic liver disease	4(3.6%)
Malignancy	4(3.6%)
Rheumatoid arthritis	2(1.8%)

Clinical features of COVID-19 patients with hypertension

As shown in Table 2, compared to the non-hypertensive group, patients in the hypertensive group were significantly older (average age, 64.8 vs 54.3) and showed a significantly higher occurrence of dyspnea [15 (41.7%) vs 10 (13.5%)], diabetes [9 (25.0%) vs 2(2.7%)], and cardiovascular disease [7(19.4%) vs 3(4.1%)]. Remarkably, the lymphocyte count on admission was significantly lower in the hypertensive group (average value, 0.96×10^9/L vs 1.26×10^9/L). There was no statistical difference in the time from onset to hospitalization between the two groups. Clinical outcomes showed the two groups had no significant differences for crude cure rate, the rate of referral to high-level hospitals, and length of stay, but the crude mortality rate was higher in the hypertensive group than that in the control group [7(19.4%) vs 2(2.7%)]. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension.

Table 2. Comparison of clinical features in hypertensive and non-hypertensive patients diagnosed with COVID-19.

	Hypertension (*n* = 36)	Non-hypertension (*n* = 74)	*P* Value[a]
Age, years, mean (SD)	64.8(10.1)	54.3(14.8)	<.001
Sex			
Female	17(47.2%)	33(44.6%)	.795
Male	19(52.8%)	41(55.4%)	
Major signs and symptoms			
Fever	30(83.3%)	64(86.5%)	.660
Dry cough	26(72.2%)	45(60.8%)	.240
Fatigue	14(38.9%)	24(32.4%)	.504
Dyspnea	15(41.7%)	10(13.5%)	<.001
Major Comorbidities			
Cardiovascular disease	7(19.4%)	3(4.1%)	.022
Diabetes	9(25.0%)	2(2.7%)	<.001
Laboratory Findings			
White blood cell count, ×109/L, mean (SD)	6.51(5.0)	4.90(1.85)	.070
Lymphocyte count, ×109/L, mean (SD)	0.96(0.38)	1.26(0.59)	<.01
Hypersensitive c-reactive protein or c-reactive protein increased	29(80.6%)	54(72.8)	.386
Prognosis			
Clinical cure	25(69.4%)	62(83.8%)	.083
Transfer to mobile cabin hospital	0	1(1.3%)	
Transfer to high-level hospital	4(11.1%)	9(12.2%)	.877
Clinical death	7(19.4%)	2(2.7%)	<.01
Onset of symptom to hospital admission, days, mean (SD)	9.0(4.7)	9.0(5.9)	.978
Hospital stay, days, mean (SD)	11.1(5.6)	11.9(6.5)	.464

[a]*P* values indicate differences between hypertensive and non-hypertensive patients. $P < 0.05$ was considered statistically significant. Means of two groups were tested for statistical difference using unpaired Student's *t*-test. The distribution of categorical variables was evaluated using Chi-square test.

Clinical features of COVID-19 patients taking ACEI or ARB

The COVID-19 patients with a history of hypertension were divided into two groups according to whether to take ACEI or ARB drugs, of which 15 patients had previously taken ACEI or ARB were divided into ACEI or ARB group, and other patients were divided as control group. The patients in ACEI or ARB group were younger than that in the control group and the difference was statistically significant (average age, 58.5 vs 69.2). While there were no significant differences in lymphocyte counts, crude cure rate, crude mortality rate, onset time, and length of hospital stay between the two groups (Table 3). We classify patients transfer to high-level hospital and clinical death as a poor prognosis, and the prognosis between the two groups was examined by logistic regression analysis with adjustment for age, sex, hospitalization time, time from onset to hospital admission, and whether to take ACEI or ARB. As shown from Table 4, whether to take ACEI or ARB was not significantly associated with prognosis.

Discussion

In this report, we recruited 110 patients with COVID-19. From the results, we found that fever was the commonest symptom during the early stage, besides, the patient also showed other symptoms such as dry cough, fatigue, and dyspnea, and so on. In terms of underlying diseases, hypertension was the commonest comorbidity (32.7%). For the first time, this report showed that compared to the non-hypertension group, the hypertension group had significantly lower lymphocyte count. In addition, we grouped the COVID-19 patients with a history of hypertension based on whether to take ACEI or ARB for antihypertensive treatment, and found that there was no difference in clinical outcomes between the two groups.

As reported by other researchers (4–6), for most patients with COVID-19, the common symptoms were fever, dry cough, and fatigue, but we should be alert to the clinical manifestations of a few patients without fever at the time of consultation. Besides, we also should be wary of a few patients without clinical manifestations of the respiratory tract, such as anorexia, nausea, vomiting, diarrhea, and other clinical manifestations of the digestive system, as well as clinical manifestations of the nervous system such as dizziness and headache.

We observed about one-third of patients with COVID-19 were complicated by hypertension. This result was consistent with Peng et al. results which showed that 31% of 138 COVID-19 cases had hypertension (3). Until now, there were no effective drugs for the treatment of COVID-19. We observed that most patients used antiviral drugs (Arbidol Tablets or Lopinavir and Ritonavir Tablets) and antibiotics, and some patients used low-dose hormones (methylprednisolone) and immune globulin, and some critically ill patients had used oxygen therapy. In studies with limited conditions and data, it can be seen that there was no difference in cure rate between the hypertension group and the non-hypertension group, while the mortality rate in the hypertension group was higher, and the prognosis seems to be worse. However, it should be noted that the patients in the hypertension group were older and had a higher proportion of major comorbidities, which indicates that the elderly and comorbidities together constitute risk factors for poor prognosis to a certain extent.

Blood pressure is affected by many molecules, such as endothelin-1 (7), AngII, etc. (8,9). Like AngII, ACE2 belongs to the renin–angiotensin–aldosterone system and kallikrein–bradykinin system family and is also a blood pressure regulating protein (10,11), which can degrade AngII to form Ang1-7 and degrade Des-Arg (9) bradykinin (DABK) to an active peptide (12). As we all know, AngII and DABK can bind to corresponding receptors and play physiological roles such as constricting blood vessels, promoting value-added, inflammation, neutrophil infiltration, and pulmonary fibrosis (12,13). While Ang1-7 can bind to specific Mas receptors and exert diastolic blood vessels, anti-inflammatory, anti-proliferative, anti-fibrotic, and anti-alveolar epithelial cell apoptosis. Therefore, ACE2 indirectly exerts anti-inflammatory and anti-lung injury effects. Animal experiments show that ACE2 expression in hypertensive rats is decreased (14,15). ACE2 is also the binding protein of novel coronaviruses (16) like severe acute respiratory syndrome (SARS) (17). In studies on SARS, researchers found that coronavirus can cause ACE 2 levels to decline or even be absent (18,19), but the expression of ACE remains unchanged, and the balance of ACE2 and ACE in lung is broken (20), leading to Ang□ elevation and activation of the DABK-BK1 receptor pathway work

Table 3. Comparison of clinical features of hypertensive patients taking different antihypertensive drugs.

	ACEI or ARB (n = 15)	Other antihypertensive drugs (n = 21)	P Value[a]
Age, years, mean (SD)	58.5(10.1)	69.2(7.5)	.001
Sex			
Female	6(40.0%)	11(52.4%)	.516
Male	9(60.0%)	10(47.6%)	
Lymphocyte count, ×109/L, mean (SD)	0.87(0.33)	1.02(0.17)	.237
Prognosis			
Clinical cure	10(66.7%)	15(71.4%)	>0.99
Transfer to high-level hospital	3(20.0%)	1(4.8%)	.287
Clinical death	2(13.3%)	5(23.8%)	.676
Onset of symptom to hospital admission, days, mean (SD)	9.6(4.0)	8.6(5.2)	.528
Hospitalization time, days, mean (SD)	10.1(5.2)	11.7(6.0)	.405

[a]P values indicate differences between ACEI or ARB group and other antihypertensive drug groups. $P < 0.05$ was considered statistically significant. Means of two groups were tested for statistical difference using unpaired Student's t-test. The distribution of categorical variables was evaluated using Chi-square test.

Table 4. Logistic regression analysis to detect the relationship between taking ACEI or ARB and prognosis.

Variables	OR	(95% CI)	p value
Age	0.864	0.753 ~ 0.990	.036
Sex	0.139	0.016 ~ 1.200	.073
Hospital stay	1.127	0.961 ~ 1.322	.251
Time from onset to hospital admission	1.14	0.920 ~ 1.413	.231
AECI or ARB	0.140	0.009 ~ 2.208	.162

The association between whether to take ACEI or ARB and prognosis in COVID-19 patients with hypertension was examined by logistic regression analysis performed by SPSS with adjustment for age, sex, hospitalization time, time from onset to hospital admission, and whether to take ACEI or ARB.

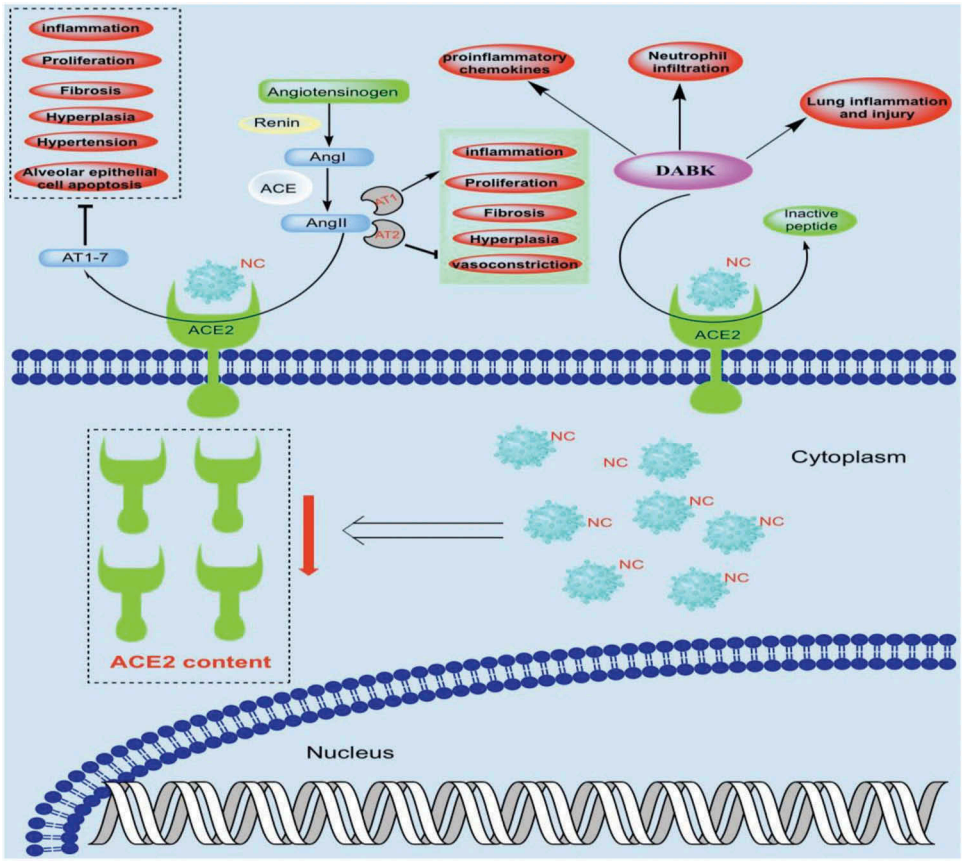

Figure 1. Possible mechanisms of ACE2-mediated coronavirus-induced lung injury. ACE: angiotensin-converting enzyme, Ang: angiotensin, NC: 2019 novel coronavirus, DABK: des-Arg (9) bradykinin. When entering alveolar cells, the novel coronavirus may reduce the expression of ACE2, resulting in reduced cleavage of AngII and DABK like SARS, leading to lung inflammation and injury, fibrosis, proinflammatory chemokine release, neutrophil infiltration, and lung inflammation.

together to cause lung inflammation, apoptosis, and accelerated lung injury. Because novel coronavirus and SARS both use ACE2 as a receptor, we speculate that novel coronavirus and SARS have similar mechanisms of action (Figure 1).

Reduced lymphocyte count is one of the diagnostic criteria in the National Health Commission's diagnosis and treatment program. The results of this study show that COVID-19 patients with a history of hypertension had lower lymphocyte count. In reports by Peng et al., a persistent decline in lymphocyte counts was observed in death cases (3). Chen et al. also reported that patients with COVID-19 who were over 50 years of age, and low lymphocyte counts can easily turn into severe cases (21). Maybe the lymphocyte count could reflect the severity of the condition in patients with COVID-19 to some extent, and this may explain the increased mortality in patients with a history of hypertension. Whether lymphopenia is due to the reduction of ACE2 caused by novel coronavirus invasion in COVID-19 patients with hypertension, the increase of AngII and Des-Arg bradykinin caused lung injury and inflammatory response, needs further basic experimental research.

After scientists announced that novel coronavirus enters target cells through the receptor ACE2, many experts in the cardiovascular field began to discuss whether COVID-19 patients with a history of hypertension should continue to use ACEI or ARB as antihypertensive drugs. Some scholars believe that ACEIs should be discontinued, while other scholars believe that the recommendations to discontinue ACEIs have no scientific basis. In our data analysis, we saw that a considerable number of cases were complicated by hypertension, so we further collected the patient's previous medication situation, and grouped them according to whether they were taking ACEI or ARB drugs. Statistical analysis under limited data showed that the prognosis of the two groups was not statistically different, but we need to note that there was a statistical difference in the age of the two groups. Further logistic regression analysis showed that patients whether had a history of taking ACEI or ARB were not correlated with prognosis. Studies show that both ACEI and ARB can cause increased expression of ACE2 (22,23). As the angiotensin type I receptor, ARB can increase Ang2, and then compensatingly increasing ACE2 expression. ACEI prevents Ang1 from forming Ang2, which in turn promotes ACE2 expression. But whether both types of drugs will affect COVID-19 patients with hypertension require further research.

This study has several limitations. First, some patients had been referred to other hospitals, so we can only calculate a crude cure rate and a crude mortality rate. Second, this is only a single-center study, and the sample size was also limited, especially for patients with hypertension. Therefore, it is difficult to accurately assess the risk factors for poor outcomes.

Conclusions

In general, our current work demonstrated that in 110 discharged patients with confirmed COVID-19 in Wuhan,

China, hypertensive patients had a significantly lower lymphocyte count on admission, the elderly and comorbidities such as hypertension may together constitute risk factors for poor prognosis. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension. However, as mentioned above, the sample size of the hypertensive patients we collected is small, and more researches are needed to confirm it.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ZX, ZJK, and XT conceived and designed the study. ZX collected all clinical data. ZX and ZJK did statistical analysis. ZX and ZJK wrote the paper. XT reviewed and edited the manuscript. All authors read and approved the manuscript.

References

1. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study Group. 2020. 2020.2002.2007.937862.
2. Yan R, Zhang Y, Li Y, Xia L, Zhou Q. Structure of dimeric full-length human ACE2 in complex with B0AT1. 2020. 2020.2002.2017.951848.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061. doi:10.1001/jama.2020.1585.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
5. Hui DS, I Azhar, Madani TA, I Azhar E, Ntoumi F, Kock R, Dar O, Ippolito G, Mchugh TD, Memish ZA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264–66.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13. doi:10.1016/S0140-6736(20)30211-7.
7. Gupta RM, Hadaya J, Trehan A, Zekavat SM, Roselli C, Klarin D, Emdin CA, Hilvering CRE, Bianchi V, Mueller C, et al. A genetic variant associated with five vascular diseases is a distal regulator of Endothelin-1 gene expression. Cell. 2017;170(3):522–533 e515. doi:10.1016/j.cell.2017.06.049.
8. Mitchell KD, Botros FT, Navar LG. Intrarenal renin-angiotensin system and counteracting protective mechanisms in angiotensin II-dependent hypertension. Acta Physiol Hung. 2007;94(1–2):31–-48. doi:10.1556/APhysiol.94.2007.1-2.5.
9. Stec DE, Juncos LA, Granger JP. Renal intramedullary infusion of tempol normalizes the blood pressure response to intrarenal blockade of heme oxygenase-1 in angiotensin II-dependent hypertension. J Am Soc Hypertens. 2016;10(4):346–51. doi:10.1016/j.jash.2016.01.023.
10. Shoemaker R, Tannock LR, Su W, Gong M, Gurley SB, Thatcher SE, Yiannikouris F, Ensor CM, Cassis LA. Adipocyte deficiency of ACE2 increases systolic blood pressures of obese female C57BL/6 mice. Biol Sex Differ. 2019;10(1):45. doi:10.1186/s13293-019-0260-8.
11. Fan Z, Wu G, Yue M, Ye J, Chen Y, Xu B, Shu Z, Zhu J, Lu N, Tan X, et al. Hypertension and hypertensive left ventricular hypertrophy are associated with ACE2 genetic polymorphism. Life Sci. 2019;225:39–45.
12. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, et al. A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000;87(5):E1–9. doi:10.1161/01.RES.87.5.e1.
13. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, McCray PB, Chappell M, Hackam DJ, Jia H, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg(9) bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol Lung Cell Mol Physiol. 2018;314(1):L17–L31. doi:10.1152/ajplung.00498.2016.
14. Tikellis C, Cooper ME, Bialkowski K, Johnston CI, Burns WC, Lew RA, Smith AI, Thomas MC. Developmental expression of ACE2 in the SHR kidney: a role in hypertension? Kidney Int. 2006;70(1):34–41. doi:10.1038/sj.ki.5000428.
15. Zhong JC, Huang DY, Yang YM, Li Y-F, Liu G-F, Song X-H, Du K. Upregulation of angiotensin-converting enzyme 2 by all-trans retinoic acid in spontaneously hypertensive rats. Hypertension. 2004;44(6):907–12. doi:10.1161/01.HYP.0000146400.57221.74.
16. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C-L, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–73. doi:10.1038/s41586-020-2012-7.
17. Nicholls J, Peiris M. Good ACE, bad ACE do battle in lung injury, SARS. Nat Med. 2005;11(8):821–22. doi:10.1038/nm0805-821.
18. Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, Simmons G, Hofmann H, Kuri T, Weber F, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol. 2010;84(2):1198–205. doi:10.1128/JVI.01248-09.
19. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther. 2010;128(1):119–28. doi:10.1016/j.pharmthera.2010.06.003.
20. Dijkman R, Jebbink MF, Deijs M, Milewska A, Pyrc K, Buelow E, van der Bijl A, van der Hoek L. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol. 2012;93(Pt 9):1924–29. doi:10.1099/vir.0.043919-0.
21. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, Zhang M, Tan J, Xu Y, Song R, et al. Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 Novel Coronavirus in the early stage. medRxiv Feb 12,2020.
22. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, Hamie QM, Meier CF, Hunziker S, Forras-Kaufmann Z, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids. 2015;47(4):693–705. doi:10.1007/s00726-014-1889-6.
23. Ferrario CM, Varagic J. The ANG-(1-7)/ACE2/mas axis in the regulation of nephron function. Am J Physiol Renal Physiol. 2010;298(6):F1297–1305. doi:10.1152/ajprenal.00110.2010.