The Effect of COVID-19 on Blood Pressure Control in Hypertension Patients– A Literature Review

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Abstract

COVID-19 is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). First identified in Wuhan, China, in December 2019, and declared an International Public Health Emergency in January 2020, the WHO declared a pandemic in March 2020. Hypertension, a disease that has long been a problem for most people in Indonesia and around the world . COVID-19 can affect blood pressure control for people with hypertension due to obstruction of the RAAS system. This research was conducted to find out what effect COVID-19 has on blood pressure control in people with hypertension. In the condition of COVID-19 patients with comorbid hypertension, SARS-CoV-2 which attacks ACE2 can eliminate the role of ACE2 in the RAAS system. Inhibition of ACE2 can also cause buildup of angiotensin II which has a vasoconstrictive effect. This results in the absence of homeostasis in the blood pressure control system and makes blood pressure conditions that continue to be at high pressure.

Keywords: ACE2, Blood Pressure Control, Comorbidity, COVID-19, Hypertension, RAAS.

Introduction

Hypertension is a condition of systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg on three tests within 5 minutes between the three examinations[1]. Hypertension is caused by a combination of genetic and environmental factors. Genetic factors in the pathogenesis of hypertension are played by at least 35 genetic locus, 12 of which are newly identified locus. Environmental factors that have the biggest role include hyperuricemia[2,3]. Smoking, alcohol, unhealthy diet, lack of physical activity, and central obesity[4,5]. This disease will arise when there is an imbalance between stroke volume and peripheral resistance due to functional / structural abnormalities of various organs that affect both chronically. Hypertension itself does not cause death directly, but can lead to various complications with high morbidity and mortality, including kidney disease, stroke, and heart disease[6] . This condition is exacerbated by the emergence of a new disease in 2019 which is pandemic, namely Corona Virus Disease 2019 (Covid-19).

COVID-19 is a respiratory disease caused by infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) virus and was identified in December 2019 in Wuhan, China[7]. Research conducted by Fang 2020 states that 23.7% of COVID-19 patients suffer from hypertension[8]. Another study conducted by Zheng 2020 shows that the complication with the highest prevalence in COVID-19 patients is hypertension with a proportion of 30%[9].

It is well known that the main transmission of SARS-CoV-2 is via droplets. However, there is a possibility of fecal-oral transmission The virus can pass through mucous membranes, especially the nasal mucosa and

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larynx, then enter the lungs through the respiratory tract. Furthermore, the virus will attack target organs that express Angiotensin Converting Enzyme 2 (ACE2), such as the heart, lungs, renal system and gastrointestinal tract[10,11]. The S protein in SARS-CoV-2 facilitates the entry of the corona virus into target cells. Viral entry depends on the ability of the virus to bind to ACE2, the extracellular membrane receptor expressed on epithelial cells, and depends on the priming of protein S to the cellular protease, namely TMPRSS2[12].

S-protein SARS-CoV-2 which binds to the ACE2 receptor causes a decrease in ACE2 regulatory activity, which in turn occurs overproduction of angiotensin by the ACE enzyme due to the small amount of ACE2 capable of becoming angiotensin (1-7). SARS-CoV-2 binds to ACE2 to stimulate peptidase incorporation and the virus can apply ACE2 from the RAAS system pathway[13].

RAAS has the same endogenous counterregulation system as any other homeostatic system. The RAAS counter-regulation system has an important component, namely ACE2. ACE2 will be widely expressed in the kidney and heart, as well as in target cells especially SARSCoV-2, pulmonary epithelial cells. ACE2 is an enzyme that determines the main regulatory activity resulting in decreased levels of angiotensin II to angiotensin (1-7). Angiotensin (1-7) has a role in the process of decreasing vasoconstrictive action and proliferation caused by angiotensin II and mediated by Angiotensin II Receptor type 1 (AT1R). An imbalance between ACE1 and ACE2 can contribute to the deregulation of the blood pressure system[14]. This research was conducted to determine the effect of COVID-19 on blood pressure control in hypertension patients.

Methodology

Articles were collected using Pubmed and Science Direct database. The search words include *ACE2*, Blood Pressure Control, Comorbidity, COVID-19, Hypertension, *RAAS*. Articles were collected from the year 2015-2020 and indexed in Scimago and Scopus.

The incidence of hypertension is one of the comorbidities in COVID-19

Hypertension is a disease that causes the highest death rate in the world. Hypertension can also kill silently and can lead to various complications affecting various organs, including cardiovascular disease, hypertensive encephalopathy, cerebrovascular hypertension, and hypertensive retinopathy[15]. Hypertension is one of the common comorbidities found in sufferers of COVID-19, about 15% of cases of hypertension are found in COVID-19 patients[16].

Based on the data that has been obtained, the most common comorbidities found in COVID-19 patients are hypertension, diabetes and cardiovascular disease. Several studies have stated that hypertension is the most common comorbidity, followed by diabetes mellitus and cardiovascular disease. Several studies show **the incidence of hypertension is one of the comorbidities in COVID-19** in table 1.

Table 1. Incidence rates of hypertension and other comorbidities in COVID-19

Reference	N	HT	DM	CVD	COPD	CKD
COVID-19 in China						
(Ye. et.al., 2020)						
(Chen, T. et al., 2020)	1.099	164	81	42	12	8
(Zhang, G. et al., 2020)	274	39	23	7	7	4
(Liu. et al., 2020)	221	54	22	37	6	10
(Wang, D. et al., 2020)	137	13	14	10	2	-
(Chen, Q. et al., 2020)	138	43	14	27	4	4
(Chen, R. et al., 2020)	145	21	14	1	3	3
(Cao. et al., 2020)	507	28	13	14	6	5
(Zhou. et al. 2020)	102	17	5	5	6	1
(Mo, P. et al., 2020)	191	58	36	15	6	2
(Wang, Z. et al., 2020)	155	37	15	22	5	6
COVID-19 in Italia	69	9	7	8	6	-
(Grasselli. et al., 2020)	1.591	509	180	223	42	36
(Benelli. et al., 2020)	411	193	67	93	48	22
COVID-19 in Amerika	167	67	38	68	36	43
(McMichael. et al., 2020)	5.700	3.026	1.808	966	920	454
(Richardson. et al., 2020)						

Notes : N : Number of patients in the study, HT : Hypertension, DM : Diabetes Mellitus, CVD : Cardiovascular Disorder, COPD : Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease

In a study conducted by Ye, et al., 2020 on 1099 patients in China, the incidence of comorbidity for hypertension, diabetes, and CVD was 164 patients, 81 patients, 42 patients. Likewise with the study conducted by Chen T et al., 2020 this study involved 274 patients infected with COVID-19, stating that the incidence of hypertension, diabetes and CVD was 39 patients, 23 patients, 7 patients. With similar results, Zhang, G et al 2020 in a study involving 221 patients stated that the incidence of hypertension, diabetes and CVD was 54 patients, 22 patients, 37 patients. Liu et al., 2020 in their study involving 137 patients stated that the incidence of hypertension, diabetes and CVD was 13 patients, 14 patients, and 10 patients. Wang D, et al., 2020 in their study also showed that hypertension was the most comorbid among the 138 patients involved, with the incidence of comorbidity for hypertension, diabetes and CVD being 43 patients, 14 patients, and 17 patients. Chen Q et al., 2020 in their study involving 145 patients stated that the incidence of hypertension, diabetes and CVD was 21 patients, 14 patients, and 1 patient. In a study conducted by Chen R et al., 2020 on 507 patients, the comorbidity for hypertension, diabetes and CVD was 28 patients, 13 patients, and 14 patients. Cao et al., 2020 in their study involving 102 patients stated that the incidence of comorbid hypertension, diabetes, and CVD was 17 patients, 5 patients, and 5 patients. Zhou et al., 2020 in his study involving 191 patients showed that the incidence of comorbidity for hypertension, diabetes and CVD was 58 patients, 36 patients, and 15 patients. Mo P, et al., 2020 in a study involving 155 patients stated that the incidence of comorbidity for hypertension, diabetes, and CVD was 37 patients, 15 patients, and 22 patients. Wang, Z. et al., 2020 in their study also showed that hypertension was the most comorbid among the 69 patients involved, with the incidence of comorbidity for hypertension, diabetes, and CVD being 9 patients, 7 patients and 8 patients.

There is research in other countries, namely in Italy, this study was conducted by Grasselli et al., 2020 with 1,591 patients showing the incidence of comorbidities for hypertension, diabetes, and CVD was 509 patients, 180 patients, and 223 patients. With similar results from Benelli et al., 2020 in their study involving 411 patients, the incidence of hypertension, diabetes and CVD was 193 patients, 67 patients, and 93 patients.

In addition, there is a study in America, this study was conducted by McMichael, et al., 2020 where 167 patients stated that the incidence of comorbid hypertension, diabetes and CVD was 67 patients, 38 patients, and 68 patients. Richardson et al., 2020 in a study involving 5,700 patients in America, showed that the incidence of comorbidity for hypertension, diabetes and CVD was 3026 patients, 1,808 patients, and 966 patients.

Table 2. The effect of COVID-19 on blood pressure control

	n : 803	**Good blood pressure control (n : 662)**	**Poor blood pressure control (n : 141)**	**p**	**ref**
Blood pressure, mmHg					
SBP DBP Average DBP SD of BP MAP Pulse Pressure Sex Female Male Age <65 years ≥65 years Status Severity of COVID-19 Mild Moderate Severe Critical	137.0 ± 19.7 84.2 ± 12.8 9.5 ± 4.2 6.5±2.6 95.7±7.0 51.6±8.3 394 (49.1%) 409 (50.9%) 338 (42.1%) 465 (57.9%) 6 (0.8%) 468 (58.3%) 282 (35.1%) 47 (5.9%)	134.0 ± 18.0 82.7 ± 12.2 9.2 ± 3.9 6.3±2.5 93.6±5.3 49.9±6.8 320 (48.3%) 342 (51.7%) 282 (42.6%) 380 (57.4%) 216(0.5%) 394 (59.5%) 224 (33.8%) 41 (6.2%)	153.0 ± 18.5 91.2 ± 13.0 11.0 ± 5.0 7.0±3.0 105.0±5.8 59.8±9.8 74 (52.5%) 67 (47.5%) 56 (39.7%) 85 (60.3%) 3 (2.1%) 74 (52.5%) 58 (41.1%) 6 (4.3%)	<0.001 <0.001 <0.001 0.017 <0.001 <0.001 0.423 0.592 0.005	(22)
	n : 2828	Good blood pressure (n : 1.437)	Poor blood pressure (n : 1.391)	p	ref
Blood pressure, mmHg					
SBP DBP Average DBP SD of BP Sex Female Male Age <60 years ≥65 years	135.0±18.5 82.5±11.2 9.2±4.0 6.2±2.4 1.386(48.8%) 1.442 (51.2%) 1.148(44.3%) 1.680(55.7%)	132.0±16.8 80.7±10.8 8.9±3.7 5.8±2.2 672(47.8%) 698(48.2%) 526(46,5%) 689(41,6%)	162.0±17.3 98.5±11.7 10.3±4.3 6.7±2.7 714(52.2%) 745(51/8%) 622(53,5%) 991(58,4%)	<0.001 <0.001 <0.001 0.0016 0.424 0.593	(37)
Notes : n : Number of patients in the study, SBP: systolic blood pressure, DBP : diastolic blood pressure, MAP : mean arterial pressure, SD : standard deviation, RR :Respiratory rate					

Zhuang, Z et al. in his study of 803 patients in the above study, 609 had control of blood pressure at admission, and 295 (48.4%) had normal blood pressure at admission (SBP / DBP <140/90 mmHg). The mean systolic blood pressure and diastolic blood pressure at admission were 137.0 mmHg (± 19.7) and 84.2 mmHg (± 12.8), respectively. 82.4% (662/803) of COVID-19 patients had good blood pressure control, and 17.6% (141/803) had poor blood pressure control during hospitalization. Compared to those with good blood pressure control, patients with poor blood pressure control had higher mean systolic and diastolic blood pressure, higher SD SBP and DBP, and higher MAP and PP during this period. Patients with poor blood pressure control are more likely to have COPD and chronic kidney disease. Zhuang Z, et al. in his research also stated that the severity status of COVID-19 was also an influence on good and bad blood pressure control. Zhuang Z, et al in their study also stated that age ≥65 years had more poor blood pressure control results than those aged <65 years. Zhuang Z, et al. in his research also stated that the incidence of COVID-19 with comorbid hypertension in men was more than in women. In a retrospective study of 803 coexisting COVID-19 patients with hypertension, it was found that a high mean SBP and high SBP / DBP variability during hospitalization were independently associated with death in hospital, ICU admission, and heart failure. The findings suggest that low and stable blood pressure control is optimal to achieve a favorable prognosis for coexisting hypertensive COVID-19 patients.

Gao X, et al. in his study of 2828 patients in the above study, 2828 patients had blood pressure control and 1437 (50.4%) had normal blood pressure at admission (SBP / DBP <140/90 mmHg). As many as 50.4% (1497/2828) COVID-19 patients had good blood pressure control and 49.6% (1391/2828) had poor blood pressure control.

Discussion

Hypertension is a disease that causes the highest death rate in the world. Hypertension can also kill silently and can lead to various complications affecting various organs, including cardiovascular disease, hypertensive encephalopathy, cerebrovascular hypertension, and hypertensive retinopathy[15]. Hypertension is one of the common comorbidities found in sufferers of COVID-19, about 15% of cases of hypertension are found in COVID-19 patients[16].

Based on the data that has been obtained, the most common comorbidities found in COVID-19 patients are hypertension, diabetes and cardiovascular disorders, with an incidence of 5.6% to 53%. In the study of Richardson et al, the co-morbid incidence rates of hypertension, diabetes and cardiovascular disorders were 56%, 31.8%, and 17%.

SARS-CoV-2 is the newest β-coronavirus type. There are seven species of β-coronavirus that have been identified to cause infection in humans, with four species causing the flu effect, and three of them (SARS, MERS and COVID-19) causing illness that results in death. SARS-CoV-2 contains S-protein which has the ability to push viruses into host cells. The SARS-CoV-2 virus envelope consists of glycoproteins that bind to ACE2 receptors. SARS-CoV-2 enters cells through the process of fusion of the viral membrane with the plasma membrane. After the virus enters the cell, the RNA genome from the virus will be released into the cytoplasm and the genome will be translated into two polyproteins and structural proteins. Then the viral genome that has been translated will begin to replicate. The newly formed glycoprotein envelope will enter the membrane of the endoplasmic reticulum or golgi body, and the combination of genomic RNA and nucleocapsid proteins will form the nucleocapsid. Then there is the growth of viral particles in the endoplasmic reticulum-golgi compartment (ERGIC). Finally, the virus particles contained in the vesicles will combine with the plasma membrane to release the virus[17].

S-protein SARS-CoV-2 which binds to the ACE2 receptor causes a decrease in ACE2 regulatory activity, which in turn occurs overproduction of angiotensin by the ACE enzyme due to insufficient amounts of ACE2 which can convert it into angiotensin (1-7). SARS-CoV-2

binds to ACE2 to stimulate peptidase incorporation and the virus can remove ACE2 from the RAAS system pathway[13].

Renin-Angiotensin-Aldosterone System (RAAS) is an important regulator that regulates blood volume and systemic vascular resistance. Meanwhile, when the baroreceptor reflex reacts to a short-term drop in arterial pressure, this RAAS has a role in systemic adjustment. There are three essential compounds in the RAAS system consisting of renin, angiotensin II and aldosterone. Of the three essential compounds, they function to increase the pressure of arterial blood flow to the distal tubule and increase beta-agonism as a reaction to increased renal blood flow. From this mechanism, the body can increase blood pressure for a long time. The binding of Angiotensin II which is the main active substrate of RAAS with Angiotensin II Receptor Type 1 (AT1R) causes vasoconstriction, salt retention and fibrosis[14].

RAAS has the same endogenous counterregulation system as any other homeostatic system. The RAAS counter-regulation system has an important component, namely ACE2. ACE2 will be expressed extensively in the kidney and heart, as well as in target cells especially SARSCoV-2, pulmonary epithelial cells. ACE2 is an enzyme that determines the main regulatory activity resulting in decreased levels of angiotensin II to angiotensin (1-7). Angiotensin (1-7) has a role in the process of decreasing vasoconstrictive action and proliferation caused by angiotensin II and mediated by Angiotensin II Receptor type 1 (AT1R). An imbalance between ACE1 and ACE2 can contribute to the deregulation of the blood pressure system[18].

Increased activity or expression of these compounds can occur in ACE2. In elderly people and male sex has the potential to have a higher ACE2 expression. Research conducted on mice shows that administration of ACE inhibitors and Angiotensin II Receptor blockers (ARBs) can increase mRNA expression for ACE2 in the heart, kidneys, aorta and various organs and tissues of the body. In a study conducted on ACEi-treated healthy humans and controls, the results showed that the duodenal ACE2 mRNA expression level increased by an average of 1.9 times compared to the untreated controls. Apart from gender and age, arterial hypertension and diabetes mellitus can be a factor in increasing ACE2. On the other hand, ACE2 levels decrease when there is inflammation and acute respiratory distress syndrome[19].

Consumption of ACEi or ARB class drugs causes an increase in ACE2 activity and expression in the heart of patients with COVID-19 with hypertensive comorbidities, so that they can play a protective role in the cardiovascular system. It is currently unknown whether ACE inhibitors or ARBs present in ACE2 in other organs can affect the level of ACE2 expression and activity in the lungs or not. If ACEi and ARB have a role in increasing the activity and expression of ACE2 in the lungs, then these two components play a dual role in handling COVID-19. On the other hand, if there is a higher level of ACE2 it can increase the susceptibility of cells to SARS-CoV-2 and activation of ACE2 can repair acute lung injury caused by SARS-CoV-2[20].

Therefore, ACE2 expression in patients infected with SARS-CoV-2 who are accompanied by comorbidities such as chronic hypertension who are treated with ARB-class drugs may protect against acute lung injury rather than put them at a higher risk of developing SARS. This can occur because of two complementary mechanisms, namely: preventing the activation of AT1R which is mediated by excessive angiotensin due to viral infection and increasing ACE2 so that angiotensin production by ACE decreases and increases the production of angiotensin vasodilators (1-7)[21].

ACE 2 receptors attacked by SARS-CoV-2 can decrease the activity of ACE2 in the RAAS system. ACE2 which has decreased its effectiveness can inhibit the process of angiotensin formation (1-7). In the RAAS feedback system, Angiotensin (1-7) is one of the compounds that plays a role. Inhibited ACE2 can also be a contributing factor to the buildup of angiotensin II which has a vasoconstrictive effect. This causes no homeostasis or imbalance in the blood pressure control system and results in blood pressure that continues

to be in a high pressure state. So that SARS-CoV-2 infection indirectly worsens the condition of patients with hypertension. Compared to those with good blood pressure control, patients with poor blood pressure control had higher mean systolic and diastolic blood pressure, higher SD SBP and DBP, and higher MAP and PP during this period. . Patients with poor blood pressure control are more likely to experience COPD and chronic kidney disease. In this study coexisting co-existing co-morbid co-patients with co-morbid hypertension, it was found that a high mean SBP and high SBP / DBP variability during hospitalization were independently associated with heart failure. Findings suggest that low and stable blood pressure is optimal for achieving a favorable prognosis for coexisting hypertensive COVID-19 patients[22].

Conclusion

Based on the data that has been obtained, the most common comorbidities found in COVID-19 patients are hypertension, diabetes and cardiovascular disorders, with an incidence of 5.6% to 53%. In the study of Richardson et al, the co-morbid incidence rates of hypertension, diabetes and cardiovascular disorders were 56%, 31.8%, and 17%.

SARS-CoV-2 infection that attacks ACE2 can eliminate the role of ACE2 in the RAAS system. Inhibition of ACE2 can also cause buildup of angiotensin II, which has a vasoconstrictive effect. This results in the absence of homeostasis in the blood pressure control system and makes blood pressure conditions that continue to be at high pressure.

Ethical Clearance – Not required since it is a literature review

Source of Funding – Nil

Conflict of Interest – Nil

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