The Relationship Between COVID-19 History and Arterial Vascular Elasticity Measured Using Accelerated Photoplethysmograph Analyzer in Medical Students

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ABSTRACT

Introduction: *COVID-19 is a global health issue that can affect the cardiovascular system at various levels and cause damage to the endothelium, leading to decreased arterial elasticity and vascular dysfunction. This study investigates the relationship between COVID-19 history and arterial vascular elasticity in medical students.* ***Methods:*** *This study used a case-control design and a purposive random sampling technique. Data on COVID-19 history and characteristics of the subjects were collected using questionnaires, while arterial vascular elasticity was measured using the accelerated photoplethysmograph (APG) analyzer, SA-3000P. The sample consisted of 24 COVID-19 survivors (case) and 24 subjects without COVID-19 history (control).* ***Results:*** *This study found that three subjects (6.25%) had optimal arterial vascular elasticity, 28 subjects (58.3%) had normal elasticity, and 17 subjects (35.45%) had sub-optimal elasticity. No significant differences were found in age, gender, physical activity, dietary habits, body mass index, and family history of hypertension, diabetes mellitus, heart disease, and obesity between the case and control groups ($p > 0.05$). The Chi-square test results showed a significant relationship between COVID-19 history and arterial vascular elasticity ($p = 0.003$; OR = 9.8; CI = 2.2-42.0).* ***Conclusion:*** *COVID-19 survivors are nine times more likely to have sub-optimal arterial vascular elasticity compared to those who have not been infected with the virus. COVID-19 survivors are advised to adopt healthy lifestyles and undergo regular check-ups to mitigate the risk of developing vascular diseases.*

Keywords*: arteries, COVID-19, vascular elasticity, students.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was declared a global health emergency. There have been 362,657 confirmed cases of COVID-19 in the age group of 15-24 years, which includes students and college students.[1] The mortality rate of COVID-19 is often associated with cardiovascular disease. COVID-19 can affect the cardiovascular system at various levels and cause damage to the endothelium.[2] This damage can lead to decreased arterial elasticity and potentially result in vascular dysfunction. Several previous studies have examined the relationship between COVID-19 history and cardiovascular health. Zanoli et al. (2022) from the University of Catania in Italy conducted research on a population with an average age of 55 years who were treated in three Italian hospitals from March 2020 to February 2021. The study revealed that 17 out of 90 individuals with a COVID-19 history had a decrease in arterial vascular elasticity based on pulse wave velocity measurements[3]. Additionally, Estabragh et al. (2022) conducted research on a population

aged 40-69 years and found that 534 out of 1,616 patients with a COVID-19 history experienced complications related to cardiovascular diseases.[4]

This study aims to investigate the relationship between COVID-19 history and arterial vascular elasticity in young subjects, specifically medical students. The rationale for this investigation is that COVID-19 infection may reduce arterial elasticity. The results of this study are expected to provide valuable information for developing preventive measures against vascular dysfunction.

METHODS

This study used a case-control design. The inclusion criteria for this study were students of the Faculty of Medicine at Universitas Pembangunan Nasional "Veteran" Jakarta aged between 18 and 25 years, with light to moderate physical activity (measured by the Global Physical Activity Questionnaire), good dietary habits (measured by the Adolescent Food Habit Checklist), and willingness to participate in this study. This study excluded individuals who had been diagnosed with cardiovascular diseases prior to COVID-19 infection, were active smokers, had a history of diabetes mellitus or dyslipidemia, and were taking medication for cardiovascular diseases.

Questionnaires in the form of a Google Form were distributed to active students of the Faculty of Medicine at Universitas Pembangunan Nasional "Veteran" Jakarta in 2023. The questionnaires contained questions about subject identity and criteria, including disease history, social history, treatment history, physical activity (GPAQ), dietary habit (AFHC), and family history of hypertension, diabetes mellitus, heart disease, and obesity. A purposive random sampling technique was used to select subjects with COVID-19 history and to select control subjects.

Arterial vascular elasticity was examined using the accelerated photoplethysmograph (APG) analyzer, SA-3000P. Photoplethysmography (PPG) is a simple, inexpensive, and commonly used method for monitoring heart rate. Its popularity as an alternative heart rate monitoring technique has recently been on the rise mainly due to its ease of use, convenience, and cost effectiveness. However, PPG-based monitoring techniques face a major challenge in accurately tracking PPG signals during routine daily activities and light physical exercise due to their susceptibility to motion artifacts (MA) caused by hand movements. In addition, environmental noise can also interfere with PPG signal acquisition, further compromising the accuracy of PPG signal estimation.[5]

PPG uses infrared light and a photodetector on the skin surface to measure volumetric changes in blood circulation.[5] The movement of blood in the vascular is indicated by the shape of the PPG waveform. The first derivative waveform of the PPG, also known as the velocity photoplethysmograph (VPG), shows the velocity of blood flow in the finger. Meanwhile, the accelerated photoplethysmograph (APG), the second derivative of the PPG, is used to determine the acceleration of blood flow. Analyzing the second derivative waveform of PPG can help to evaluate various cardiovascular diseases, including atherosclerosis, which causes arterial wall hardening.[6] The results of the examination on central vascular elasticity were categorized as optimal, normal, or sub-optimal.

This study was conducted at the Medical Education Research Center, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta from August to November 2023. This study received ethical approval from the Research Ethics Committee of Universitas Pembangunan Nasional "Veteran" Jakarta with certificate number 403/XI/2023/KEP.

RESULTS

In this study, 152 students completed the questionnaires, but only 81 students met the research criteria. A total of 24 subjects with COVID-19 history, diagnosed by swab examination (RT-Antigen) and RT-PCR, and 24 control subjects were selected by purposive sampling.

Table 1 shows the characteristics of the research subjects. The research subjects consisted of nine males (18.75%) and 39 females (81.25%) with a median age of 20 years. This study found that five subjects (10.5%) engaged in light physical activity, while 43 subjects (89.5%)

engaged in moderate physical activity with good dietary habits. The results of statistical tests indicated no significant differences in age (p = 0.857), dietary habit score (p = 0.155), sex (p = 1.000), physical activity (p = 1.000), body mass index (p = 0.489), and family history of hypertension (p = 0.770), heart disease (p = 0.739), diabetes mellitus (p = 1.000) and obesity (p = 0.837) between the case and control groups.

The results of the data analysis indicated that 58.5% of the subjects were diagnosed with COVID-19 by swab examination, and the majority had a mild form of the disease (87.5%). The majority of subjects were infected with COVID-19 once with a mild form of the disease, 12 to 24 months prior to the study (**Table 2**).

The Chi-square test results indicated a significant relationship between COVID-19 history and arterial vascular elasticity (p = 0.003; OR = 9.8; CI = 2.2 - 42.0). Specifically, COVID-19 survivors were found to be nine times more likely to have sub-optimal arterial vascular elasticity compared to those with no history of COVID-19 infection (**Table 3**).

Table 1. Characteristics of Research Subjects

Characteristics	Case	Control	p-Value
Age Median (min ± max)	20 (18-22)	20 (18-22)	0.857[a]
Sex n (%)			
Male	5 (20.8%)	4 (16.7%)	1.000[b]
Female	19 (79.2%)	20 (83.3%)	
Physical Activity n (%)			
Light	3 (12.5%)	2 (8.3%)	1.000[b]
Moderate	21 (87.5%)	22 (91.7%)	
Dietary Habit Score Median (min ± max)	15 (12-20)	12.5 (12-22)	0.155[a]
BMI n (%)			
Underweight	0 (0%)	2 (8.3%)	0.489[b]
Normoweight	24 (100%)	22 (91.7%)	
Family History n (%)			
Hypertension	13 (54,2%)	15 (62,5%)	0.770[c]
Heart Disease	5 (20,8%)	7 (29,2%)	0.739[c]
Diabetes Mellitus	11 (45,8%)	10 (41,7%)	1.000[b]
Obesity	7 (29,2%)	8 (33,4%)	0.837[c]

a = Mann-Whitney U test
b = Fisher's exact test
c = Chi-square test

Table 2. Overview of COVID-19 History in Research Subjects

COVID-19 History	Frequency (n)	Percentage (%)
Degree of Severity		
Mild	21	87.5
Moderate	2	8.3
Severe	1	4.2
Frequency of COVID-19 Infection		
Once	18	75
Twice	6	25
Last Time Infected with COVID-19 (months)		
12-24	17	70.8
25-36	6	25
37-48	1	4.2

Table 3. Relationship between COVID-19 History and Arterial Vascular Elasticity

COVID-19 History	Arterial Vascular Elasticity				Total		OR (95% CI)	*p*-Value
	Sub-Optimal		Optimal + Normal					
	N	%	N	%	n	%		
Yes	14	58	10	42	24	100	9.8 (2.2 - 42.0)	0.003
No	3	12.5	21	87.5	24	100		

DISCUSSION

Arterial blood vessels serve a dual function, both as fast transit channels for blood from the heart to the organs and as pressure reservoirs that generate a driving force during diastole.[7] They are adapted to the wide radius of the heart and offer little resistance to blood flow. The arterial endothelial layer, surrounded by a thick wall of smooth muscle and connective tissue, supports the elastic properties of the arteries. The wall contains many collagen fibers, which generate the elastic force for the high driving pressure of the blood coming from the heart, and many elastin fibers, which contribute to the elasticity of the arterial wall.[8]

Elastin is a protein found in the extracellular matrix and is the primary component of elastic fibers, which provide the elastic properties that is necessary for the large arteries of the cardiovascular system to function properly. A decrease in elastin can cause changes in the arterial wall structure, resulting in narrowing of the arterial lumen, increased arterial stiffness, and hypertension. In addition, abnormal arrangement or degradation of elastin fibers can alter the passive mechanical properties of the arterial wall. Fragmentation of elastin fibers can lead to inflammation and arterial wall hardening, which are major factors in cardiovascular diseases.[9]

The median age of the research subjects in both the case and control groups was 20 years, with no significant difference in age between the two groups (p = 0.857) (**Table 1**). Although endothelial aging is known to typically begin at age 60 and above, it can also occur every eight years at a young age.[10] Aging cells experience a decline in function, produce pro-inflammatory molecules, and degrade the matrix. Aging endothelial cells also tend to produce less of the vasodilator nitric oxide (NO), which can lead to decreased elasticity of arterial vascular.[11]

This study included a majority of female subjects in both case and control groups. This is due to the higher number of female students enrolled in the Faculty of Medicine at Universitas Pembangunan Nasional "Veteran" Jakarta in 2023 compared to male students. According to the data on Indonesian students in 2020, including new students and graduates, 56.10% were female and 43.90% were male.[12] The results of the Fisher's exact test showed no significant difference in sex between the two groups (p = 1.000). **Figure 1** shows that out of 48 subjects, nine were male. Among them, four subjects had normal arterial vascular elasticity, while five subjects had sub-optimal arterial vascular elasticity. Among female subjects, three had optimal arterial vascular elasticity, 25 had normal arterial vascular elasticity, and 11 had sub-optimal arterial vascular elasticity. It is important to note that sex may affect the structure and function of the carotid artery, which is a central artery. Arterial elasticity is an indicator of the risk of cardiovascular diseases. Studies have shown that women have a higher carotid quality intima-media thickness (QIMT) compared to men. In addition, the arterial vascular stiffness index based on pulse wave velocity (PWV) and aortic augmentation index (AIx) is higher in women than in men, suggesting that women are more susceptible to arterial aging.[13]

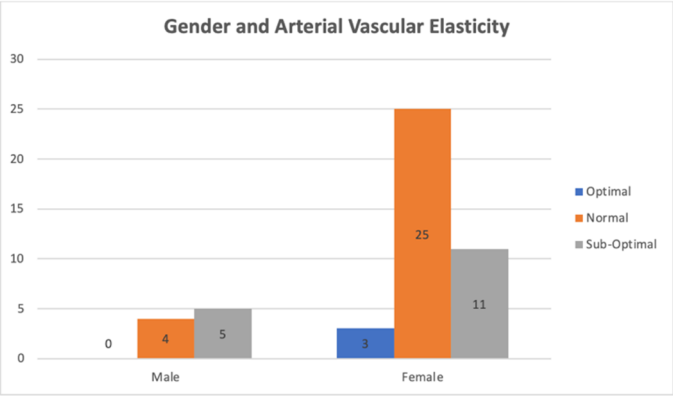

Figure 1. Sex and Arterial Vascular Elasticity

Furthermore, physical activity affects arterial vascular elasticity. This study found that the majority of subjects engaged in moderate physical activity. Among the five subjects with light physical activity, three had sub-optimal arterial vascular elasticity and the other two had normal arterial vascular elasticity. Of the 42 subjects with moderate physical activity, three had optimal arterial vascular elasticity, 25 had normal arterial vascular elasticity, and 14 had sub-optimal arterial vascular elasticity. The results of the Fisher's exact test showed no significant difference in physical activity levels between the case and control groups ($p = 1.000$). Regular physical activity can reduce arterial stiffness and may be a determinant of arterial hardening. This is due to the functional adaptation of the arteries.[14]

The results of the Mann-Whitney U test showed no significant difference in dietary habit scores between the case and control groups ($p = 0.155$). An unbalanced diet can cause various health problems. The intake of protein, carbohydrates, sodium, potassium, and vitamins can affect the elasticity of arterial vascular.[15] A poor diet can lead to hyperglycemia, increased fatty acid levels, and insulin resistance, which can cause endothelial dysfunction and arterial stiffness.[16]

This study included 24 subjects with COVID-19 history. The diagnosis was confirmed by swab examination (RT-Antigen) for 14 individuals (58.3%) and RT-PCR for 10 individuals (41.7%). Based on the severity of COVID-19, 21 subjects (87.5%) had a history of mild COVID-19, two subjects (8.4%) had a history of moderate COVID-19, and one subject (4.1%) had a history of severe COVID-19. On average, the subjects were infected with COVID-19 once approximately 22 ± 7.3 months prior to this study. The research subjects experienced several symptoms of COVID-19, including fever, cough, runny nose, sore throat, nasal congestion, loss of taste, headache, and loss of smell.

Arterial vascular elasticity data were obtained using the accelerated photoplethysmograph (APG) analyzer, SA-3000P. The examination results showed that three subjects (6.25%) had optimal arterial vascular elasticity, 28 subjects (58.3%) had normal arterial vascular elasticity, and 17 subjects (35.45%) had sub-optimal arterial vascular elasticity. Arterial vascular elasticity may be influenced by several factors. In this study, age, nutritional intake, social history, and medical history were controlled by the inclusion and exclusion criteria of the research subjects. The results of this study were not influenced by physical activity because there was no difference in physical activity between the arterial vascular elasticity groups.

The expression of SARS-CoV-2 on endothelial cells, which play a role in the regulation of immune responses, inflammatory reactions, coagulation, and platelet function, can lead to endothelial dysfunction and vascular disintegration. Enzymatic damage leads to the accumulation of bradykinin, which increases vascular permeability. Endothelial dysfunction can result in hyperinflammation and hypercoagulability, leading to changes in endothelial morphology, cell detachment from the basement membrane, and cell hypertrophy. Endothelial cell disintegration may expose the basement membrane to circulating platelets, resulting in platelet aggregation and thrombosis. In response to interleukin (IL)-1β and tumor necrosis factor (TNF)-α, endothelial cells express P-selectin, von Willebrand Factor (vWF), and fibrinogen, causing platelets to bind directly to them and become activated. This, in turn, leads to hypercontractile-activated endothelial cells, which can disrupt cell junctions and cause vascular leakage.[17]

SARS-CoV-2 also causes a decrease in ACE-II expression, which impairs the enzyme's ability to provide a protective effect and can lead to organ damage. This impaired activity can increase vascular inflammation, plaque formation, and vascular stiffness.[2] Endothelial cells lining the inside of the vascular secrete smooth muscle-relaxing material, namely endothelial-derived relaxing factor (EDRF), later identified as nitric oxide (NO), a gaseous second messenger molecule.[18] This viral attack reduces the bioavailability of nitric oxide by decreasing its production or increasing its degradation through reactive oxygen species

(ROS), which can alter vessel wall homeostasis.[19] Oxidative stress and pro-inflammatory cytokines activate nuclear factor kappa-B, leading to the transcription of pro-inflammatory cytokine genes and increased ROS production in NADPH oxidases. Furthermore, acute infection is strongly correlated with elevated C-reactive levels, which can cause arterial hardening by reducing the expression of endothelial nitric oxide synthase (eNOS), interleukin (IL)-6, and matrix metalloproteinase-9 (MMP-9). Elevated levels of MMP-9 can result in decreased elastin synthesis and fragmentation.[11]

The results of the Chi-square test showed a significant relationship between COVID-19 history and arterial vascular elasticity ($p = 0.003$). Another study conducted on 90 male survivors of severe COVID-19 and 180 healthy male subjects with an average age of 55 years also found a significant relationship between COVID-19 history and arterial vascular elasticity as measured using electocardiography.[3] Research on 40 men and women aged 50-60 years with moderate COVID-19 and overweight or obese body mass index showed endothelial dysfunction and decreased vascular elasticity as measured by peripheral artery tonometry (EndoPAT-2000).[19] Estabragh et al. (2022) found that COVID-19 patients aged 40-69 years had an increased risk of developing cardiovascular diseases, according to medical records.[4] The study found that the risk of cardiovascular diseases was lower in COVID-19 patients who were not hospitalized compared to those who were hospitalized. Additionally, the risk was higher in patients diagnosed with secondary COVID-19 than primary.[19] This study conducted on medical student subjects demonstrated that COVID-19 history is one of the important factors affecting arterial vascular elasticity at a young age.

COVID-19 can cause damage and inflammation to the endothelium due to viral toxicity, which can lead to vascular dysfunction and a decrease in vascular integration, resulting in decreased elasticity.[17,19] In Manisha Kar's 2022 research, which used pulse wave velocity, found that vascular elasticity was significantly higher in mild COVID-19 patients compared to moderate and severe COVID-19 patients.[20] In addition, arterial vascular elasticity can partially improve within 48 weeks after COVID-19 infection. An increase in the subendocardial viability ratio (SEVR) can indicate a balance of oxygen perfusion and arterial load, as well as improvements in heart rate variability. The therapy performed, comorbidities, and the age of the subject can affect the improvement in vascular elasticity.[3] **Figure 2** shows that out of 21 subjects with a history of mild COVID-19, 13 subjects had sub-optimal arterial vascular elasticity. Of these 13 subjects, eight were infected with COVID-19 within the past 12-24 months, and five were infected within the past 25-36 months. The remaining eight subjects had normal arterial vascular elasticity, with six having been infected with COVID-19 within the past 12-24 months, one infected 25 months ago, and one infected 40 months ago. Two subjects

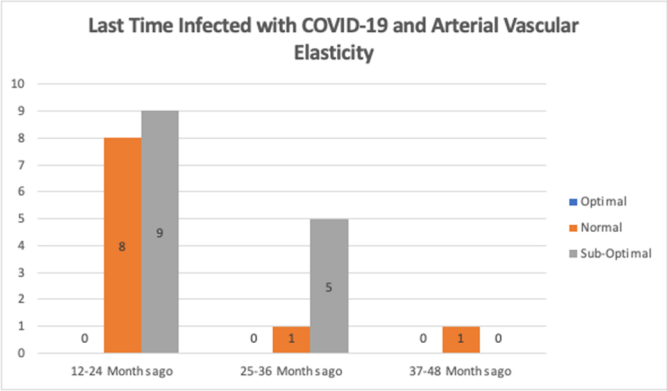

Figure 2. Last Time Infected with COVID-19 and Arterial Vascular Elasticity.

with a history of moderate COVID-19 were also assessed for central arterial vascular elasticity. One subject who was infected 12 months ago had normal elasticity, while the subject who was infected 24 months ago had sub-optimal elasticity. A third subject, who was severely affected by COVID-19 12 months ago, also had normal artery vascular elasticity. Although previous studies have suggested that arterial vascular elasticity is lower in patients with a history of moderate and severe COVID-19, the limited sample size of this study prevents the authors from drawing definitive conclusions. However, this study did find that 14 COVID-19 survivors (58,3%) had sub-optimal vascular elasticity, although they had recovered from COVID-19 more than 12 months ago. Therefore, efforts should be made to improve the vascular health of the research subjects.

Maintaining vascular health can be achieved through a balanced diet that includes sufficient energy intake to maintain an ideal body mass index. It is recommended to consume low-fat and high-fiber foods. Replacing red meat with fish, margarine with olive oil, and sweets with vegetables can be the first step in reducing body fat. In addition, fermented dairy products (without butter), fish, and lean meat are good sources of protein that can reduce arterial stiffness. Honey can also be used as a natural sweetener without affecting postprandial hyperglycemia. Moreover, reducing salt intake is crucial for vascular health. Maintaining a proper ratio of potassium intake is important to maintain blood pressure and reduce arterial stiffness. Vitamins and phytochemicals found in foods contain antioxidant, antiproliferative, and anti-inflammatory properties essential for preventing chronic diseases. These properties may also provide protection against atherosclerosis and arterial degeneration[21]. This study employed the Adolescent Food Habits Checklist to select the sample, which describes the dietary habits of high-calorie foods, fruits, and vegetables. Therefore, the nutritional intake of the research subjects could not be assessed to determine the relationship between food intake and improvements in arterial vascular elasticity.

Regular physical activity can help prevent arterial vascular hardening. It is recommended that both aerobic and resistance training be engaged on a weekly basis. These exercises can improve aerobic capacity, increase muscle mass and strength, and benefit bone mineral density and insulin sensitivity. Moderate intensity exercises such as yoga or Pilates are recommended for aerobic exercises.[22] This study assessed the subjects' physical activity using the Global Physical Activity Questionnaire, which includes questions about their work, transportation, and daily physical activity. However, it does not provide evidence of a causal relationship between their physical activity and the improvement of arterial elasticity following COVID-19 infection.

This study has some advantages, including the use of new tools, the inclusion of young subjects, and the fact that there are few related studies in Indonesia. However, there are also some limitations. This study did not examine the lipid profile of the research subjects to rule out dyslipidemia factors that affect vascular elasticity. In addition, no antibody examination was conducted to ensure that the control subjects had not been infected with COVID-19.

CONCLUSION

The results of the study indicated a relationship between COVID-19 history and arterial vascular elasticity. COVID-19 survivors are nine times more likely to experience sub-optimal arterial vascular elasticity than those who have not been infected with COVID-19. It is recommended that COVID-19 survivors adopt a healthy lifestyle and undergo regular check-ups to reduce the risk of vascular diseases.

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