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Original Article

Physiology Section

Assessment of Arterial Stiffness in Patients Recovered from Mild COVID-19 Disease using Pulse Wave Velocity: A Cross-sectional Study

VISHALKUMAR DASHOUNDHI[1], GIREESH P KHODNAPUR[2], AMRIT PODDAR[3], SUMANGALA M PATIL[4], JYOTI P KHODNAPUR[5]

ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) may manifest with different grades, such as mild, moderate, or severe. COVID-19 has many post-viral implications on different organ systems, including the vascular system. As the pandemic load increases, it is vital to identify any post-recovery complications and functional impairments of the arteries in patients who have recovered from mild COVID-19 disease.

Aim: Present study aimed to evaluate the functional impairment of the arteries, specifically arterial stiffness, in patients recovered from mild COVID-19 disease by assessing Pulse Wave Velocity (PWV).

Materials and Methods: The present cross-sectional study was conducted at Shri BM Patil Medical College and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India, from April 2021 to June 2021. A total of 18 patients who had recovered from mild COVID-19 disease (Group 1: n=18) and age- and sex-matched healthy participants (Group 2: n=18) accessing health services at the hospital were included in the study. Data were collected for physiological parameters such as height, weight, Body Mass Index (BMI), Pulse Rate (PR), Blood Pressure (BP), and arterial stiffness parameters like PWV. The data were statistically analysed using the Mann-Whitney U test and Spearman's correlation.

Results: The study included 36 participants aged between 18 and 65 years. In the present study, patients recovered from mild COVID-19 disease showed a statistically significant increase in brachial-ankle Pulse Wave Velocity (b-a PWV) ($p=0.001$) and carotid-femoral Pulse Wave Velocity (c-f PWV) ($p<0.01$) compared to the controls and positively correlated with Mean Arterial Pressure (MAP).

Conclusion: The present study concluded that even a mild degree of COVID-19 enhanced PWV, reflecting an increase in arterial stiffness. This study may assist clinicians in follow-up visits and rehabilitation to reduce the burden of the disease.

Keywords: Arteries, Arterial stiffness, Coronavirus disease-2019, Rehabilitation

INTRODUCTION

The COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. This disease was declared a universal pandemic by the World Health Organisation (WHO) in March 2020 [1]. Even though this disease primarily affects the respiratory system, Hendren NS et al., reported that different stages, like moderate to severe cases of COVID-19, had acute endothelial damage involving various cardiovascular target organs [2]. The European Society of Cardiology (ESC) review noted a clear two-way relationship between Cardiovascular Disease (CVD) and COVID-19 [3].

In the initial stages of COVID-19, respiratory symptoms are commonly observed. These can range from mild symptoms such as cough, fever, and shortness of breath to more severe symptoms like severe pneumonia and Acute Respiratory Distress Syndrome (ARDS). The virus primarily affects the respiratory system by targeting the lungs and airways. In some cases, particularly in severe or critical cases, COVID-19 can progress to affect the cardiovascular system. This can occur through various mechanisms, including direct viral invasion of the heart muscle, inflammation, and the body's immune response. COVID-19 can cause myocarditis (inflammation of the heart muscle), arrhythmias (irregular heart rhythms), and in severe cases, it may lead to heart failure or cardiovascular complications [4,5].

It has also been noticed that the prognosis is not favourable in patients suffering from CVD [6]. COVID-19 has been observed to affect the cardiovascular system in several ways, and it can lead to complications and target organ failure, particularly in severe cases. One of the early steps in the progression of COVID-19 is the involvement of endothelial cells, which line the blood vessels. The SARS-CoV-2 virus, which causes COVID-19, can directly infect and damage these endothelial cells. This endothelial involvement can lead to inflammation, disruption of normal blood vessel functioning, and the formation of blood clots [6-10].

The extent of structural changes in the arterial wall is not well understood in patients recovered from mild COVID-19 disease. Structural changes in the arterial system, such as arterial stiffness, can lead to alterations in arterial elasticity. PWV is a commonly used measure to assess arterial stiffness and elasticity. PWV is the speed at which the pressure wave travels along the arterial tree, typically measured between two arterial sites, such as the carotid and femoral arteries. Higher PWV values are associated with increased arterial stiffness and serve as an independent marker of cardiovascular risk. Incorporating PWV measurements into cardiovascular risk assessment can enhance risk stratification and aid in the management of individuals at risk for cardiovascular events. The carotid-femoral PWV (c-f PWV) and brachial-ankle PWV (b-a PWV) are gold standard measures of aortic stiffness [11].

By assessing the functional impairment of the arteries, researchers can gain insights into the potential cardiovascular effects of COVID-19 and provide information on the recovery process for these patients. The present research can contribute to authors' understanding of the long-term consequences of COVID-19 on arterial health and guide appropriate interventions or recommendations for post-recovery care. The present study may help stratify cardiovascular risk and treatment based on the severity of arterial stiffness.

Hence, focusing on the presence of arterial stiffness in COVID-19, the present study aimed to evaluate the functional impairment of the arteries, specifically arterial stiffness, in patients recovered from mild COVID-19 disease by assessing PWV.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Physiology, Shri BM Patil Medical College and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India, between April 2021 and June 2021. The Institutional Ethical Committee (IEC) approved the present study (IEC Ref No-588/2021-22 dated December 21, 2021), and informed consent was obtained from all participants.

Inclusion criteria: The study included all patients with mild COVID-19 disease (confirmed with a positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test), between the ages of 18 to 65 years, with a BMI <30 kg/m^2, and resting Blood Pressure (BP) <140/90 mmHg, who consented to participate. The study also included healthy controls from the general population of Vijayapura City, who came to the medical center for health services, either admitted and discharged or advised for quarantine at home. The participants were invited for a telephonic follow-up.

Exclusion criteria: Patients who had a history of hypertension, diabetes mellitus, sleep disorders, hypercholesteremia, psychiatric disorders, chronic fatigue syndromes, angina, and neuromuscular disorders, along with those who had cognitive or communication impairment that made telephonic conversation difficult, were excluded from the study. Participants who had contracted any other infections during the 3-month window and those taking medications like statins, antidiabetics, diuretics, antihypertensives, beta-blockers, sympathomimetic drugs, vasodilators, or alcohol, were also excluded.

Based on World Health Organisation (WHO) guidelines [12], mild COVID-19 disease was defined as follows:

1. Mild clinical symptoms, such as fever <38°C (quelled without treatment).
2. With or without cough (no dyspnea, no gasping, no underlying chronic lung disease).
3. No imaging findings of pneumonia.
4. Mild COVID-19 may also include symptoms such as cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell, along with fever.

Sample size: The study required a sample size of 18 participants for each group (a total sample size of 36, assuming equal group sizes) to achieve a power of 80% and a significance level of 5% (two-sided) for detecting a true difference in means between the test and reference groups [13]. The following formula was used [14]:

"n=(Zα/2+Zβ)2*2*σ2/d2,"

Where "Zα/2 is the critical value of the Normal distribution at α/2 (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (e.g., for a power of 80%, β is 0.2, and the critical value is 0.84), σ2 is the population variance, and d is the difference you would like to detect".

The study included 36 participants and divided the total sample size into two groups: Group 1 consisted of COVID-19 recovered patients with mild disease, and Group 2 consisted of age and sex-matched healthy participants.

Study Procedure

After a detailed screening, recordings were made by an experienced investigator between 8.30 am to 10.30 am at a constant room temperature, following supine rest for 10 minutes. All recordings were made 6-9 months after the participants tested positive for COVID-19. The following parameters were recorded:

1. **Physiological and anthropometric parameters:** The participants underwent recording of physiological parameters, including heart rate (PR beats/min), Systolic Blood Pressure (SBP, mmHg), Diastolic Blood Pressure (DBP, mmHg), Pulse Pressure (PP, mmHg), Mean Arterial Pressure (MAP, mmHg), as well as anthropometric parameters like height (cm), weight (kg), and Body Mass Index (BMI, kg/m^2).
2. **Arterial stiffness parameters:** Arterial stiffness was assessed using a certified non-invasive automatic device based on the oscillometric method (Periscope, Genesis Medical Systems, India). Periscope utilises 2-channel ECG leads to record the Electrocardiogram (ECG) and four blood pressure cuffs to record arterial pressure waveforms [15]. The oscillometric pulse wave was recorded by placing limb-specific sphygmomanometer cuffs around both upper arms and just above the ankles of both lower limbs. PWV was measured in a supine participants, position after a 10-minute acclimatisation period.

The brachial-ankle PWV (b-a PWV) was calculated by measuring the time delay between the brachial artery (located in the upper arm) and the ankle artery (located in the lower leg), providing an estimate of overall arterial stiffness along the upper and lower extremities. The carotid-femoral PWV (c-f PWV) was calculated by measuring the time delay between the carotid artery (located in the neck) and the femoral artery (located in the groin area), reflecting the stiffness of the central arteries, which are the large elastic arteries closer to the heart [16,17]. The cutoff range for PWV in the present study was considered to be 500-1500 cm/sec [18].

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 16.0. The baseline data was presented in tabular form, and metric variables were represented as differences between mean values. Parametric tests were not conducted as the variables did not meet the assumption of normality. Differences in numerical data were analysed using the Mann-Whitney U test. Spearman's correlation was performed to determine the relationship between b-a PWV, c-f PWV, and MAP. All tests were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

In the present study, there were 18 COVID-19 patients with mild disease (11 females and 7 males) with a mean age of 31.83±9.75 (range: 18.0-65.0) years. The control group consisted of 18 age- and sex-matched apparently healthy participants without COVID-19 (11 females and 7 males) with a mean age of 30.61±10.11 (range: 18.0-65.0) years. There were no significant differences in heart rate, height, weight, and BMI between the group 1 and group 2. However, there were significant differences in systolic blood pressure (p=0.001), diastolic blood pressure (p=0.001), and mean arterial pressure (p<0.01) between the two groups [Table/Fig-1].

Variables	Group 1	Group 2	p-value
Females/Males (N)	11/7	11/7	1.0
Age (years)	31.83±9.75	30.61±10.11	0.714
Physiological parameters			
Heart rate (bpm)	75.4±6.3	72±9.3	0.21
Systolic Blood Pressure (SBP) (mmHg)	127±7.74	117±9.4	0.001
Diastolic Blood Pressure (DBP) (mmHg)	76.9±7.2	68.6±6.14	0.001
Mean Arterial Pressure (MAP) (mmHg)	93.4±6.69	84.1±6.4	<0.01
Anthropometric parameters			
Height (cm)	161.67±10.18	161.89±5.97	0.937
Weight (Kg)	62.5±12.1	61.72±7.8	0.592
Body Mass Index (BMI) (kg/m^2)	23.7±2.7	23.5±1.8	0.434

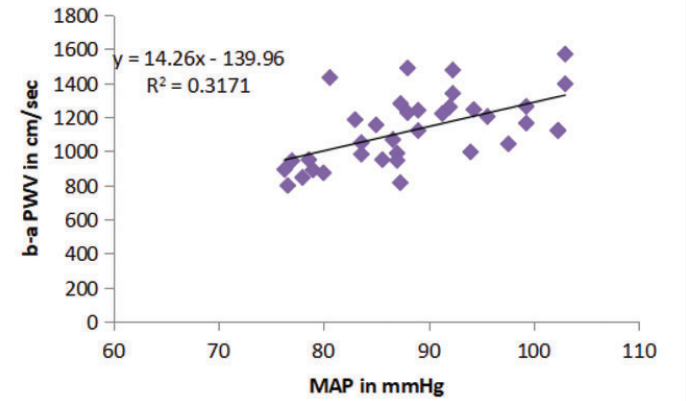
[Table/Fig-1]: Showing physiological, anthropometric and arterial stiffness parameters of Group 1 and Group 2.
Data were represented as Mean (SD); COVID-19: Coronavirus disease-2019

Both brachial-ankle pulse wave velocity (b-a PWV) (p=0.001) and carotid-femoral pulse wave velocity (c-f PWV) (p<0.01) were significantly higher in Group 1 compared to Group 2 [Table/Fig-2].

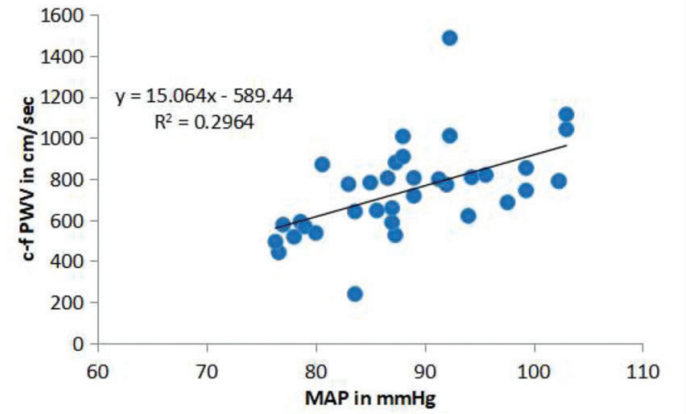
Variables	Group 1	Group 2	p-value
Arterial stiffness parameters			
b-a PWV (cm/s)	1313.7±330.05	992.94±140.69	0.001
c-f PWV (cm/s)	883.91±194.5	610.86±154.34	<0.01

[Table/Fig-2]: Showing arterial stiffness parameters of Group 1 and Group 2. Data are represented as Mean (SD), b-a PWV: Brachial-ankle pulse wave velocity; c-f PWV: Carotid femoral pulse wave velocity; COVID-19: Coronavirus disease 2019

In the present study, a significant positive correlation was found between MAP and b-a PWV (r=0.425, p=0.01) [Table/Fig-3], as well as between MAP and c-f PWV (r=0.544, p=0.001) [Table/Fig-4].



[Table/Fig-3]: Pearson's correlation between brachial-ankle Pulse Wave Velocity (b-a PWV) and Mean Arterial Pressure (MAP) among participants. Correlation (r)=0.425; p=0.01



[Table/Fig-4]: Pearson's correlation between carotid femoral Pulse Wave Velocity (c-f PWV) and Mean Arterial Pressure (MAP) among participants. Correlation (r)=0.544; p=0.001.

DISCUSSION

The findings of the present study indicate a substantial difference in arterial stiffness between COVID-19-recovered patients with mild COVID-19 disease. MAP, b-a PWV, and c-f PWV were all significantly higher in COVID-19-recovered patients with mild disease compared to the control group. Additionally, there was a positive correlation between MAP and both b-a PWV and c-f PWV. These results suggest that COVID-19 may have an impact on arterial stiffness, which is an important marker of cardiovascular health.

Furthermore, the study also observed higher SBP, DBP, and MAP in COVID-19 recovered patients with mild disease compared to the control group. These findings are consistent with a study conducted by Akpek M, where they also observed elevated SBP (120.9±7.2 vs. 126.5±15.0 mmHg, p<0.001) and DBP (78.5±4.4 vs. 81.8±7.4 mmHg, p<0.001) in the post-COVID-19 period compared to the patients' initial admission [19].

The increased arterial stiffness observed in COVID-19-recovered patients with mild disease can potentially be attributed to various pathophysiological mechanisms. Here are some possible explanations: Firstly, increased blood pressure: Elevated blood pressure among COVID-19-recovered patients may contribute to arterial stiffness [20]. Persistent high blood pressure can cause vascular damage and accelerate the stiffening of conduit arteries [21]. Secondly, reduced Nitric Oxide (NO) bioavailability: SARS-CoV-2 infection can trigger the release of cytokines and systemic inflammation, which may decrease the availability of NO. NO plays a crucial role in maintaining vascular health and regulating arterial tone. A decrease in NO availability can compromise the integrity of the vascular endothelium and potentially lead to arterial stiffness [22,23]. Thirdly, endothelial dysfunction: The binding of SARS-CoV-2 to endothelial Angiotensin-Converting Enzyme-2 (ACE2) receptors can result in endothelial cell infection and dysfunction [5]. Endothelial cells play a vital role in regulating vascular tone and maintaining vascular health. Impaired endothelial function can contribute to arterial stiffness [24]. Fourthly, hypercoagulable state: COVID-19 patients often exhibit a hypercoagulable state, which can lead to endothelial cell damage. Endothelial cell injury, in turn, affects the regulation of vascular tone and may contribute to arterial stiffness [25,26].

The authors determined b-a PWV and c-f PWV as measures of arterial stiffness. PWV is the most commonly used marker to measure arterial stiffness. Studies by Vlachopoulos C et al., and Wu LD et al., have shown that an increase in PWV is commonly associated with cardiovascular risk [27,28]. Regular measurement of PWV among COVID-19-recovered patients may contribute to early diagnosis and management of cardiovascular risk. Examining the specific effects of yoga, which combines physical activity with mindfulness and relaxation techniques, on arterial stiffness in COVID-19-recovered patients could provide evidence-based recommendations for post-recovery rehabilitation strategies.

Limitation(s)

Failure to follow-up and non-involvement of the moderate illness group were limitations of the study.

CONCLUSION(S)

The SBP, DBP, and MAP were higher in COVID-19 recovered patients with mild COVID-19 disease than in controls. High blood pressure is positively correlated with arterial stiffness, as measured through PWV, in COVID-19-recovered patients with mild disease compared to controls. The subsequent difference in arterial stiffness appears to be independent of other co-existing factors like age, diabetes, smoking, and other cardiovascular risk factors. Based on the study findings, it can be concluded that COVID-19 increases arterial stiffness. The authors suggest regular follow-up of COVID-19-recovered patients and regular measurement of PWV to mitigate the burden of cardiovascular risk.

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PARTICULARS OF CONTRIBUTORS:
1. Undergraduate Student, Department of Physiology, Shri BM Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.
2. Assistant Professor, Department of Orthopaedics, Shri BM Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.
3. Postgraduate Student, Department of Physiology, Shri BM Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.
4. Professor and Head, Department of Physiology, Shri BM Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.
5. Associate Professor, Department of Physiology, Shri BM Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Jyoti P Khodnapur,
Associate Professor, Department of Physiology, Shri BM Patil Medical College and Research Centre, BLDE (Deemed to be University),
Vijayapura-586103, Karnataka, India.
E-mail: jyoti.khodnapur@bldedu.ac.in

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