What are the long-term vascular effects of mild COVID-19 on arterial stiffness and hemodynamics?

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Abstract

COVID-19 took root in 2020, running rampant around the world since then. While contraction rates have decreased, five years later, their effects are still prevalent today. This study utilizes extensive literature reviews to examine the long-term health effects of COVID-19, finding implications for the overarching health of communities as a whole after the pandemic. By using various sources to compile multiple facets of the differences between aging and a condition's long-term effects, we can pinpoint which is which and how much it affects the community as a whole. Realizing the differences between aging effects and the actual consequences of COVID-19 is important to better understand and research ways to keep similar viruses at bay in the future. Conditions such as worsening health, poor eyesight, and overall physical weakness can be accelerated by having a history of COVID-19, compounding on already existing phenomena when it comes to aging. This study provides critical insights into the long-term burden of COVID-19, informing clinical management, rehabilitation strategies, and public health policies aimed at mitigating the enduring impact of the pandemic.

Introduction

COVID-19 is primarily known for its acute respiratory symptoms, ranging from cold-like symptoms to respiratory failure. These effects can persist for months or even years after the initial infection has resolved, impacting various organs and systems across the body. Aging is a gradual decline in cellular function, tissue repair, and immune system efficiency. An example of a biological mechanism that contributes to aging is inflammation. Over time, the immune system's ability to regulate inflammation diminishes, leading to systemic inflammation that contributes to age-related diseases such as cardiovascular disease, neurodegenerative disorders, and metabolic syndrome. The inflammation triggered by SARS-CoV-2 infection could potentially accelerate the inflammatory processes seen in aging. As it is a new disease, there is

currently a relatively insufficient amount of research and information about the long-term effects (Gorna 2020). The limited research on the long-term effects includes persistent symptoms of palpitations, peripheral neuropathy, and cognitive issues up to a year after infection, which suggests that cellular stress and sustained inflammatory responses can lead to biological aging, telomere shortening, and aged lungs compared to blood (Campisi 2024). Additionally, there has been a study finding accelerated epigenetic aging in COVID-19 patients, which can significantly impact the biological clock, causing aging diseases in the future (Bejaoui 2023). While there exists research in specific DNA degradation and biological aging, there is a lack of clear knowledge on specific aging diseases that are correlated with COVID-19, such as certain lung diseases, heart disease, cancer, and more. Current studies on the long-term aging effects of COVID-19 infection are limited by insufficient data on specific age groups and a lack of longitudinal studies that track patients over extended periods. Most existing research focuses on short-term outcomes or specific populations like hospitalized patients or those with existing health issues, leaving a gap in our understanding of how COVID-19 impacts aging across diverse demographics and various degrees of infection. Addressing these gaps is crucial for understanding the long-term health outcomes of aging populations post-COVID.

With a lack of targeted research on various age groups, we may overlook specific vulnerabilities that influence aging. Long-term studies are necessary to discern delayed or cumulative effects of the virus, like accelerated cognitive decline, cardiovascular issues, and poor immune function, which all may become apparent years after the initial infection. Understanding these effects can positively influence public health strategies, improve support for aging populations, and hopefully induce healthier aging processes as we enter the post-COVID times. Millions of people have had experience with getting the disease, and with the major wave of COVID-19 over, there begs the question arises of its effects in the future. What are the long-term aging effects of COVID-19 infection in patients? There are worries about what it means for the future, for while the disease is curbed and at bay with various treatments being created to battle infection, the virus will always be there, running the risk of coming back to prevalence again. It’s important to see its long-term effects to determine the risk of it coming back, and to understand any negative effects that may arise in the large population that did have exposure to COVID-19 during its peak.

Methods

The study aimed to examine the long-term vascular effects of COVID-19, specifically assessing changes in arterial stiffness and central hemodynamics in individuals who had mild cases of the virus. This longitudinal pre-post observational study collected baseline measurements up to two years before infection, with follow-up assessments conducted 2-3 months after symptom onset.

A cohort of 32 predominantly healthy young individuals (mean age: 36.6 ± 12.6 years) participated. While the study did not focus on older adults, its findings are highly relevant for aging populations, as vascular changes tend to be more pronounced with age-related decline. The study employed linear and mixed-effects regression models to analyze key vascular markers, including arterial stiffness (cfPWV, AIx@HR75) and hemodynamic parameters (DBP, MAP, cDBP), both before and after infection.

Results

The results revealed significant vascular impairments following mild COVID-19. Carotid-femoral pulse wave velocity (cfPWV), a key indicator of arterial stiffness, increased by 1.4 m/s, signaling reduced vascular elasticity and heightened cardiovascular risk. Additionally, the augmentation index (AIx@HR75), a measure of arterial wave reflection, rose by 15%, further suggesting compromised vascular function. Alongside these structural changes, significant increases in diastolic blood pressure (DBP), mean arterial pressure (MAP), and central DBP (cDBP) were observed, each rising by approximately 8 mmHg. These findings highlight a widespread disruption in vascular regulation, even in young, otherwise healthy individuals.

Figures included in the study visually reinforce these trends. Figure 1 demonstrates the progressive increase in cfPWV over time post-infection, with panel (a) showing a steady rise in arterial stiffness following recovery and panel (b) illustrating the natural age-related increase in cfPWV. The latter suggests that older adults, who already experience vascular decline, may be at

even greater risk for accelerated vascular aging post-COVID-19. Similarly, Figure 2 presents a positive trend in AIx@HR75, emphasizing the persistence of arterial wave reflection abnormalities months after infection. The scatter plot in Figure 3 further supports these observations by showing a shift in vascular responses among individuals over 40. The vertical dashed line in each panel indicates a potential threshold beyond which post-infection vascular

Changes become more pronounced, underscoring the heightened vulnerability of older populations.

Although the study primarily examined a young cohort, its implications extend to aging individuals, who may experience more severe and lasting vascular dysfunction following mild COVID-19. Given that the immune response to infection can exacerbate existing cardiovascular risks, these findings suggest that COVID-19 may accelerate vascular aging, potentially leading to long-term cardiovascular consequences. The statistical significance of these changes ($p \leq 0.013$) reinforces the robustness of the results. Overall, the study highlights that even mild COVID-19 can have lasting effects on vascular function, with potentially greater risks for older adults who are already predisposed to cardiovascular disease.

There is currently only speculation about what causes worsened vascular impairment as the period from COVID-19 infection increases. Although age could impact vascular impairment post-infection because age modulation has been suggested to affect vascular responses, including infection and autoimmune inflammation, the paper controlled for this confounding variable in the analyses. There have also been multiple studies that have had various age groups, all showing an increase in autoimmune inflammation post-COVID-19 infection. The paper discusses emerging evidence that shows the failure to resolve autoantibodies during the acute phase of the disease or the generation of pathogenic autoimmune responses post-recovery causes long COVID, along with residual inflammatory cytokines; The inflammation from an autoimmune response may cause inflammation-induced arterial stiffening. Additionally, circulating levels of anti- and extractable nuclear auto-antibodies existed in higher levels among patients 3 months—some even 12 months—post recovery from COVID-19 compared to those who were healthy and non-infected. The explanation for heterogeneous responses between those in the study could be

due to the inflammation post-recovery not being triggered in all patients. Furthermore, after 12 months of recovery, 30% of COVID survivors still had anti- and extractable nuclear auto-antibodies detected, which could have been the reason for these vascular changes. Lastly, the paper emphasizes a retrospective study including 4 million patients, finding an increase in the risk of autoimmune diseases in COVID-19 patients, showing the possible risks of infection that could explain vascular changes (Podrug et al., 2023).

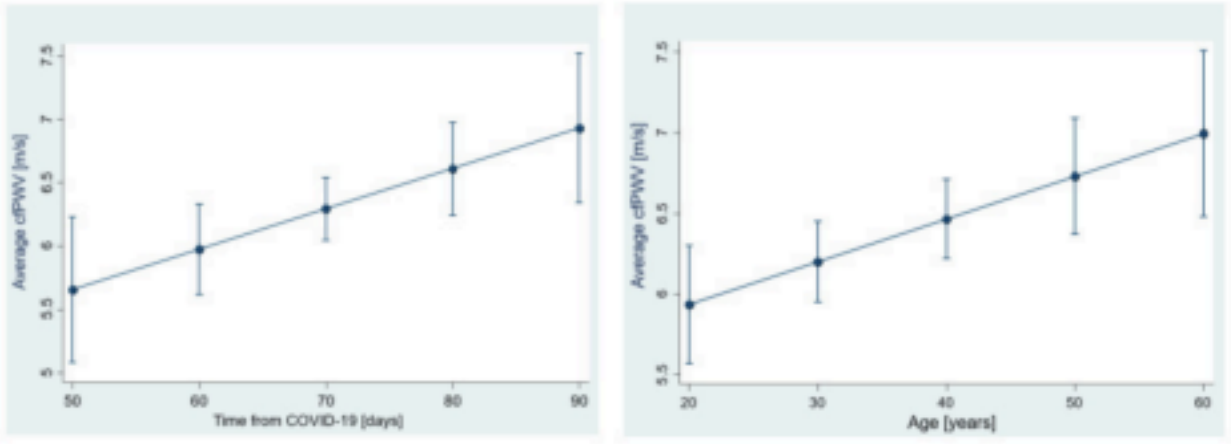

Figure 1 The relationship between the average cfPWV values in the sample and: (a) the time since COVID infection; (b) age, as estimated with the mixed-effects model (R2 = 27% at the level of sample, R2 = 31% for individual changes). Shown are predictive margins of cfPWV values with 95% CIs. (

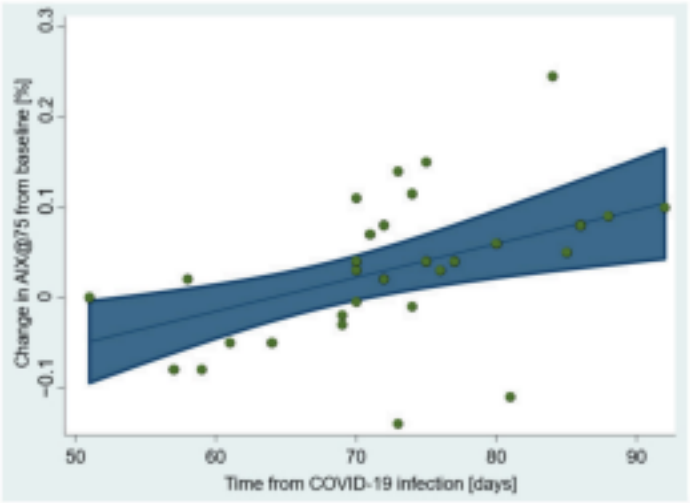

Figure 2. The change in AIx normalized to the heart rate of 75 bpm (AIx@HR75) from the

baseline depends on the time from acquiring the COVID-19 infection. Shown are predictive margins with 95% CI estimated by the LR model (R2 = 26%) and the scatter plot of observations.

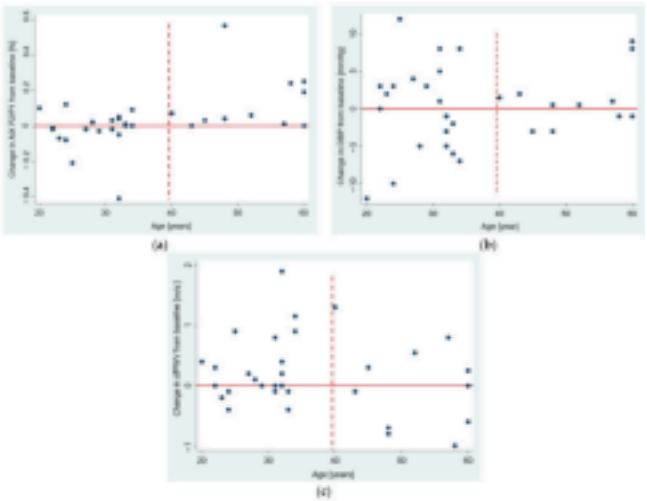

Figure 3 Scatter plots showing the relationship between age and pre–post change in: (a) augmentation index AIx P2/P1, (b) diastolic blood pressure, and (c) cfPWV. The horizontal reference line is set at zero pre-–post post-change, and the vertical dashed line is set at 40 years that separates parts of a plot with apparently different dispersion patterns.

Discussion

There is currently only speculation about what causes worsened vascular impairment as the period from COVID-19 infection increases. Although age could impact vascular impairment post-infection because age modulation has been suggested to affect vascular responses, including infection and autoimmune inflammation, the paper controlled for this confounding variable in the analyses. There have also been multiple studies that have had various different age groups, all showing an increase in autoimmune inflammation post-COVID-19 infection. The paper discusses

emerging evidence that shows the failure to resolve autoantibodies during the acute phase of the disease or the generation of pathogenic autoimmune responses post-recovery causes long COVID, along with residual inflammatory cytokines; Inflammation-induced arterial stiffening may be caused by the inflammation from an autoimmune response. Additionally, circulating levels of anti- and extractable nuclear auto-antibodies existed in higher levels among patients 3 months—some even 12 months—post recovery from COVID-19 compared to those who were healthy and non-infected. The explanation for heterogeneous responses between those in the study could be due to the inflammation post-recovery not being triggered in all patients. Furthermore, after 12 months of recovery, 30% of COVID survivors still had anti- and extractable nuclear auto-antibodies detected, which could have been the reason for these vascular changes. Lastly, the paper emphasizes a retrospective study including 4 million patients, finding an increase in the risk of autoimmune diseases in COVID-19 patients, showing the possible risks of infection that could explain vascular changes.

Conclusion

This study provides critical insights into the long-term vascular effects of mild COVID-19, highlighting significant impairments in arterial stiffness and hemodynamics even in predominantly healthy young individuals. The observed increases in carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx@HR75), alongside elevations in blood pressure parameters, underscore a widespread disruption in vascular regulation post-infection. These findings suggest that COVID-19 may accelerate vascular aging, potentially leading to long-term cardiovascular consequences. The persistence of autoimmune responses and residual inflammatory cytokines post-recovery could contribute to these vascular changes. Given the heightened vulnerability of older adults to cardiovascular disease, these results have important implications for clinical management and public health strategies aimed at mitigating the enduring impact of the pandemic. Further longitudinal studies are necessary to fully clarify the delayed or cumulative effects of COVID-19 on vascular health across diverse demographics and age groups, ultimately informing strategies to support healthier aging processes in the post-COVID era.

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