Arterial stiffness in acute COVID-19 and potential associations with clinical outcome

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Abstract. Schnaubelt S, Oppenauer J, Tihanyi D, Mueller M, Maldonado-Gonzalez E, Zejnilovic S, Haslacher H, Perkmann T, Strassl R, Anders S, Stefenucci T, Zehetmayer S, Koppensteiner R, Domanovits H, Schlager O (Medical University of Vienna; Vienna Health Care Group, Vienna, Austria). Arterial stiffness in acute COVID-19 and potential associations with clinical outcome (Brief Report). J Intern Med 2021; https://doi.org/10.1111/joim.13275

Background. Coronavirus disease 2019 (COVID-19) interferes with the vascular endothelium. It is not known whether COVID-19 additionally affects arterial stiffness.

Methods. This case-control study compared brachial-ankle pulse wave (baPWV) and carotid-femoral pulse wave velocities (cfPWV) of acutely ill patients with COVID-19 and age- and sex-matched controls.

Results. Twenty-two COVID-19 patients (50% females, 77 [67–84] years) were compared with 22 age- and sex-matched controls. In COVID-19 patients, baPWV (19.9 [18.4–21.0] vs. 16.0 [14.2–20.4], P = 0.02) and cfPWV (14.3 [13.4–16.0] vs. 11.0 [9.5–14.6], P = 0.01) were higher than in the controls. In multiple regression analysis, COVID-19 was independently associated with higher cfPWV (β = 3.164, P = 0.004) and baPWV (β = 3.532, P = 0.003). PWV values were higher in nonsurvivors. In survivors, PWV correlated with length of hospital stay.

Conclusion. COVID-19 appears to be related to an enhanced PWV reflecting an increase in arterial stiffness. Higher PWV might be related to an increased length of hospital stay and mortality.

Keywords: COVID-19, SARS-CoV-2, cardiovascular risk, arterial stiffness, pulse wave velocity.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic gravely affects the international community. Whilst the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily spread via aerosols [1] and the infection has its onset in the respiratory tract, it frequently spreads into various other tissues, including the cardiovascular system [2, 3].

Cardiovascular comorbidities in severe COVID-19 are common, thereby impacting on mortality [4]. SARS-CoV-2 potentially damaging the vascular endothelium could be a trigger for vascular disease complications [5]. However, besides endothelial damage, it is not well known to what extent structural changes of the vascular wall occur.

In the arterial system, structural wall changes result in deterioration of arterial elasticity, which can be revealed by measuring pulse wave velocity (PWV). Apart from reflecting arterial stiffness, PWV is a well-established surrogate marker of cardiovascular risk [6].

Focussing on arterial stiffness in COVID-19, the goal of the present study was to investigate whether, and to which extent PWV differs between acutely ill COVID-19 patients and acutely ill medical patients without COVID-19. Further, this study aimed to assess the prognostic value of PWV on clinical outcomes in severe COVID-19.
Methods

Study design and recruitment

Acutely ill, hospitalized adult patients with reverse-transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19 infection were included in this case–control study. Patients were included at designated COVID-19 isolation wards of two Viennese hospitals (Clinic Penzing and Clinic Donaus-tadt). At time of inclusion, all patients were hemodynamically stable without catecholamine support or mechanical ventilation.

In order to compare COVID-19 with non-COVID-19 patients, we recruited age- and sex-matched controls from a cohort of acutely ill medical patients that had been investigated in the scope of a previous cross-sectional study. Those patients, who had presented with cardiorespiratory symptoms such as dyspnoea or chest pain, systemically underwent pulse wave velocity (PWV) measurements at the Emergency Department of the Medical University Hospital of Vienna. The leading clinical condition in the control group was shortness of breath according to the ‘Reason for Visit Classification’ by the Center for Disease Control (www.cdc.gov).

The study was approved by the respective ethical committees (ethical committee of the Medical University of Vienna [No. 2197/2017] and the ethical committee of the city of Vienna [No. 20-134-VK]).

Arterial stiffness

Arterial stiffness was assessed by measuring PWV, using a certified oscillometric pulse wave device (BOSO ABI Systems 100 PWV®, Bosch & Sohn GmbH, Jungingen, Germany) [7]. For oscillometric pulse wave recordings, appropriate sphygmomanometer cuffs were placed around both patients’ upper arms and lower limbs, just above the ankles. Trained nurses performed the measurements under the supervision of one experienced investigator in quiet rooms with constant room temperature. PWV was measured in a supine patients’ position and after an acclimatization period of 10 min.

Brachial-ankle pulse wave velocity (baPWV) and carotid-femoral pulse wave velocity (cfPWV) were calculated from the time difference between the peripherally recorded pulse waves, considering the height of the respective patient. Following previous studies, the mean PWVs of the left and right sides were used for baPWV analyses [8, 9].

To determine variability, we performed three individual repetitive measurements in ten volunteers: The mean coefficients of variation were 1.9% for baPWV and 2.8% for cfPWV.

Clinical data

COVID-19 patients and non-COVID-19 controls underwent a complete physical examination, measurements of blood pressure and heart rate, an electrocardiogram and routine blood tests. Besides, an ankle-brachial index (ABI) screening for peripheral arterial disease was obtained in all included patients.

Data on length of hospital stay and all-cause 30-day mortality of COVID-19 patients were collected from the Viennese hospital electronic patients’ database and confirmed by reviewing the patients’ medical reports.

Statistical analysis

The control cohorts of 22 COVID-19 patients and 22 non-COVID-19 patients were matched for age and sex, and subsequently analysed. Baseline and demographic data were tabulated. Categorical variables are expressed as absolute and relative frequencies. Metric variables are presented as medians with interquartile ranges (IQRs). Boxplots were used to visualize data. Distributional assumptions were checked visually by quantile–quantile (Q-Q) plots. As none of the variables met the assumption of normality, only nonparametric tests were conducted. For comparison of categorical data between two groups, the chi-square or Fisher exact tests were used. Differences in numerical data were analysed using the Wilcoxon rank-sum test. Multiple linear regression was performed to determine the influence of COVID-19 on the pulse wave velocity; integrated variables into the model were chosen considering the Bonferroni-niveau in order to avoid overadjusting. To further reduce bias of overadjusting, additional regression analyses were conducted: one only taking into account blood pressure values and one only considering markers of inflammation. All tests were two-sided, and P-values < 0.05 were considered statistically significant. Statistical analyses were
performed using the statistical software R (RStudio Version 1.1.456, RStudio Inc., Boston, MA, USA).

Results

Between May 2020 and June 2020, 22 acutely ill patients with RT-PCR-confirmed COVID-19 infections (11 females, 76.5 (67.0–84.0) years) were included in this study. Twenty-two age- and sex-matched acutely ill medical non-COVID-19 patients (12 females, 76.5 (67.0–83.0) years) served as controls. These controls were recruited from a cohort of 102 acutely ill medical patients, who had been investigated in the scope of a cross-sectional study between December 2017 and January 2020.

Demographic and clinical data of COVID-19 patients and matched controls are shown in Table 1. Respective data of the total cohort of 102 acutely ill medical patients in comparison with included COVID-19 patients are depicted in Table S1.

Arterial stiffness

BaPWV and cfPWV were higher in patients with COVID-19 than in age- and sex-matched controls without COVID-19 (Fig. 1a + b). Similarly, baPWV and cfPWV were higher in COVID-19 patients than in the entire group of 102 acutely ill medical patients without COVID-19 (Figure S1).

In a multiple regression model including confounders on PWV (systolic and diastolic blood pressure, C-reactive protein, absolute lymphocyte count, procalcitonin, D-dimer, COVID-19), the presence of COVID-19 remained associated with baPWV and cfPWV (COVID-19 and baPWV: $\beta = 3.532$, $P = 0.003$; COVID-19 and cfPWV: $\beta = 3.164$, $P = 0.004$). COVID-19 remained independently associated with increased baPWV and cfPWV in additional regression models adjusted for only systolic and diastolic blood pressure (COVID-19 and baPWV: $\beta = 3.414$, $P = 0.001$; COVID-19 and cfPWV: $\beta = 4.034$, $P < 0.001$), and only for markers of inflammation (COVID-19 and baPWV: $\beta = 3.001$, $P < 0.001$; COVID-19 and cfPWV: $\beta = 3.517$, $P < 0.001$; Table S2).

Clinical outcome

Of 22 included COVID-19 patients, 11 (50%) died after a mean period of 20.7 ± 4.8 days of hospital stay (8 patients died from circulatory failure following sepsis or multi-organ failure; 3 patients died from respiratory failure defined as fulminant pneumonia in terms of acute respiratory distress syndrome). Eighteen patients were treated solely at a normal ward, and 4 patients were treated at an intermediate care unit before death. BaPWV and cfPWV were higher in nonsurvivors of COVID-19 than in COVID-19 survivors (Fig. 2).

In survivors of COVID-19, the mean length of hospital stay was 12.6 ± 4.3 days. In this subgroup of patients, baPWV and cfPWV were related to hospital length of stay (Figure S2). No association was found between patients’ age and hospital length of stay ($\rho = 0.445$, $P = 0.17$).

Discussion

As the main finding, this study revealed substantial differences in arterial stiffness between acutely ill patients with and without COVID-19. Further, PWV appeared to be related to clinical outcomes in COVID-19 patients. We found typical, known clinical and laboratory values of COVID-19 patients, rendering them internationally comparable [10].

The association between COVID-19 and arterial stiffness could be attributed to various pathophysiological mechanisms:

First, arterial stiffness potentially increases as a consequence of indirect endothelial damage: The integrity of the vascular endothelium is likely to be harmed by SARS-CoV-2-induced systemic hyperinflammation and cytokine release [3, 11]. In this acute systemic inflammation, the cytokine cascade reduces nitric oxide (NO) bioavailability, increasing arterial stiffness [12].

Secondly, SARS-CoV-2 additionally directly infects endothelial cells by binding to endothelial angiotensin-converting enzyme-2 receptors, which subsequently promotes cellular injury [3]. This results in endothelial dysfunction with abnormal medial vascular smooth muscle cell behaviour and structural changes of the extracellular matrix of the vascular wall (e.g., an increase in matrix metalloproteinase levels, enhancing central aortic stiffness [12-14]).

Thirdly, apart from promoting a hypercoagulable state commonly seen in COVID-19 patients [15], endothelial cell damage potentially hampers...
vascular tone regulation [13, 14]. Since the endothelium serves as a critical regulator of vascular homeostasis, endothelial alterations impact the balance of vasoconstriction and vasodilation [16].

Finally, severe systemic inflammation results in vascular adrenoceptor hyporeactivity, low endogenous vasopressin levels and corticosteroid insufficiency, which conjointly decreases the vascular tone and might thereby affect measures of arterial stiffness [17].

For measurements of arterial stiffness, we determined baPWV and cfPWV. PWV is a well-established surrogate marker of arterial stiffness, and several studies have demonstrated that an increase in PWV is associated with an elevated risk of future cardiovascular events and mortality [18]. The advantages of PWV measurements are the high

| Table 1 | Demographic and clinical characteristics of 22 acutely ill patients with COVID-19 and 22 age- and sex-matched acutely ill medical patients without COVID-19 |
|-----------------|-----------------|-----------------|
| COVID-19 | Non-COVID-19 | P-value |
| Females [N] | 11 (50) | 12 (55) | 1.00 |
| Age [years] | 76.5 (67.0-84.0) | 76.5 (67.0-83.0) | 0.79 |
| Obesitya [N] | 2 (9) | 5 (23) | 0.34 |
| Heart rate [bpm] | 80.0 (71.0-86.0) | 74.0 (62.0-82.0) | 0.13 |
| Systolic blood pressure [mmHg] | 136.0 (127.0-146.0) | 151.0 (145.0-166.0) | 0.001 |
| Diastolic blood pressure [mmHg] | 78.0 (73.0-85.0) | 91.0 (82.0-96.0) | 0.01 |
| CfPWV [m/s] | 14.3 (13.4-16.0) | 11.0 (9.5-14.6) | 0.007 |
| BaPWV [m/s] | 19.9 (18.4-21.0) | 16.0 (14.2-20.4) | 0.019 |

Comorbidities

| | COVID-19 | Non-COVID-19 |
|-----------------|-----------------|
| Diabetes mellitus [N] | 7 (32) | 3 (14) | 0.28 |
| Arterial hypertension [N] | 15 (68) | 16 (73) | 1.00 |
| Hyperlipidaemia [N] | 6 (27) | 7 (32) | 1.00 |
| Smoker [N] | 8 (36) | 2 (9) | 0.07 |
| Coronary artery disease [N] | 8 (36) | 6 (27) | 0.75 |
| Cerebrovascular disease [N] | 2 (9) | 2 (9) | 1.00 |
| Peripheral arterial disease [N] | 2 (9) | 0 (0) | 0.47 |
| Chronic kidney disease [N] | 5 (23) | 5 (23) | 1.00 |

Laboratory data

| | COVID-19 | Non-COVID-19 | P-value |
|-----------------|-----------------|-----------------|
| C-reactive protein [mg/dL] | 10.2 (3.1-23.3) | 0.2 (0.1-0.5) | <0.001 |
| Leucocyte count [G/L] | 7.2 (5.3-11.1) | 6.9 (5.4-8.1) | 0.60 |
| Absolute lymphocyte count [G/L] | 1.0 (0.7-1.3) | 1.6 (1.2-1.8) | <0.001 |
| Relative lymphocyte count [%] | 13.8 (8.8-20.1) | 24.8 (20.7-28.8) | <0.001 |
| LDH [U/L] | 225 (180-295) | 201 (187-217) | 0.22 |
| Fibrinogen [mg/dL] | 475 (348-555) | 325 (273-380) | 0.002 |
| IL-6 [pg/mL] | 33.6 (20.0-63.2) | 4.1 (2.4-13.6) | 0.001 |
| Procalcitonin [ng/mL] | 0.2 (0.1-0.3) | 0.0 (0.0-0.1) | <0.001 |
| D-dimer [lgl/mL] | 2.1 (1.5-3.6) | 0.0 (0.0-0.1) | <0.001 |
| Creatinine [mg/dL] | 1.0 (0.8-1.1) | 1.1 (0.8-1.2) | 0.82 |

Data are given as absolute counts (percentages) or median (interquartile range). cfPWV, carotid femoral pulse wave velocity; COVID-19, coronavirus disease 2019; baPWV, brachial-ankle pulse wave velocity; LDH, lactate dehydrogenase; IL-6, interleukin 6.

aObesity defined as body mass index >30 kg/m².
sensitivity as well as their potential to efficiently capture short-term changes in arterial stiffness [19, 20]. In our personal experience, an additional benefit of oscillometric PWV determination is the practicability of this noninvasive method in acutely ill patients since it is quick and does not additionally burden the patient or medical personnel.

Referring to the determination of PWV in patients with COVID-19, the present study further revealed differences in PWV between survivors and nonsurvivors of the disease. Also, PWV appeared to be related to hospital length of stay in COVID-19 patients. These observations suggest that a more pronounced increase in arterial stiffness appears to be associated with unfavourable clinical courses of COVID-19, rendering increased PWV a marker or risk. Therefore, the determination of PWV in COVID-19 admission wards could help identify patients at risk of clinical deterioration.

Notably, this study has to be discussed in light of its strengths and limitations: the sample size of this case-control study can be viewed critically. Our primary aim was to compare two homogenous age- and sex-matched cohorts with as few additional influencing factors as possible, leading to a reduction of included subjects. Furthermore, the
two cohorts were not assessed in parallel through the same period. One explanation is the difficulty to simultaneously assess patients with and without COVID-19, according to COVID-19 precautions during a national lockdown period. Therefore, according to the rapid spread of the COVID-19 pandemic, we recruited controls from a previously assessed cohort of acutely ill medical patients with cardiorespiratory symptoms. In this respect, it appears plausible that a simultaneous assessment of the two cohorts would not have changed the findings of the present investigation. In addition, follow-up PWV data of COVID-19 patients are yet to be provided.

Perspectives

COVID-19 has been identified as a multi-organ disease, affecting the circulatory system throughout the body – respective patients should be treated in a generalized approach. PWV serves as a surrogate for arterial stiffness and can reflect the extent of present endothelial and vascular damage. We found that COVID-19 is independently associated with an enhanced PWV, reflecting an increase in arterial stiffness. As PWV appeared to be related to length of hospital stay and mortality, it could be used for identifying patients at risk of clinical deterioration. Up to now, this is the first study assessing arterial stiffness in COVID-19 patients in a small sample and might be the steppingstone for future research. Further studies are warranted to assess whether the observed changes in arterial stiffness sustain last in patients after recovering from COVID-19.

Conclusion

Arterial stiffness, measured through pulse wave velocity, is higher in COVID-19 patients than in age- and sex-matched acutely ill medical patients without COVID-19. The difference of arterial stiffness appears to be independent of other coexisting diseases. Higher pulse wave velocity values were observed in COVID-19 patients who did not survive the disease. In COVID-19 survivors, the pulse wave velocity was related to the length of hospital stay.

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Conflicts of interest

None of the authors declare any financial or intellectual conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Comparison of (A) baPWVmax and (B) cfPWV values between COVID-19 and non-COVID-19 patients (both \( P < 0.001 \)).

Figure S2. Correlation of baPWVmax and cfPWV values with the length of hospital stay in days.

Table S1. Demographic and clinical characteristics of 22 acutely-ill patients with COVID-19 and 102 acutely-ill medical patients without COVID-19.

Table S2. Results of (A) the multivariate analysis to test the association with pulse wave velocities, (B) the multivariate analysis only adjusted for systolic and diastolic blood pressure and COVID-19, (C) the multivariate analysis only adjusted for markers of inflammation and COVID-19, and (D) the various single multivariate analyses of the variables only adjusted for systolic blood pressure.