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Retinal Vessel Analysis shows distinct endothelial dysfunction in hospitalized COVID-19 patients (The CoViThel Study) Measuring endothelial dysfunction in COVID-19 with RVA

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Abstract

Aims: Patients with SARS-CoV-2 infection exhibited a heterogenous disease course, ranging from asymptomatic or mild to critical ill patients. One factor contributing to the severity, is endothelial dysfunction, which is difficult to quantify in clinical routine. We hypothesized that retinal vessels may serve as a promising target to analyze endothelial dysfunction in these patients.

Methods and Results: 90 COVID-19 patients were consecutively included in the study and received an examination of retinal vessels using Static Vessel Analyzer (SVA) and Dynamic Vessel Analyzer (DVA 3). Matched healthy individuals were used as a control group in this prospective cohort study.

After matching there was no difference in age and gender between the two groups. We found a higher BMI in the COVID-19 group. SVA showed both wider arterial (209.1 MU (SD 18.6) vs. 181.3 MU (SD 16.4), $p < 0.001$) and venular (256.5 MU (SD 20.9) vs 210.8 MU (SD 24.7), $p < 0.05$) diameters in the COVID-19 group ($p < 0.001$). DSVA showed both less arterial dilatation (2.35% (SD 1.70) vs. 3.70 % (SD 1.69) and arterial constriction (-1.02% (SD 1.024) vs. -1.41% (SD 1,43) in COVID-19 patients compared to healthy controls. Subgroup analysis showed a continuous decline in arterial dilatation ($p < 0.01$) and constriction ($p < 0.05$) with increasing disease severity

Conclusion: Parameters of retinal microcirculation are impaired in COVID-19 patients as examined by Static and Dynamic Vessel analyzer. Further studies including longitudinal analysis are needed to further investigate diagnostic potential of the examination.

Keywords: COVID-19; endothelial dysfunction; Retina; Microvasculature; Virus; Retinal vasculature; Retinal vessel analysis

Introduction

Since first being discovered in 2019, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has become a worldwide pandemic, leading to over 650 million infected, nearly seven million deaths, and worldwide economic turmoil [1,2]. Firstly, coronavirus disease 2019 (COVID-19) was described as a respiratory disease, impaired breathing and hypoxia being the predominant clinical symptoms in infected patients [3] but soon it became obvious that SARS-CoV-2

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was a multisystem infection. SARS-CoV-2 enters the cells via the angiotensin-converting enzyme (ACE) - 2 Receptor [4]. ACE2 is expressed in various cells of the body, including pericytes and endothelial cells in blood vessels. The viral invasion probably triggers endotheliitis and contributes to endothelial injury [5-11]. Endotheliitis has been directly shown in COVID-19 victims [6] and 3D in-vitro models of endothelium infected with SARS-CoV-2 show a unique form of vascular dysfunction [12]. Endothelial cells are an important regulator of vessel tone, homeostasis, and coagulation [13-18]. Thus, COVID-19 prominently impairs the regulation of all functions mentioned above leading to systemic illness characterized by endothelial dysfunction, coagulation problems, lung injury, cardiac collapse and multiorgan failure in severely affected patients [14,18-21]. The European society for cardiology issued a statement demanding that measurements of endothelial function should be assessed as a risk stratification tool for COVID-198. This research is deemed highly important, there is a plethora paper calling for it [8,22].

The Dynamic Vessel Analyzer (DVA) is a device that continuously measures the diameter of retinal vessels before, during and after photostimulation. Photostimulation by flicker light increases the oxygen demand of the retina, thereby leading to a dilation of the retinal capillaries by neurovascular coupling. Capillary dilation leads to an increase in retinal blood flow and blood velocity through the major retinal vessels (arteries and veins). This increases the shear stress on the vessel wall with the release of NO by the flow-induced autoregulation [23]. This is measured as flicker-induced dilatation of the retinal arteries and veins (aFID and vFID). After terminating flickering light arterial vessels show a reactive constriction, measured as flicker-induced constriction (aCon) [23-26]. The flicker-induced dilation of the arterial vessels has been shown to be impaired in systemic endothelial dysfunction, e.g., due to hypertension, dyslipidaemia, diabetes and in older age [27-35]. A review of the methodology and results in systemic vascular risk patients and diseases is described in detail by Hanssen et al [36]. Parameters of DVA are an individual prognostic marker for cardiovascular (CV) risk and adverse events in cardiac patients and high CV risk cohorts [37-41].

The Static Vessel Analyser (SVA) determines arterial and venous vessel diameters from a single retinal image, which provides information about the current state of vessels like narrowing or widening. The combination of SVA and DVA helps to better understand the underlying pathophysiology of microvascular dysfunction. Parameters of the SVA provide quantitative and objective supplementary information on the current vascular state (dilated or constricted) whereas DVA measures endothelial function directly [36]. Microvascular risk factors or chronic CV illness, such as hypertension leads to narrowing of arterioles, whereas inflammatory states lead to widening of retinal venules [42-44]. Both changes are associated with adverse CV outcomes, myocardial infarction, and stroke [45-47]. In addition, reduced aFID and vFID have been shown to independently predict mortality [37,48].

One of the difficulties in treating COVID-19 patients is the wide span of clinical courses. There is a substantial lack of prognostic factors especially in the early course of illness. There also is a lack of knowledge how endothelial dysfunction is linked to severity of illness. Furthermore, endothelial dysfunction has mostly been shown in vessels of the macrocirculation and laboratory markers [49-51]. As most pathophysiological processes in the early course of the systemic illness seem to stem from microvasculature, there is still little knowledge about this topic [8].

We hypothesized that COVID-19 leads to systemic vascular dysfunction of the microcirculation that can be quantified by impaired retinal vessel structure and function. In addition, we hypothesized that retinal vessel endothelial dysfunction is correlated with disease severity in acute exacerbation of the disease.

Materials and Methods

We conducted a monocentric prospective cohort study at the University Hospital Jena, department for infectious diseases Thuringia, Germany, called “The SARS-CoV-2 Endotheliitis Study by use of retinal vessel analyzer (CoViThel)”. The Study was approved by the local ethics committee (Protocol Number: 2020-1805-BO) and written consent was obtained from all participants. The study adhered to the guideline of the declaration of Helsinki. It was filed in the study database DRKS (Deutsches Register für Klinische Studien).

Population

All patients admitted to the infectious disease ward of the university hospital Jena with the diagnosis of a COVID-19 infection were screened for inclusion in the study. Inclusion criteria were: (1) positive COVID-19 PCR of a nasopharyngeal swab, (2) informed consent, (3) the ability to sit for at least 15 minutes to obtain the images by examiners. Exclusion criteria were: (1) Glaucoma, (2) epilepsy, (3) recent operation of the eye or severe eye disease that prevented the use of mydriatic eyedrops or the DVA procedure, (4) more than 30 days after first positive COVID-19 PCR.

Demographic data, including age, gender, weight, BMI and comorbidities (Diabetes mellitus, hypertension, dyslipidaemia, nephropathy) as well as therapy for COVID-19 (dexamethasone, remdesivir), symptoms (tachy-/dyspnoea, coughing, loss of taste and smell) and mode and extent of respiratory support (oxygen, high-flow, non-invasive / invasive ventilation) were extracted from the electronic health charts. Patients were followed up until discharge or death.

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As control group we used the data from the reference Value Study from Streese et al., which were obtained with a Static and Dynamic Vessel Analyzer, using the same protocol as ours [52]. The subjects were validated healthy individuals from the Basel region. Healthy individuals were defined as non-smoking men and women with a body mass index (BMI) <30 kg/m^2, <140 mmHg systolic and <90 mmHg diastolic blood pressure, without any history of CV disease, chronic or inflammatory disease or chronic eye disease [52]. The matching criteria were age and gender.

Retinal Vessel Analysis and Procedure

Retinal Vessel Analysis was performed using Static Vessel Analyzer (SVA) and Dynamic Vessel Analyzer (DVA 3) (both systems from Imedos Systems GmbH Jena, Germany). SVA was based on the conventional nonmydriatic retina camera DRS for imaging the retinal vessels and the software Vesselmap (VM 2) for determining the static vessel parameters retinal arteriolar (CRAE) and venular diameter equivalents (CRVE) were semi-automatically analysed using standard operating procedures [52]. DVA 3 was used to measure aFID, vFID, and aCon based on three flicker cycles as previously described [52]. Due to the unknown imaging scale of the individual patient's eye, the measured vessel diameters are given in measurement units (MU). One MU is equal to one µm vessel diameter if the individual patient's eye corresponds to Gullstrand's normal eye.

After inclusion participants received mydriatic eyedrops (Tropicamid 5mg/ml) for pupil dilatation about 20 to 30 minutes before examination. The subjects were placed in front of the SVA respectively DVA under cardiovascular monitoring. Oxygen was titrated to a saturation of 92 - 97% via pulsoxymetry, blood pressure and heart frequency was recorded. All lights were switched off and the blinds of the rooms were closed. A static image of both eyes was always acquired first using Static Vessel Analyzer before the dynamic analyzation was started.

Static Vessel analysis was done by obtaining a sharp image centred on the optic nerve. The retinal images were analysed using the semi-automated software VM 2. The arterioles and venules were marked manually between 0.5 – 1 disc diameter from the optic disc margin and the software automatically measured and calculated the static vessel parameters.

We used the eye with the wider pupil for dynamic analysis. After obtaining a sharp image of the retinal vessel at least one artery and one vein were marked following specific rules: (1) minimum diameter 90 µm, (2) distance one to two optic disc diameters from the optic nerve, (3) straight course of a temporal vessel, (4) sharp image of both vessel edges. After starting the examination patients were encouraged to sit straight and move as little as possible and fixate on the fixation point. The examiner continuously corrects for small patient movements. The flicker protocol was used as follows: total examination took 350 seconds; baseline measurement lasted 50 seconds followed by three flicker and recovery periods of 20 and 80 seconds each as recommended by the standard operating procedure [52]. The analysis was done by the integrated Dynamic Retinal Analyzer software automatically. In case of insufficiency the following adaptations were made to improve the automatic analysis: adjustment of the baseline and extinction of maximal one out of three flicker periods if unambiguous disturbances during one period are recognizable.

All video and photography material were quality checked by both main researchers, as well as a technician from Imedos for image quality, artifacts, and adherence to the protocol. If the material was deemed to be unreadable due to poor image quality, artifacts or blurred imaging, the subject was excluded.

Demographic and clinical data of all patients were collect using electronic medical records: age, sex, height, weight, body-mass index, significant pre-existing conditions (diabetes, hypertension, dyslipidemia, nephropathy, stroke) and medications (blood pressure medications, statins, ASS). Furthermore, maximum oxygen requirement, need for invasive or non-invasive respiratory support, length of stay. Patients were monitored until discharge or death. Levels of interleukin-6 and c-reactive protein (CrP) were also collected.

Statistical analysis

For the main statistical analysis, including subgroup comparisons we included 90 COVID-19 patients. The data of the control group was extracted from the student population of the study performed by Streese et al. (n = 277) [52]. As there were significant differences in age and gender between the two groups, we performed a matched pairs analysis. Data of 90 healthy individuals could be included as control group. Since most of the continuous data were normally distributed, we used the mean and standard deviation for data presentation and description. Two-sample t-test or ANOVA were performed to compare continuous data between groups. For subgroup analysis most data were not normally distributed. We used Kruskal-Wallis Test with post-hoc adjustment for multiple testing (Bonferroni). An adjusted, two-tailed p-value <0.05 was considered to indicate statistical significance. Statistical analysis was performed with SPSS V28.0 (IBM Inc, Armonk, NY).

Results

Cohort Composition

A total of 133 patients were enrolled in the study between 09/2020 and 02/2021 on the infectious diseases ward of the university clinic of jena. 43 had to be excluded due to poor quality of the image acquired by DVA. Main reasons for

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exclusion were: (1) lacking ability to fixate the fixation mark for 5 minutes, (2) exertion due to sitting upright, (3) gross eye movements. Thus, in total 90 patients were included in the primary analysis. Demographic and clinical data are represented in Table 1. The control group were 90 healthy subjects used to establish normal ranges of DVA [52].

Parameter of static vessel analysis:

All parameters of the static vessel analysis showed significant differences between healthy individuals and COVID-19 patients. In the COVID-19 group we found both wider arterial (209.1 MU (SD 18.6) vs. 181.3 MU (SD 16.4)) and venular (256.5 MU (SD 20.9) vs 210.8 MU (SD 24.7) diameters of the central equivalent ($p < 0.001$).

Table 1: Demographic and clinical features of patients

	COVID-19 patients n = 90	Control group N = 90	p-value (t-test)
Age, mean years (SD, Range)	57 (13.61, 18 – 83)	57 (13.38, 20-80)	p = 0.935
Gender n (%) females	24 (26,9)	23 (25.5)	p = 0.849
Gender n (%) males	66 (73,1)	67 (74.4)	p = 0.849
BMI mean (SD, range)	28,8 (6.7, 16 – 57)	24.72 (2.28, 20-29)	P < 0.001
Comorbidities n (%)	51 (62,2)		
- Diabetes mellitus n (%)	9 (11,0)		
- Systemic hypertension n (%)	46 (56,1)		
- Dyslipidemia n (%)	17 (20,7)		
- Nephropathy n (%)	9 (11,0)		
COVID-19 Therapy n (%)	64 (78,1)		
- Remdesivir n (%)	42 (51,2)		
- Dexamethason n (%)	56 (68,3)		

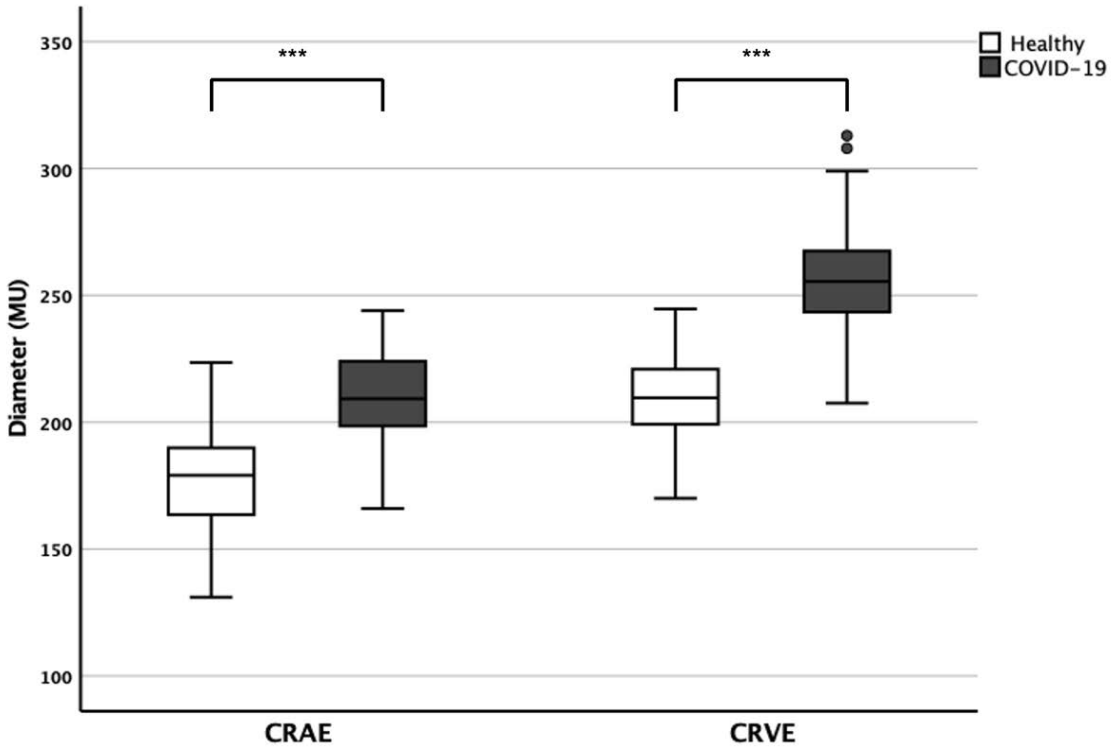

Figure 1: Central retinal arterial (CRAE) and venular (CRVE) equivalent in 90 healthy individuals and 90 COVID-19 patients. COVID-19 patients showed wider CRAE (209.1µm (SD 18.6) vs. 181.3 µm (SD 16.4)) and wider CRVE (256.5 µm (SD 20.9) vs 210.8 µm (SD 16.5) compared to the control group.

***, p-value < 0.001; t-test; n = 180 subjects.

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Parameters of the dynamic vessel analysis

Comparison COVID-19 versus healthy patients

Both arterial dilatation (2.35% (SD 1.70) vs. 3.70 % (SD 1.69), p <0.01) and arterial constriction were reduced (-1.02% (SD 1.024) vs. -1.41% (SD 1,43), p = 0.045) in the COVID-19 group compared to healthy individuals. Furthermore, venous dilatation showed a numerical trend towards reduced dilatation (3.54% (SD 1.95) vs 3.95% (SD 1.69)). These results are illustrated in Fig. 2.

Subgroup Analysis

For a disease severity correlated subgroup-analysis the study group was further divided into subgroups. Subgroups were defined as: 1) asymptomatic (positive COVID-19 PCR during hospitalisation for other cause, e.g. fractures), 2) symptomatic but without oxygen requirement during the clinical course (e.g., coughing, trouble breathing, tachy-dyspnoea), 3) requirement for oxygen only, 4) requirement for intensive care (high-flow nasal cannula, continuous positive airway pressure, invasive ventilation, extracorporeal membrane oxygenation).

The parameters of static vessel analysis CRAE (Kruskal-Wallis test p = 0.225) and CRVE (Kruskal-Wallis test, p = 0.346) did not show any differences between subgroups. For parameters of dynamic retinal analysis, we found that aFID decreased with increasing severity of illness as illustrated in Fig. 3. The ability to adequately constrict deteriorated (aCon increased) with increasing disease severity (see Fig. 3 and 4).

Cardiovascular and laboratory parameters

Oxygen saturation, heart frequency and blood pressure (systolic / diastolic) were within the expected age adjusted normal ranges and did not differ between subgroups. Both CrP and Interleukin-6 were elevated but did not differ between subgroups. This is illustrated in Table 2. There were no differences in comorbidities between the subgroups (data not shown).

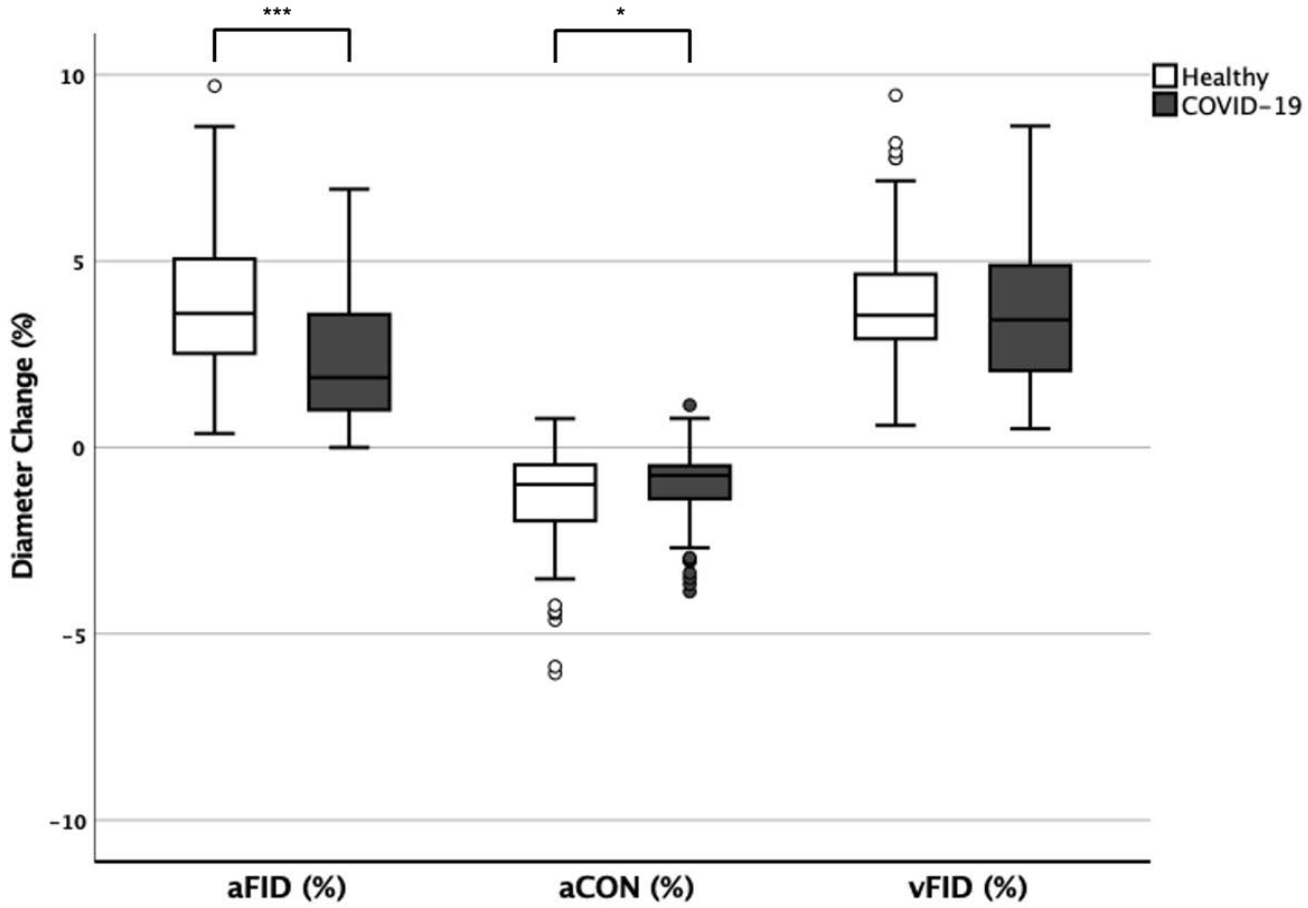

Figure 2: Dynamic retinal vessel analysis in 90 COVID-19 patients and 90 healthy controls. Arterial dilatation (aFID) was lower (2.35% (SD 1.70) vs. 3.70 % (SD 1.69) and arterial constriction (aCon) less intense (-1.02% (SD 1.024) vs. -1.41% (SD 1,43) in COVID-19 patients compared to healthy controls. Venous dilatation (vFID) was not statistically significant different between COVID-19 patients and healthy individuals (3.54% (SD 1.95) vs 3.95% (SD 1.69)).

* p-value <0,05; *** p-value < 0.001; ANOVA; post-hoc Bonferroni, n = 180.

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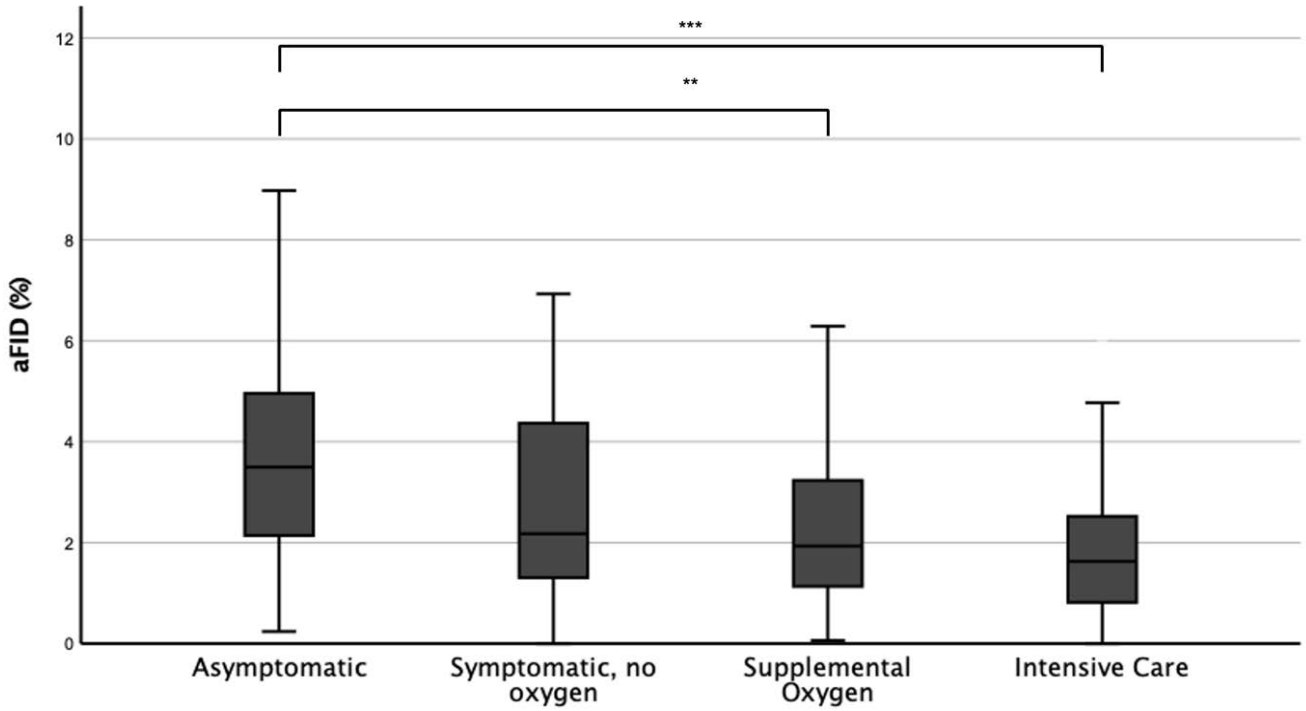

Figure 3: Subgroup analysis for severity of disease. Increasing disease severity is associated with less arterial dilatation during flicker provocation.
** p-value < 0.01; *** p-value p < 0.001, Kruskal-Wallis test, post-hoc Bonferroni, n = 90.

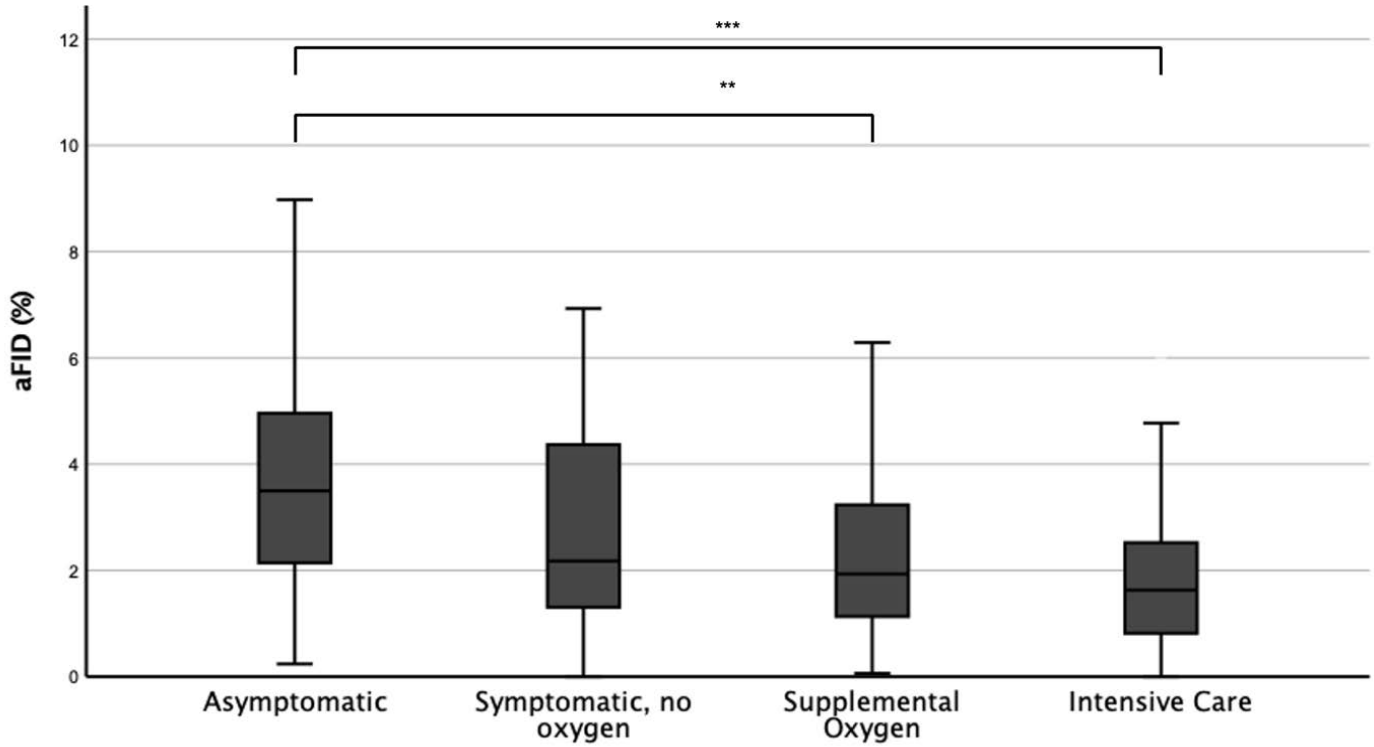

Figure 4: Subgroup analysis for severity of disease. Increasing disease severity is associated with less arterial constriction after flicker provocation.
* p-value < 0.05, Kruskal-Wallis test, post-hoc Bonferroni, n = 90

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Table 2: Cardiovascular and laboratory parameters of COVID-19 patients

	COVID-19-group n = 90	Subgroup Analysis for Severity of disease (Kruskal-Wallis test)
Age, mean years (SD, Range)	57 (13.61, 18 – 83)	p = 0.797
Oxygen Saturation (%, mean, SD, range)	95.46 (1.71, 92 – 99)	p = 0.136
Heart frequency (bpm, mean, SD, range)	77.46 (11.18, 54 – 111)	p = 0.610
Blood pressure systolic (mmHg, mean, SD, range)	122.71 (16.36, 84 – 167)	p = 0.174
Blood pressure diastolic (mmHg, mean, SD, range)	72.97 (10.92, 44 – 99)	p = 0.645
CrP (µmol/l, mean, SD, range)	46.89 (55.9, 0 – 245.55)	p = 0.067
Interleukin-6 (pg/ml, mean, SD, range)	27.02 (34.5, 2.5 – 127)	p = 0.250

Discussion

Several studies have shown that retinal vessel closely resemble systemic vessels of microcirculation and are predictive of overall endothelial function [27,33,35,53-56]. In this study we found significant arterial and venous widening in the SVA. DVA showed a significantly decreased arterial and venous flicker dilation and arterial flicker constriction in COVID-19 patients compared to healthy individuals. Furthermore, we saw a significant correlation of the impairment in vessel reaction to the severity of COVID-19 illness, being most pronounced in patients requiring intensive care.

There is direct evidence of the SARS-CoV-2 Virus infecting endothelial cells leading to endotheliitis [6], thus there have been a paucity of studies trying to quantify endothelial dysfunction measuring circulatory parameters like tissue-factor, mid-regional pro-adrenomedullin, von Willebrand factor complex or NO [51,57-59]. It could be shown that elevated levels of endothelial dysfunction biomarkers in COVID-19 patients are related with poor outcome60. An impaired response of macrovascular vessels to stress has been demonstrated [50,61]. However, microvasculature is the region of interest for most systemic pathophysiological processes in COVID-19, for example thrombosis, inflammation, and loss of vessel function [62-65]. The eye give us a unique possibility to directly visualize the microvasculature in vivo under physiological or pathophysiological conditions and our study examines for the first time hospitalized Covid 19 patients using SVA und DVA. This method measures the state of the microvasculature of the eye (dilated, normal or constricted) using SVA as well as microvascular function and endothelial response to stress via DVA. Flicker light is used to simulate stress. It increases the oxygen demand in the retina, thus triggering an increased blood flow through neurovascular coupling, leading to a widening of retinal capillaries and therefore a dilatation of the retinal vessels in healthy conditions [66-68]. It is important to acknowledge that SVA and DVA does not only measure the microvasculature of the eye, but it closely mirrors systemic microvascular function and dysfunction. It has been shown to be predictive for cardio- and cerebrovascular disorders [35,69]. This has been extensively studied in chronic diseases like heart-failure, diabetes and hypertension and several known factors of endothelial dysfunction have been linked to a decrease in arterial and venular response to flicker light [33,53]. Interestingly these disease processes are linked to constricted arteries in SVA due to lower basal NO-secretion [70]. In our group 62.2% of COVID-19 patients displayed one or more pre-existing conditions associated with arterial narrowing, however both retinal arteries and veins were significantly dilated. Widening of retinal veins can be attributed to circulating inflammatory markers, however arterial widening is only mildly associated with inflammatory markers [44]. Dynamic Vessel analysis showed a significantly decreased response to flicker light in COVID-19 patients. This indicates that vessels of COVID-19 patients are unable to adapt to increased oxygen demand. This process depends on an intact endothelial NO-pathway; thus, it is a quantifiable measure of microvascular and endothelial dysfunction [26,71].

It is important to acknowledge that these changes in microvascular function could be attributed to a paucity of confounders. For example, an increase in heart minute volume could lead to a widening of arteries with diminished functional reserve, however heart frequency and blood pressure of our patients were within normal ranges at the time of the measurements. Also, hypoxia leads to a similar process, yet again all patients were titrated to normoxia (oxygen saturation 93-97%) before the examination was conducted, which also precludes hyperoxia as a confounder for a reduced functional reserve. Diminished functional reserve could be attributed to pre-existing conditions like severe diabetes, hypertension, or dyslipidemia, but all these conditions lead to a narrowing of retinal arteries, which was not present in our cohort. We therefore hypothesise that the changes resemble a unique process within COVID-19 disease that is governed by a systemic endotheliitis, leading to widening of microvascular vessels and a loss of endothelial function.

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We could also provide evidence that the severity of microvascular dysfunction is linked to the severity of COVID-19 disease, showing the highest reduction in aFID and aCon in patients requiring intensive care. Interestingly CRAE and inflammation markers showed no differences in the COVID-19 subgroups which precludes the assumption that the loss of arterial dilatation is simply an effect of an increased widening of retinal vessels. Additionally, reactive arterial constriction after stress induced dilatation, which is an important hallmark of functional neurovascular coupling was also diminished. These findings could be an indicator that endotheliitis and an increasing loss of endothelial function indicates and governs the progression of COVID-19 from a simple upper respiratory tract infection to a systemic disease with high mortality. Various pathophysiological mechanisms underlying loss or reduction of endothelial function in COVID-19 have been reported in studies. All these mechanisms interact and aggravate each other, ultimately leading to deterioration of endothelial function. There is evidence of oxidative stress, endothelial glycocalyx injury, hyperpermeability and loss of barrier function, hypercoagulability/thrombosis, inflammation and cytokine release, amongst others more [12,72-74]. Probably best established are disturbances in the NO-pathway during inflammation due to the occurrence of reactive oxygen species in the vessel milieu [75]. There seems to be a shift from NO production by eNOS (endothelial nitrous oxide synthetase) to iNOS (inducible nitrous oxide synthetase). Large amounts of NO from iNOS can induce a cytotoxic effect thereby further inhibiting endothelial function. This results in further uncoupling of eNOS, loss of endothelial function and possibly cardiovascular collapse requiring intensive care treatment [17].

Montiel et al identified decreased NO bioavailability as a likely pathogenic factor of endothelial dysfunction in ICU COVID-19 patients [76]. Other studies of macrovascular endothelial dysfunction in COVID-19 patients speculate a loss of NO production during the acute phase of COVID-19 disease [9,50]. A loss of NO, however, would also lead to constricted arterial vessels. The reason for the vessel dilatation is still speculative, the imbalance between iNOS and eNOS could be a possible explanation for this. A direct effect of inflammatory markers could also play a role, however increased CrP and leucocytes primarily dilate retinal veins rather than arteries [44], and we found no difference in inflammatory markers between subgroups. Overall, in our cohort, COVID-19 patients seem to present with an overactivated NO system, that leads to maximally dilated microvasculature with very little reserve to further dilate or constrict to photostimulation. Invernizzi et al. found that both retinal arteries and veins were larger in COVID-19 patients compared to unexposed subjects, especially veins diameter was larger in more severe cases [77]. Most of the retinal vasculature alterations characterizing acute COVID-19 regress with time, but patients who suffer from severe COVID-19 had long lasting retinal vessels dilation persisting at least 6 months after complete resolution of the disease. He suggested a possible correlation with the generalized inflammatory and pro-coagulant status typical of acute COVID-19 as well as an irreversible structural damage in a part of the patients [78].

Microvascular dysfunction in retinal vessel serves as a direct surrogate of the microvasculature of the brain and the heart [26,79]. Impaired cognitive function, decrease of brain volume or the increased risk for CV diseases are known following SARS-CoV-2 infection [80,81]. Thus, DVA revealing endothelial dysfunction, offers potential explanations for cardiovascular collapse in acute COVID-19 patients as well as many symptoms of people suffering from long covid. A reduction in aFID has been shown as an important risk factor for severe CV events like myocardial infarction and stroke underlining the importance of monitoring patients for these events after COVID-19 infection, especially in the high-risk population.

We cannot conceal some limiting factors of our study. Firstly, systemic diseases like hypertension, obesity and diabetes may both reduce microvascular function and be a risk-factor for severe COVID-19 disease, the control group was extracted from a group of age- and gender matched individuals without pre-existing conditions, which could be a major confounder. However, in our subgroup analysis we could show a steady decline of endothelial function associated with increasing severity of COVID-19 disease. As we could not find a difference in risk factors between these subgroups, we hypothesized that this seems to be an independent effect, but the study was not powered to discriminate these differences. As mentioned before CV diseases would also lead to a reduction in CRAE, which we could not find. Secondly, due to the method, we could only investigate relatively stable patients which hindered us from gathering data of patients which were already ventilated and could be a possible confounder as the sickest patients could possibly not be included. The reliance on a control group from another study group could also possibly lead to disbalances in our results and interpretations. However, establishing of an adequately sized control group during lockdowns and still ongoing closing of hospitals to the public did not seem feasible. Small sample size prevented us from performing a more in-depth analysis, especially comparing different comorbidities and systemic medications. Also, there were no longitudinal measurements and follow-up measurements that could have allowed us to gather more information about resolution of the disease process.

Conclusions

In conclusion, we report that COVID-19 patients

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have significantly dilated arterioles and venules with reduced arteriolar vessel reactivity to increased oxygen demand due systemic endotheliitis resulting in endothelial dysfunction. This is the first study to demonstrate impaired microcirculation in COVID-19 patients using retinal vessel analysis and to show the extent of endothelial dysfunction in relation to disease severity. This offers a possible explanation for the pathophysiological transition process of COVID-19 in patients leading from asymptomatic to intensive care treatment and offers a potential risk-assessment screening tool for hospitalized patients, albeit the limitations.

The retinal vessel analysis offers a unique solution to monitor microvascular changes in COVID-19, further research should focus on exact distinction between chronic diseases and acute disease processes, predictive cut-off values for DVA parameters as well as longitudinal measurements during the course and resolution of COVID-19 and especially in long COVID-19 patients.

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RB and DV conceived of the study and wrote the manuscript. RB, SK, LS, WV performed statistical analysis. PAR, KK recruited patients on the ward, RB, KF and DV performed the examination of the patients. HP, AS, HH, WV gave important input in data interpretation, LN reviewed the language. All authors critically revised the manuscript for important intellectual content.

Conflict of interests

All authors report no conflict of interest regarding the content of the manuscript.

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Data availability statement

Data underlying this manuscript is available from the corresponding authors upon reasonable request.

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