Cerebral hemodynamic alterations in patients with Covid-19

Abstract

Background/aim: Coronavirus 2019 disease (Covid-19) was first seen in December 2019 and afterwards it became a pandemic. Several systemic involvements have been reported in Covid-19 patients. In this study, it was aimed to investigate the cerebrovascular hemodynamics in patients with Covid-19.

Materials and methods: The sample of this study was conducted on 20 patients hospitalized in our clinic diagnosed with Covid-19 via PCR modality and 20 healthy volunteers of similar age and sex. Bilateral middle cerebral arteries were investigated with Transcranial Doppler Ultrasonography. Basal cerebral blood flow velocities and vasomotor reactivity rates were determined and compared as statistically.

Results: When patient and control groups were compared, the mean blood flow velocity was found to be higher in Covid-19 patients than the healthy volunteers and it was statistically significant (p = 0.00). The mean vasomotor reactivity rates values were found to be lower in Covid-19 group than the healthy group and also it was statistically significant (p = 0.00).

Conclusion: An increase in cerebral basal blood velocity and a decrease in vasomotor reactivity rates in patients with Covid-19 can be considered as an indicator of dysfunction of cerebral hemodynamics in central nervous system and this can be evaluated as a result of endothelial dysfunction.

Key words: Covid-19, SARS-Cov-2, blood flow velocity, vasomotor reactivity

1. Introduction
It has been drawn an attention to the pneumonia cases which increased in December 2019 in Wuhan, China and not fully determined. A new virus belonging to the coronavirus family has been isolated in the studies that conducted for the cause of this disease, which is more mortal despite influenza-like symptoms. Firstly, this virus was named 2019-nCoV, but in the following days it was identified as SARS-CoV-2. The disease that developed depending on this virus was called COVID-19 [1].

Coronaviruses (CoV) are commonly seen in society such as influenza. People affected with coronaviruses may be asymptomatic or have symptoms ranging from mild influenza-like symptoms to severe respiratory distress. Other viruses, such as MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome) belonging to the CoV family have recently caused outbreaks by causing varying clinical status [2-5]. Covid-19 spread rapidly all over the world and was declared as a pandemic by the World Health Organization (WHO) in March 2020. Advanced age, immunosuppression, or concomitant systemic diseases (such as hypertension, diabetes mellitus, cardiovascular diseases, malignancy etc.) were determined as the most important factors on mortality [6, 7]. Symptoms occur approximately 5 days after viral exposure (incubation period) [8]. Fever, cough and fatigue are seen in many of patients while neurological symptoms such as headache, epileptic seizure, stroke, odor-taste disturbance, neuralgias and changes in consciousness have also been reported as well [3, 9, 10]. Causes of neurological manifestations are not still fully understood.

Besides the respiratory symptoms, there are many systemic (neurologic, dermatologic and gastrointestinal) manifestations may be seen in humans and sometimes these symptoms -except respiratory system- are being the first and unique clue of Covid-19
diagnose [11-14]. Endothelial dysfunction may be determined as the reason of these manifestations.

Transcranial Doppler (TCD) is a non-invasive ultrasonography modality that allows to dynamic monitoring of cerebral blood flow velocity and its changes [15-17]. With this modality, cerebral blood flow cannot be directly demonstrated, but its velocity can be monitored. In this study, it was aimed to investigate the cerebrovascular hemodynamics in patients with Covid-19 via TCD and to evaluate the vasomotor reactivity capacity with the Breath-Holding Index (BHI).

2. **Materials and methods**

The sample of this study was conducted on 20 patients hospitalized in our clinic diagnosed with Covid-19 via PCR modality and 20 healthy volunteers of similar age and sex. The person who needs intubation, who had history of performed cranial surgery, who had unsuitable temporal window for TCD, and pregnant patients were excluded from the study. Demographic data such as age and sex were recorded. TCD measurements of patients were evaluated immediately after hospitalization. All participants were informed about the examination and their written consents were taken before the study. This study was approved by the Ministry of Health (Protocol No: 2020-05-04T10-38-53) and the Local Ethic Committee (Protocol No: 2020-07-165).

DWL Multi-Dop T tool and QL software 2.8 were used for TCD examination. The middle cerebral arteries were insonated at an average depth of 45-60 mm through temporal bone window by means of 2 Mhz probs. After the vascular structures were determined bilaterally, two probs were fixed to the head with a frame. Patients were at rest for 10 minutes before the records in a quiet room. In order to evaluate mean basal cerebral blood
velocity a 5-minute record was obtained. The mean of blood flow velocity in these 5-minute records were calculated and the average of these recordings was determined as the basal blood flow velocity. Afterwards patients were informed, and it was asked to participants to hold their breath for 30 seconds to calculate the BHI. In the BHI study, maximum point of blood flow velocity increase, which occurs with the first breath taken after 30 seconds of breath-holding, was determined as the maximum speed. Cerebral blood flow velocity and BHI were calculated as shown in figure 1 and 2.

For statistical analysis, SPSS 26.0 was used. Descriptive statics were used for demographic data. Qualitative variables were indicated with frequency and percentage and numerical variables were summarized by mean ± standard deviation. Shapiro-Wilk test was used for determining normality. The Shapiro-Wilk Test is more appropriate for small sample sizes. For this reason, Shapiro-Wilk test was used as numerical means of assessing normality. Between group comparisons chi-square and Mann-Whitney U tests were used and p<0.05 is accepted as statistically significant.

3. Results

The study was conducted on 20 patients (13 male + 7 female) with diagnosed Covid-19 and 20 healthy volunteers (14 male + 6 female). The lowest age was 21 and the highest age was 81 in the patient group. The mean age of the patient group was 50.15 ± 19.07. In the control group, the lowest age was 21 and the highest age was 79. The mean age of the patient group was 47.90 ± 18.80. There was no significant difference between the two groups with respect to age and sex (p > 0.05).

In the right and left MCAs, there were no significant differences between the patient and control groups in terms of both basal blood flow velocity values and VMR (p = 0.61, p =
0.89 vs p = 0.24, p = 0.40 respectively) (Table). The mean blood flow velocity was found to be higher in patients’ group than the control group and it was statistically significant (p = 0.01). The mean VMR values were found to be lower in patients’ group than the control group and it was statistically significant (p = 0.01).

4. Discussion

In this study, it was investigated to VMR evaluated with basal blood flow and BHI obtained from bilateral MCAs via TCD in patients with Covid-19 and healthy volunteers. According to the results, basal blood flow velocity rates of patients with Covid-19 were found to be higher than the healthy group. In contrast to the basal blood flow velocity, VMR values of patients with Covid-19 were found to be lower than the healthy group.

Cerebral autoregulation is a homeostatic process that maintains cerebral blood flow at regular intervals, despite fluctuations in cerebral perfusion pressure [18]. Changes in the vascular tonus have a key role on ensuring cerebral hemodynamics. Cerebral blood flow is particularly sensitive to blood carbon dioxide exchange, but in some cases where the level of carbon dioxide remains constant, it is known that cerebral blood flow can be regulated by adjusting the heart rate or peripheral circulation [19].

The mechanisms of cerebral autoregulation remain poorly understood, especially in human. Generally, three different mechanisms -metabolic, myogenic and neurogenic- are thought to contribute to the process of cerebral autoregulation. These mechanisms affect the cerebral blood flow and this provides the regulation [20]. Vasomotor reactivity provides information about the capacity of the cerebral autoregulation and can be evaluated with several modalities such as BHI method.
TCD is a non-invasive, reproducible, bedside practicable diagnostic tool that can demonstrate the blood flow velocity and direction in major intracranial arteries. Cerebral arterial autoregulation is constituted with changes in the diameters of small arteries. There are no significant changes in the diameters of these vessels during normal pressure changes, or the constituted changes are negligible. Therefore, relative blood flow alterations resulting from diameter changes in small vessels can be evaluated as autoregulation response [20, 21].

There are several studies have been made about cerebral autoregulation especially in patients with migraine, and changes in the vasomotor reactivity and basal blood flow velocity were observed in many of these studies [22, 23]. In the Rotterdam study which was conducted by Portegies and et all., decreased VMR results were found to be related with mortality. Authors reported that stroke was independent of this relationship and the decreased VMR values were based on impairment of vascular system [24]. In similar with this study, Ju et al., also reported that the decreased VMR is an important prognostic factor for stroke [25]. In one study carried out by Mamontov et al, the low neurogenic reactivity against increased peripheral vascular tonus was found to be the worst prognostic factor in hypertensive patients [26].

Hypertension is one of the most important factors of poor prognosis in patients with Covid-19 [6, 7]. In addition, many different studies have showed that patients with Covid-19 tend to thrombosis, and also stroke cases have been reported in these studies [27-33]. In particular in cases related to thrombus, an underlying endothelial dysfunction has been accused. Varga et al., have histopathologically showed that the SARS-CoV-2 virus caused endothelial damage [34]. In addition to endothelial physical barrier function, it has paracrine, endocrine and autocrine effects as well. In this way, it affects the vascular tonus
and provides the vascular homeostasis [35]. Endothelial damage disrupts the balance in the vascular tonus and it causes the ischemia, edema and procoagulant state in the organ in which it is located [36].

As a result of this study, it was found to be an increase in cerebral basal blood velocity and a decrease in VMR in patients with Covid-19. It is thought that this can be evaluated as a result of endothelial dysfunction in the vascular structures of central nervous system.

References


Figure 1: Cerebral blood flow changes during breath holding (Vrest: Mean blood flow velocity in rest, Vmax: Maximum blood flow velocity). Blood flow velocity is measured by TCD from the right (Green) and left (Red) middle cerebral arteries bilaterally.
Figure 2: Calculation of Breath-Holding Index. (Vrest: Mean blood flow velocity in rest, Vmax: Maximum blood flow velocity)
<table>
<thead>
<tr>
<th>Covid-19 (mean±sd)</th>
<th>p value</th>
<th>Healthy (mean±sd)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>LMCA BFL</strong></td>
<td>61.32±3.58</td>
<td><strong>RMCA BFL</strong></td>
<td>60.77±4.82</td>
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<tr>
<td><strong>LMCA VMR</strong></td>
<td>1.18±0.03</td>
<td><strong>RMCA VMR</strong></td>
<td>1.17±0.02</td>
</tr>
</tbody>
</table>

Table. Comparison between Right and Left MCAs in the patient and control groups in terms of BFV and VMR

(LMCA BFL: Left Middle Cerebral Artery Blood Flow Velocity, RMCA BFL: Right Middle Cerebral Artery Blood Flow Velocity, LMCA VMR: Left Middle Cerebral Artery Vasomotor Reactivity, RMCA VMR: Right Middle Cerebral Artery Vasomotor Reactivity)