EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Effect of surgical mask and N95 respirator mask use on cerebrovascular reactivity

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| English | https://doi.org/10.18071/isz.77.0263 | www.elitmed.hu

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Érkezett:
2023. augusztus 17.
Elfogadva:
2023. október 27.

Background and purpose – Face masks are crucial parts of personal protective equipment (PPE) to reduce the risk of respiratory infections. The COVID-19 outbreak has increased healthcare workers' use of face masks. This study aimed to evaluate changes in cerebrovascular response among healthcare workers using surgical and N95 respirator masks.
Methods – 90 healthcare workers: 30 wearing surgical masks, 30 wearing N95 respirators, and 30 without masks were included. After two-hour of face mask use, the baseline mean flow velocity (MFV) and the mean breath-holding index (BHI) of the bilateral middle cerebral arteries (MCAs) were evaluated with transcranial Doppler ultrasound. The presence of de-novo headache was recorded. BHI values below 0.69 were evaluated as a sign of impaired cerebrovascular reactivity (CVR).
Results – The rate of de-novo headache was significantly higher in the N95 respirator mask group (p = 0.004). Compared to the control and surgical mask groups, the N95 respirator mask group had significantly lower values of the baseline MFV of the right MCA (p = 0.003 and p = 0.021, respectively) and mean BHI (p = 0.003 and p = 0.012, respectively). Still, only one N95 respirator mask user had a mean BHI value below 0.69.
Conclusion – Surgical masks did not significantly affect cerebral hemodynamics.

A sebészeti maszk és az N95 respirátor maszk használatának hatása a cerebrovascularis reaktivitásra

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Háttér és cél – Az arcmaszkok a légzőszervi fertőzések kockázatának csökkentésére alkalmazott személyes védőfelszerelés (PPE) elengedhetetlen részét képezik. A Covid-19-járvány hatására fokozódott az egészségügyi dolgozók arcmaszkhasználata. Tanulmányunk célja az volt, hogy értékeljük a sebészeti és az N95 respirátor maszkot viselő egészségügyi dolgozók körében bekövetkező cerebrovascularis válasz változásait.
Módszerek – Összesen 90 egészségügyi dolgozót vontunk be a tanulmányba: 30-an sebészeti maszkot és 30-an N95 respirátor maszkot viseltek, míg 30-an nem viseltek maszkot. Kétórás maszkhasználat után transcranialis Doppler-ultrahanggal értékeltük a bilaterális középagyi artériák (MCA) átlagos áramlási sebességét (MFV) és átlagos légzéstartási indexét (BHI). Rögzítettük a de novo fejfájás jelenlétét. A 0,69 alatti BHI-értékeket a károsodott cerebrovascularis reaktivitás (CVR) jelének tekintettük.
Eredmények – A de novo fejfájás előfordulási aránya szignifikánsan magasabb volt az N95 légzőmaszkot viselő csoportban (p = 0,004). Az N95 légzőmaszkot viselő csoportban a jobb MCA átlagos áramlási sebességének kiindulási értéke (p = 0,003, illetve p = 0,021) és az átlagos BHI-értékek (p = 0,003 és p = 0,012) szignifikánsan alacsonyabbak voltak a kontroll- és a sebészeti maszkot viselő csoportok értékeihez képest. Mindazonáltal, csak egy N95 légzőmaszkot

Although N95 respirator mask use significantly decreased BHI values, the CVR is still within normal limits, and the development of de-novo headache is not directly associated with low CVR.

Keywords: breath-holding index, cerebrovascular reactivity, healthcare workers, n95 respirator mask, surgical mask

viselő személy esetében volt az átlagos BHI-érték 0,69 alatt.
Következtetés – A sebészeti maszk használata nem befolyásolta szignifikánsan a cerebralis hemodinamikát. Habár az N95 légzőmaszk használata szignifikánsan csökkentette a BHI-értékeket, a CVR-értékek továbbra is a normáltartományban voltak, és a *de novo* fejfájás kialakulása nem volt közvetlen összefüggésben az alacsony CVR-rel.

Kulcsszavak: légzéstartási index, cerebrovascularis reaktivitás, egészségügyi dolgozók, N95 respirátor maszk, sebészeti maszk

The Coronavirus-19 (COVID-19) pandemic, in which the use of surgical masks were recommended as a protection strategy, had caused serious difficulties for the whole world as a global health problem[1]. The World Health Organization (WHO) recommended the use of surgical masks only for infected individuals and healthcare workers in April 2020[2], but in June 2020, this recommendation was revised to support mask use for all individuals in crowded places[3]. While the April 2020 recommendations[2] pointed out a risk of self-contamination and potential breathing difficulties during mask use, the June 2020 recommendations[3] also referred to additional possible side effects, such as headaches associated with mask use.

Wearing a surgical mask may cause discomfort due to various factors such as increased difficulty in breathing, heightened temperature, accumulation of carbon dioxide (CO2) inside the dead space of the mask, and pressure of the mask's elastic ear loops. There are very few studies investigating the physiological effect of medical masks on humans, and the results are conflicting[4].

The sensitivity of cerebral blood vessels to changes in partial pressure of CO_2 ($PaCO_2$) is called cerebrovascular reactivity (CVR). Arterial hypercapnia results in vasodilation and leads to an increase in cerebral blood flow (CBF). Transcranial Doppler ultrasound (TCD) is a technique used to assess the velocity of cerebral blood flow in intracranial vessels originating from the Willis polygon. Breath-holding index (BHI) testing is a real-time, reproducible, and well-tolerated method to induce hypercapnia and examine CBF[5].

This study aimed to assess the impact of surgical and N95 respirator masks on the cerebral hemodynamic changes of healthcare workers using the breath-holding test.

Materials and methods

The study was conducted at the Bezmialem Foundation University Hospital between May 2021 and February 2022. A total of 90 healthcare workers were included in this study: 30 wore surgical masks for two hours, 30 wore N95 respirator masks for two hours, and 30 wore no face mask. All participants in the surgical mask group wore Evony® (Hayat Chemistry, Kocaeli, Turkey) three-layer surgical masks, and all in the N95 respirator mask group used Era® (Başaran Work Clothes Co. Ltd., Tuzla, Istanbul) N95 respirator masks that filtered out 95% of particles larger than 0.3 μm in size. Healthcare workers with a history of ischemic or hemorrhagic stroke, carotid artery occlusion, respiratory disease, atrial fibrillation, space-occupying central nervous system lesions, an inappropriate temporal window, chronic alcohol consumption, and beta-blocker use were excluded. The Clinical Research Ethics Committee of Bezmialem Foundation University (No: E-54022451-050.05.04-16606, date: April 29, 2021) approved the study. The principles stated in the Declaration of Helsinki were followed during the study. All participants were verbally informed and provided written informed consent.

Demographic data, medical history, other comorbidities, current medications, smoking, and alcohol consumption habits, presence of newly onset headache after the use of the face mask, hemoglobin, hematocrit, mean corpuscular volume (MCV), platelet values, systolic and diastolic blood pressure levels were recorded. In addition, electrocardiography recordings were obtained. At the time of study enrolment, carotid arteries were assessed with Doppler ultrasound (General Electric Logic 9R4). Participants with significant carotid stenosis (>50%) in one or both arteries were excluded. Following the ultrasound examination, the breath-holding test was performed using the SONORA TCD system (CareFusion, San Diego, CA, USA).

At the beginning of the TCD protocol, the participants in all three groups were taken to a quiet room to rest for 10 minutes. Two pulsed-wave Doppler probes (2 MHz) were attached to a headframe and placed on the right and left temporal windows to perform uninterrupted measurements. The mean arterial blood flow velocities of the right and left MCAs were defined as the baseline velocity ($MFV_{baseline}$) during the last three minutes of an initial 10-minute resting period[6]. CVR against CO_2 stimulation was evaluated using the breath-holding test. Following the stabilization of the cerebral blood flow velocity, the subjects were explained to hold their breath for up to 30 seconds after a normal inspiration with a face mask on. As a safety measure, the participants were instructed prior to the test to cease holding their breath in case they experienced discomfort. The MFV value of the last three seconds during breath-holding was recorded as MFV_{max}. If an individual was unable to hold their breath for 30 seconds, the maximum breath-hold time was taken into consideration in the calculation of BHI[7, 8]. The breath-holding test was repeated three times during mask use at five-minute intervals, and data were collected. The breath-holding test was repeated 30 minutes after the masks were removed. We separately calculated the BHI of MCA on each side and then obtained the mean BHI of the MCAs (BHI_{mean}MCA). We used the following formula for the calculation of BHI: BHI = (MFV_{max} – $MFV_{baseline}$) (cm/s)/breath-holding duration (s).

Data from healthy individuals in previous studies determined a BHI cutoff value of 0.69[9, 10] to distinguish between impaired and normal CVR.

For the statistical analysis, the SPSS package program for Windows version 20 (IBM Corporation, Armonk, NY, USA) was utilized. Categorical variables were defined according to frequency and percentage values. Continuous values were expressed using mean and standard deviation (SD) for variables with a normal distribution. For the non-normal distribution, measurements were expressed as median with minimum and maximum values. To assess the distribution of data, the Shapiro-Wilk test was performed to determine its normality. A Student's t-test was used to compare quantitative data for variables with a normal distribution. A Mann-Whitney U test was conducted to compare variables that did not have a normal distribution. For three or more groups, comparisons were undertaken with the one-way analysis of variance test if data were normally distributed and the Kruskal-Wallis test otherwise. During multiple comparisons, the Bonferroni adjustment was applied to the p-values to prevent type I errors. To determine statistical significance, P-values less than 0.05 were taken into consideration.

Results

The study included a total of 90 healthcare workers: 30 (20 females, ten males) wearing surgical masks, 30 (21 females, nine males) wearing N95 respirator masks, and 30 (18 females, 12 males) not wearing a mask (controls), with median ages of 27 (20-48), 24 (20-46), and 27 (19-46) years, respectively.

The three groups had no significant differences in terms of age, gender, smoking history, hypertension, hemoglobin, hematocrit, MCV, platelet, and systolic and diastolic blood pressure levels. Between the three groups, the rate of diabetes mellitus and hyperlipidemia significantly differed ($p = 0.046$, $p = 0.046$), they were significantly higher in the control group than in the surgical mask and N95 respirator mask groups ($p = 0.032$, $p = 0.032$). In the surgical mask group 6 (20%), in the N95 respirator mask group 17 (56%) individuals reported de-novo headache after donning face masks. The rate of de-novo headache was significantly higher in the N95 respirator mask group compared to the surgical mask group ($p = 0.004$) **(Table 1)**.

The N95 respirator mask group had significantly lower values for the $MFV_{baseline}$ of the right MCA compared to the control group and surgical mask group ($p = 0.003$ and $p = 0.021$, respectively). There were no significant differences in the $MFV_{baseline}$ values of the right MCA between the control group and the surgical mask group ($p > 0.05$). No significant differences were detected between the three groups in the $MFV_{baseline}$ of the left MCA ($p = 0.051$). Still, the N95 respirator mask group had lower values for the $MFV_{baseline}$ of the left MCA (49.40 ± 6.27) compared to the control group (53.56 ± 7.12) and surgical mask group (51.55 ± 6.03) **(Table 2)**.

The N95 respirator mask group had significantly lower BHI_{mean}MCA values (1.15 ± 0.30) compared to the control group (1.44 ± 0.32) and surgical mask group (1.40 ± 0.35) ($p = 0.003$ and $p = 0.012$, respectively). There were no significant differences in the BHI_{mean}MCA values of the control and surgical mask groups ($p > 0.05$) **(Table 3)**. After the masks were removed, no significant differences were observed in the BHI_{mean}MCA, breath-holding time, and $MFV_{baseline}$ of the right and left MCA between the control, N95 respirator mask, and surgical mask groups ($p>0.05$).

In the control group, the right and left BHI values and BHI_{mean}MCA values were above 0.69 in all healthcare workers. In the surgical mask group, only one mask user had the right BHI value under 0.69. In the N95 respirator mask group, six individuals (20%) had BHI values below 0.69 on the right side, two individuals (6.7%) had BHI values below 0.69 on the left side, and one individual (3.33%) had a BHI_{mean}MCA value below 0,69 **(Table 4)**.

In the N95 respirator mask group, two of six individuals (11.7%) with right BHI values below 0.69 presented

Table 1. *Demographic data and laboratory test results of the mask groups*

	Control (n = 30)	Surgical mask (n = 30)	N95 respirator mask (n = 30)	p
Age	27 (20–48)	24 (20–46)	27 (19–46)	0.312[a]
Gender				0.711[a]
Female	18 (60%)	20 (66.7%)	21 (70%)	
Male	12 (40%)	10 (33.3%)	9 (30%)	
Smoking status				0.591[a]
Smoker	7 (23.3%)	5 (16.7%)	4 (13.3%)	
Nonsmoker	23 (76.7%)	25 (83.3%)	26 (86.7%)	
Hypertension				0.355[a]
Present	2 (6.7%)	–	2 (6.7%)	
Absent	28 (93.3%)	30 (100%)	28 (93.3%)	
Diabetes mellitus				0.046[a]
Present	3 (10%)	–	–	
Absent	27 (90%)	30 (100%)	30 (100%)	
Hyperlipidemia				0.046[a]
Present	3 (10%)	–	–	
Absent	27 (90%)	30 (100%)	30 (100%)	
De-novo headache	–	6 (20%)	17 (56%)	0.004[b]
Hemoglobin	13.59 ± 1.64	13.67 ± 1.79	13.72 ± 1.95	0.054[c]
Hematocrit	41.13 ± 4.09	40.99 ± 4.68	40.31 ± 5.52	0.087[c]
MCV	85.36 ± 5.30	85.69 ± 4.24	85.19 ± 4.83	0.924[c]
Platelet	255.67 ± 64.25	262.70 ± 68.08	278.27 ± 59.83	0.184[a]
Systolic BP	122.67 ± 13.11	116.67 ± 8.44	121 ± 11.55	0.130[a]
Diastolic BP	74.33 ± 7.73	72 ± 8.05	72.33 ± 10.06	0.571[a]

Percentage, median (minimum-maximum), and mean ± standard deviation values were used as descriptive statistics.
[a]Kruskal-Wallis test, [b]Mann-Whitney U test, [c]Student's t-test; $p < 0.05$.
MCV: mean corpuscular volume; BP: blood pressure

Table 2. *$MFV_{baseline}$ values of right and left MCAs of the mask groups*

	Control[a] (n = 30)	Surgical mask[b] (n = 30)	N95 respirator mask[c] (n = 30)	p*	Post-hoc comparisons
$MFV_{baseline}$, right MCA, cm/s	54.27 ± 7.32	52.96 ± 4.95	48.20 ± 7.42	0.002	a-b: 1 a-c: 0.003 b-c: 0.021
$MFV_{baseline}$, left MCA, cm/s	53.56 ± 7.12	51.55 ± 6.03	49.40 ± 6.27	0.051	–

Mean ± standard deviation values were used as descriptive statistics.
*One-way analysis of variance test. Post-hoc significance values have been adjusted using the Bonferroni correction.
MFV: mean flow velocity; MCA: middle cerebral artery

a de-novo headache. Two individuals who had left BHI values below 0.69 didn't develop de-novo headache during the study **(Table 5)**.

When the whole sample was considered, the $BHI_{mean\text{-}MCA}$ measurements did not significantly differ according to gender, smoking status, or the presence of hyperten-

Table 3. *Breath-holding times and BHI values of the groups*

	Control[a] (n = 30)	Surgical mask[b] (n = 30)	N95 respirator mask[c] (n = 30)	p*	Post-hoc comparisons
Breath-holding time, right MCA, (second)	30.03 ± 1.49	29.30 ± 1.29	27.47 ± 1.47	<0.001	a-b: 0.148 a-c: <0.001 b-c: <0.001
Breath-holding time, left MCA, (second)	29.53 ± 1.16	29.40 ± 1.22	27.93 ± 1.36	<0.001	a-b: 1 a-c: <0.001 b-c: <0.001
BHI, right MCA	1.44 ± 0.40	1.41 ± 0.44	1.12 ± 0.43	0.009	a-b: 1, a-c: 0.017 b-c: 0.034
BHI, left MCA	1.44 ± 0.38	1.40 ± 0.39	1.18 ± 0.35	0.022	a-b: 1 a-c: 0.030 b-c: 0.008
BHI_{mean}MCA	1.44 ± 0.32	1.40 ± 0.35	1.15 ± 0.30	0.002	a-b: 1 a-c: 0.003 b-c: 0.012

Mean ± standard deviation values were used as descriptive statistics.
*One-way analysis of variance test. Post-hoc significance values have been adjusted using the Bonferroni correction.
BHI: breath-holding index; MCA: middle cerebral artery

sion, diabetes mellitus, or hyperlipidemia ($p > 0.05$). There was also no correlation between the BHI measurements and age, hemoglobin, hematocrit, MCV, platelet, and blood pressure levels ($p > 0.05$).

Table 4. *BHI levels of mask groups according to the cutoff value*

	Control[a] (n = 30)	Surgical mask[b] (n = 30)	N95 respirator mask[c] (n = 30)
BHI, right MCA			
≤ 0.69	0 (0%)	1 (3.33%)	6 (20%)
> 0.69	30 (100%)	29 (96.7%)	24 (80%)
BHI, left MCA			
≤ 0.69	0 (0%)	0 (0%)	2 (6.7%)
> 0.69	30 (100%)	30 (100%)	28 (93.3%)
BHI_{mean}MCA			
≤ 0.69	0 (0%)	0 (0%)	1 (3.33%)
> 0.69	30 (100%)	30 (100%)	29 (96.7%)

Percentage values were used as descriptive statistics.
BHI: breath-holding index; MCA: middle cerebral artery

Discussion

It is well known that alterations in arterial blood gas cause changes in the cerebral circulation[11]. The increase in CO_2 content in the interstitial compartments and endothelial cells and the reduction in pH secondary to this increase result in the relaxation of vascular smooth muscle cells (SMCs) in the arteries and consequently lead to vasodilation[12]. CO_2 also indirectly affects potassium (Kþ) channels, causing SMCs to hyperpolarize and decrease voltage-dependent calcium channel activation, leading to vasodilation. In addition, changes in CO_2 and pH lead to the activation of nitric oxide (NO) synthase in the endothelium, and an increased NO concentration causes vasodilation[13]. Hypoxia also exhibits variable effects on cerebral circulation, and these effects alter depending on the depth of hypoxia[11]. Although the mechanisms causing vasodilation have not yet been clarified, the direct effect of low partial pressure of oxygen or the indirect release of vasodilator metabolites is primarily considered involved[12]. Vasodilation via adenosine triphosphate-sensitive potassium channels[13] and NO production[14] are among the proposed mechanisms.

Studies have shown that the use of masks alters the concentrations of oxygen and CO_2 in arterial blood. In a study including 128 dental healthcare workers using N95 respirator masks, *Manerkar* et al.[15] reported that oxygen saturation significantly decreased after one hour and increased after the second hour. However, in another study completed by 76 healthcare professionals using different types of masks for 68-480 minutes, no significant changes were observed in arterial oxygen saturation (SaO_2)[4]. In many studies evaluating the effect of masks on exercise capacity, no difference was observed between the post-exercise SaO_2 of participants using different types of masks[16–18]. In a study undertaken by *Bharatendu* et al.[19], there was an increase of 3.1 ± 1.2 mmHg in the end-tidal CO_2 (ET-CO_2) levels of healthcare workers after the use of N95 respirator masks ($p < 0.001$). Other studies have also indicated a significant increase in post-exercise ET-CO_2 values among participants using different types of masks[20–22]. Although the effect of face mask use on arterial oxygen saturation remains unclear, studies have shown that ET-CO_2 levels increase with mask use.

Increased arterial CO_2 causes increased CBF through arteriolar dilation[5]. Although increased ET-CO_2 is supposed to be achieved with mask use, we did not notice increased flow velocity in the MCAs. As is well known, cerebral blood flow velocity is not equal to CBF[23]. It might reflect CBF only when the vessel diameter remains constant[24]. *Willie* et al.[25] demonstrated that hypoxia or hypercapnia-induced high CBF values cannot be accurately predicted by blood flow velocities measured by TCD. In addition, studies have shown that the changes in CBF values after acetazolamide administration vary widely, ranging from 25% to 70%. This considerable range in CBF values depends on the different age and sex characteristics of the different populations and is partly based on the measurement technique[26]. Inconsistent with our results, in a study that included 154 healthcare workers, Bharatendu et al.[19] found that the use of N95 respirator mask increased the mean MFV values of the MCA from 56.7 ± 18.2 cm/s to 61.1 ± 17.0 cm/s ($p < 0.001$). The authors evaluated changes in cerebral hemodynamic parameters after just five minutes of wearing the masks and noted impaired cerebrovascular responses, but the long-term effects are still unclear. In another study, no statistically significant difference was found in the baseline flow velocity values measured by TCD between 20 healthy participants and 14 patients with chronic hypercapnia that developed secondary to the common cold before and after the intravenous acetazolamide administration or rebreathing test[27]. While sudden changes in $PaCO_2$ resulted in a quick increase in CBF, the stable changes in $PaCO_2$ did not result in an increase in CBF. The authors reported that the CBF values were within normal limits, but the cerebral vascular responses were decreased in patients with chronic hypercapnia. *Levasseur* et al.[28] showed that in an awake rabbit exposed to hypercapnia (7% CO_2) or hypoxia (10% oxygen) for six days, the vasodilator response to 3-10% CO_2 inhalation in the pial arterioles was reduced after prolonged hypercapnia, and this was due to a change in bicarbonate ion concentration. In our study, $MFV_{baseline}$ values were obtained after two-hour of N95 respirator mask use. In addition to the lack of relationship between MFV and CBF in different individuals, another explanation for the absence of the expected MFV increase with N95 respirator mask use may be related to the duration of mask use, and it could be the effect of long-lasting hypercapnia.

Table 5. *De-novo headache rates according to BHI values of the N95 respirator mask group*

	De-novo headache rates		
	Absent (n=13)	Present (n=17)	Total (n=30)
BHI, right MCA			
≤0.69	4 (30.8%)	2 (11.7%)	6 (20%)
>0.69	9 (69.2%)	15 (88.2%)	24 (80%)
BHI, left MCA			
≤0.69	2 (15.4%)	0 (0%)	2 (6.7%)
>0.69	11 (84,6%)	17 (100%)	28 (93.3%)

Percentage values were used as descriptive statistics.
BHI: breath-holding index; MCA: middle cerebral artery

In a study by *Mapelli* et al.[18], 12 healthy individuals performed the cardiopulmonary exercise test three times (unmasked, with a surgical mask, and with a filtering facepiece class 2 (FFP2 mask). There was a progressive decrease in the forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values from the control to the FFP2 group. Rest ventilation, oxygen uptake, and CO_2 production were progressively lower from the surgical mask to the FFP2 group. In another study, in which 12 healthy men were evaluated after exercise in three groups (unmasked, surgical mask, and FFP2/N95 mask), the FEV_1, peak expiratory flow and ventilation values were found to be lower in both mask groups, being more prominent in the FFP2/N95 group[29]. *Lässing* et al.[30] evaluated the effect of wearing a surgical face mask during steady-state exercises. They found an increase in airway resistance and a decrease in FEV_1, vital capacity, and peak expiratory flow. *Zhang* et al.[22], evaluating 71 healthy participants who exercised without a mask and while wearing a surgical mask, showed that the resting oxygen uptake and CO_2 production values were lower when the mask was on compared to when it was off ($p < 0.01$). All these studies show that mask use leads to pathophysiological changes similar to those seen in patients with chronic obstructive pulmonary disease (COPD).

The central respiratory chemoreflex is a response in ventilation that occurs due to changes in $PaCO_2$. It is a regulatory system that maintains a stable pH by controlling the concentration of arterial CO_2. Changes in $PaCO_2$ levels can lead to either hyperventilation or hypoventilation. This can cause a decrease or increase in arterial CO_2 concentration through the central respiratory chemoreflex[31]. In a study by *Van de Ven* et al.[32], the association between ventilation and the response of cerebral blood volume (CBV) to changes in arterial blood $PaCO_2$

was assessed. The study involved 33 COPD patients (17 chronically hypercapnic, 16 normocapnic) and 15 healthy volunteers of the same age. Hypercapnia was induced by supplying sufficient CO_2 to the inhaled air. During normocapnia, the mean CBV values of COPD patients were significantly lower compared to healthy individuals. In a study comparing 90 patients with COPD and 30 age- and gender-matched healthy volunteers using TCD, Hlavati et al. [7] found lower MCA $MFV_{baseline}$ values in patients with COPD than in the controls. In addition, significantly lower BHI_{mean}MCA values were detected in the COPD group compared to the control group ($p < 0.001$). A significant positive correlation existed between FEV_1 and BHI_{mean}MCA (rho = 0.761, $p < 0.001$). The lower $MFV_{baseline}$ of the right MCA and BHI values of the N95 respirator mask group we showed in our study are similar to those obtained in COPD patients. No statistically significant difference was detected in the $MFV_{baseline}$ of the left MCA among the three groups. However, it was lower in the N95 respirator mask group than in the other groups, and the p-value was determined to be 0.051. In this context, in prolonged hypercapnia, the CVR–$PaCO_2$ relationship is more complex. The potential hypercapnia-induced vasodilation during the N95 respirator mask use may cause the further vasodilation to be less pronounced during the breath-holding test, resulting in decreased BHI.

In our study, the two-hour use of an N95 respirator mask during the test protocol resulted in a significant decrease in breath-holding time. It had been reported that the use of an N95 respirator mask causes more breathing difficulties and psychiatric symptoms such as panic attacks and anxiety compared to the use of a surgical mask[33]. *Kim* et al.[34] suggest that breathing difficulties may be due to factors such as facial skin temperature, the microenvironment inside the mask, humidity, heat, or inhaled air temperature. Another study showed that the feeling of suffocation was 59% with an N95 mask use and 6% with a surgical mask use[35]. Considering these findings, psychological and physiological factors may explain this decrease in breath-holding time with the use of an N95 respirator mask. Many studies conducted during and after the COVID-19 pandemic, when mask use became widespread, have shown that the occurrence of headaches increased with the use of face masks among healthcare workers[36–38]. It has been suggested that pain or discomfort is observed more frequently, especially after prolonged mask use[38]. In addition, studies have shown that cerebral hemodynamics are impaired in different headache types[39–41]. Bharatendu et al.[19] suggested that the changes in cerebral hemodynamics caused by CO_2 retention and hypoxemia contribute to the development of headaches, especially in individuals who develop headaches shortly after donning N95 respirator masks. Similar to our findings, they observed a significant decrease in cerebrovascular reactivity after only five minutes of N95 respirator mask use. Their research also indicates that combining a powered air-purifying respirator (PAPR) with an N95 respirator mask can normalize these alterations. They recommended using PAPR and N95 respirator masks together for healthcare workers. In our study, although the N95 respirator mask group had significantly lower CVR and significantly higher de-novo headache rates than the other groups, BHI_{mean}MCA was below 0.69 in only one N95 respirator mask user. When right and left BHI values were evaluated separately, only two of six individuals with right BHI values below 0.69 experienced de-novo headache during the protocol. The two individuals with left BHI values below 0.69 did not develop headache. Based on these data, higher de-novo headache development in the N95 respirator mask group cannot be explained by impaired CVR alone, and masks' elastic band pressure or tractional forces of the straps should be considered as other possible mechanisms[42].

This study had certain limitations. We did not simultaneously measure oxygen saturation and transcutaneous or ET-CO_2 values. And since the study population consisted of healthcare workers, this study reflects the results of a young and healthy group of people. Because the study focused primarily on blood flow changes, questionnaires about the discomfort caused by mask use or anxiety were not collected from the healthcare workers.

Conclusions

Prolonged use of surgical masks does not appear to alter cerebrovascular reactivity. Wearing N95 respirator masks for two hours results in changes similar to those observed in COPD and causes decreases in MFV and CVR. Although significant decreases in BHI values are recorded with N95 respirator masks, the levels are still above the cutoff limit. These alterations in CVR may have a minor contribution to the development of de-novo headache. Despite minor imperfections, the two-hour use of N95 respirator masks appears safe for healthcare workers. Further research is needed to investigate long-term N95 respirator mask use, as results may change as hypercapnia persists. Considering CVR may deteriorate with age[8] and pulmonary[7] or neurological diseases[43, 44], studies are needed to evaluate an older population, based on the previous studies[19], options such as using PPAR with N95 may be considered for a more risky population.

ACKNOWLEDGEMENT – None.
CONFLICT OF INTEREST STATEMENT – All authors have declared that they do not have any conflicts of interest.
FUNDING STATEMENT – All authors state that this study did not receive any financial support.
DATA AVAILABILITY STATEMENT – The data that support the findings of this study are available on request from the corresponding author.

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