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RESEARCH ARTICLE

CEREBRAL VASOREACTIVITY TO CARBON DIOXIDE ASSESSED BY TRANSCRANIAL DOPPLER ULTRASOUND IN POST-COVID-19 PATIENTS: A MOROCCAN COMPARATIVE STUDY

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Abstract

Background: COVID19 has been associated with multiple neurological manifestations, ranging from mild symptoms to severe cerebrovascular complications. The endothelium is a major target of SARS-CoV-2, and cerebral microvascular dysfunction may persist beyond the acute phase. The assessment of cerebral vasoreactivity (CVR) to carbon dioxide (CO₂) using transcranial Doppler ultrasound (TCD) is a noninvasive method to detect subtle alterations in cerebral hemodynamics.

Objective: To evaluate cerebral vasoreactivity and the breath-holding index (BHI) in patients who recovered from moderate or severe COVID-19, compared with non-COVID-19 controls.

Methods: A prospective observational study was conducted including 75 subjects: 50 post-COVID-19 patients and 25 controls. Middle cerebral artery (MCA) flow velocities were recorded at rest and after a breath-holding test. CVR and BHI were calculated as the percentage change in mean flow velocity relative to baseline and to Breath Holding Time, respectively.

Results: Baseline systolic, diastolic, and mean velocities in the MCA were significantly lower in the post-COVID-19 group compared with controls ($p < 0.05$). Following the Breath-holding Test, all flow velocities increased in both groups, but the magnitude of increase and the BHI were significantly lower in post-COVID-19 patients ($p < 0.05$).

Conclusion: Patients recovered from moderate or severe COVID-19 exhibited impaired Cerebral Vasoreactivity to CO₂, suggesting persistent endothelial dysfunction despite clinical recovery. Routine TCD assessment may help identify asymptomatic patients at risk for cerebrovascular complications in the perioperative or critical care setting.

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Introduction:-

Stroke remains the second leading cause of mortality worldwide, with well-established vascular risk factors [1]. In recent years, several infectious agents have been recognized as additional contributors to cerebrovascular disease through inflammatory and endothelial mechanisms. Chronic infections such as chlamydia pneumonia, cytomegalovirus, *Helicobacter pylori*, influenza virus, hepatitis C virus, etc., have been shown to contribute to the development of cerebrovascular disease through the changes they cause in the small and large blood vessels of the brain [2]. SARS-CoV-2 virus infection is no exception and could also represent a new risk factor for stroke even in patients who have had moderate or minor forms of the disease [3]. The Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has emerged as a global health crisis since March 2020, with more than 600 million confirmed cases and over six million deaths reported by September 2022 [4]. Neurological manifestations have been frequently observed in patients with severe COVID-19, including ischemic and hemorrhagic stroke, encephalitis, meningitis, polyneuropathy, and seizures [5]. In contrast, patients with mild or moderate disease often experience nonspecific neurological symptoms such as headache, dizziness, myalgia, anosmia, or fatigue [6-7]. SARS-CoV-2 enters host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in the lungs, heart, kidneys, intestines, and vascular endothelium. Viral infection leads to diffuse endothelial dysfunction, microvascular inflammation, and thrombosis—features strongly associated with multi-organ failure in severe COVID-19 [8,9].

Postmortem studies have revealed multifocal micro vascular lesions in the brain and olfactory bulbs, often without detectable viral RNA in the brain tissue suggesting secondary endothelial inflammation rather than direct viral invasion [8]. These observations raise concerns about long-term cerebrovascular consequences after recovery from COVID-19. Persistent endothelial dysfunction could compromise the brain's ability to regulate blood flow in response to metabolic or chemical stimuli—a phenomenon known as Cerebral Vasoreactivity (CVR). CVR reflects the capacity of cerebral arterioles to dilate in response to hypercapnia or other vasodilatory stimuli [10]. Transcranial Doppler ultrasound (TCD) is a noninvasive bedside tool that measures blood flow velocities within the major intracranial arteries, most commonly the middle cerebral artery (MCA). It has been widely used to study cerebral hemodynamics in various conditions, including small-vessel disease, migraine, hypertension, and traumatic brain injury [11]. Even when baseline flow velocities are within normal ranges, an abnormal CVR response may indicate impaired endothelial or neurovascular function.

Several methods can be used to assess CVR, including acetazolamide administration, CO₂ inhalation, and the breath-holding test (BHT). The BHT induces transient hypercapnia by voluntary apnea, causing vasodilation and increased cerebral blood flow [12,13]. The magnitude of velocity change during apnea, expressed as a percentage of baseline and adjusted for breath-holding time, yields the breath-holding index (BHI), a quantitative marker of CVR. Reduced BHI values have been associated with increased stroke risk and poorer neurological outcomes in several populations [14-15]. Although TCD is widely available in critical care and anesthesia settings, its use in post-COVID-19 patients has not been standardized, and data remain limited. Given the endothelial tropism of SARS-CoV-2 and the evidence of microvascular injury during infection, it is plausible that CVR could remain impaired after clinical recovery, even in the absence of neurological symptoms. The present study aimed to evaluate CVR to CO₂ in patients who recovered from moderate or severe COVID-19 using TCD and the breath-holding test. We hypothesized that post-COVID-19 patients would show reduced vasodilatory response and lower BHI values compared with non-COVID-19 controls, reflecting persistent endothelial dysfunction.

Materials and Methods:-**Study design:**

This prospective, observational, case-control study was conducted between September 1, 2021, and June 30, 2022, at the Military Hospital of Dakhla in Morocco. The study aimed to evaluate CVR to CO₂ in patients who had recovered from COVID-19 and to compare the results with a control group of non-COVID-19 subjects. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants before inclusion.

Study Population:-

A total of 75 participants were included: 50 patients who had recovered from moderate or severe SARS-CoV-2 infection (post-COVID-19 group) and 25 control subjects without a history of COVID-19.

Inclusion Criteria for the Post–COVID-19 Group:

1. Age between 18 and 75 years;
2. Confirmed diagnosis of COVID-19 by positive RT-PCR on a nasopharyngeal swab;
3. Moderate or severe symptomatic disease requiring hospitalization within the preceding 3 months;
4. Clinical recovery and negative RT-PCR at the time of inclusion.

Exclusion Criteria:

- 1- Age <18 or >75 years;
- 2- Pregnancy;
- 3- History of cerebrovascular disease or neurological complications related to COVID-19;
- 4- Uncontrolled cardiovascular or respiratory disorders (ASA $\geq$ III) precluding breath-holding;
- 5- Significant carotid or vertebro-basilar stenosis;
- 6- Current treatment with β -blockers, calcium-channel blockers, anticoagulants, or vasodilators.

Control Group:

The control group consisted of 25 patients classified as ASA I–II who were evaluated in pre-anesthetic consultation for minor elective surgical procedures. They had no history of COVID-19 within the previous 6 months and tested negative for SARS-CoV-2 by RT-PCR at inclusion.

Among 125 patients screened in the pneumology outpatient clinic during the study period, 106 were seen within 3 months of recovery. Of these, 85 met inclusion and exclusion criteria, and 64 provided informed consent. Fourteen participants were excluded due to inadequate acoustic windows for transcranial Doppler imaging, resulting in 50 post–COVID-19 patients included in the final analysis.

Data Collection and Clinical Assessment:

Demographic and clinical data were prospectively collected, including age, sex, body mass index, medical history (diabetes, hypertension, renal disease, obesity, alcohol use), and baseline vital parameters (blood pressure, heart rate, oxygen saturation). All participants underwent a complete physical and cardiovascular examination and a 12-lead electrocardiogram.

Transcranial Doppler Measurements:-

All sonographic measurements were performed by the same operator, an experienced anesthesiologist–intensivist with six years of experience in TCD ultrasonography. Participants were examined in a quiet room, lying in the supine position. Recordings were obtained using an Esaote ultrasound system (Italy) equipped with a 2 MHz probe. The insonation was performed through the temporal bone window to identify the middle cerebral artery (MCA) at a depth of 45–55 mm. Before data acquisition, a minimum of 30 seconds of stable MCA flow signals was required. Baseline systolic (Vs_r), diastolic (Vd_r), and mean (Vm_r) flow velocities, as well as the pulsatility index (PI_r), were recorded at rest. Participants were then instructed to perform a breath-hold for 30 seconds after normal breathing to avoid the Valsalva maneuver. When apnea could not be maintained for 30 seconds, the exact breath holding time (BHT) was recorded. A second set of Doppler measurements— Vs_a , Vd_a , Vm_a , and PI_a —was obtained 5 to 10 seconds after the end of apnea, while maintaining the probe in position. Each maneuver was repeated three times, allowing a 5-minute rest period between trials. The mean value of the three recordings for each variable was used for analysis.

Calculation of Cerebral Vasoreactivity and Breath-Holding Index:-

Cerebral Vasoreactivity (CVR) to CO_2 was quantified using the percentage change in mean flow velocity before and after the breath-holding test:

$$CVR = (Vm_a - Vm_r) / Vm_r$$

The breath-holding index (BHI) was calculated as:

$$BHI = [(Vm_a - Vm_r) / Vm_r] / BHT \text{ (BHT : Breath Holding Time)}$$

Both CVR and BHI were calculated separately for the right and left MCAs, and the mean of both sides was used for analysis.

Statistical Analysis:-

Statistical analyses were performed using SPSS version 20.0 .Quantitative variables were expressed as mean $\pm$ standard deviation (SD) or median [interquartile range, IQR] according to data distribution. Qualitative variables were presented as percentages.

Comparisons between groups were conducted using:

- **Student's t-test** for normally distributed quantitative data;
- **Mann–Whitney U test** for non-normally distributed data;
- **Chi-square test** for qualitative variables.

A p -value < 0.05 was considered statistically significant.

Results:-**Baseline Characteristics:-**

A total of 75 participants were included: 50 post–COVID-19 patients and 25 controls.

The patients were 59.7 ± 7.3 years old; 74.6% were male. The mean age of the patients and the sex distribution in the post-COVID-19 group were similar to those in the control group. The cohort included 40% diabetic patients, 17% hypertensive patients, and 9.3% with kidney disease, with similar incidences between the two groups.

The patients' clinical characteristics are listed in Table 1.

	Total (n = 75)	Control (n = 25)	Post-COVID-19 (n = 50)	<i>p</i>
Clinical characteristics				
Age (years), mean $\pm$ SD	59.7 $\pm$ 7.3	58.5 $\pm$ 6.2	60.3 $\pm$ 7.7	0.35
Male sex (%)	56 (74.6%)	18 (72%)	38 (76%)	0.65
Medical history, n (%)				
Diabetes	30 (40%)	11 (44%)	19 (38%)	0.53
Hypertension	13 (17%)	5 (20%)	8 (16%)	0.71
Kidney disease	7 (9.3%)	3 (12%)	4 (8%)	0.47
Alcoholism	4 (5.3%)	0 (0%)	4 (8%)	0.001
Obesity	19 (25%)	4 (16%)	15 (30%)	0.001

Table 1: Clinical characteristics

Transcranial Doppler Parameters at Rest:

At rest mean flow velocities were significantly lower in the post–COVID-19 group compared with controls: (table2)

	Total	Control	Post-COVID-19	<i>p</i>
Systolic velocity (cm/s)	104 $\pm$ 10.5	112 $\pm$ 8.4	101 $\pm$ 12.5	0.001
Diastolic velocity (cm/s)	47 $\pm$ 6.7	50 $\pm$ 7.5	46 $\pm$ 5.6	0.001
Mean velocity (cm/s)	65 $\pm$ 7.5	71 $\pm$ 6.3	63 $\pm$ 7.8	0.001
Pulsatility index	0.72 $\pm$ 0.05	0.74 $\pm$ 0.04	0.72 $\pm$ 0.07	0.45

Table 2: Flow velocities at rest (at the middle cerebral artery)

Response to Breath-Holding Test:

All participants successfully completed the breath-holding maneuver.

After BHT, flow velocities in the MCA increased significantly in both groups. However, the magnitude of increase was markedly lower among post–COVID-19 patients: Table 3

	Total	Control	Post-COVID-19	<i>p</i>
Systolic velocity (cm/s)	137 $\pm$ 10.5	151 $\pm$ 9.5	110 $\pm$ 10.7	0.001
Diastolic velocity (cm/s)	68 $\pm$ 5.8	75 $\pm$ 6.5	54 $\pm$ 4.5	0.001
Mean velocity (cm/s)	90 $\pm$ 7.3	95 $\pm$ 5.8	73 $\pm$ 8.1	0.001
Pulsatility index	0.73 $\pm$ 0.05	0.74 $\pm$ 0.04	0.74 $\pm$ 0.08	0.39
Breath Holding Time (s)	27.6	27.6	26.8	0.53

Table 3: flow velocities after BHT (at the middle cerebral artery)

Cerebrovascular Reactivity and Breath-Holding Index:

The Cerebral Vasoreactivity (CVR) and Breath-holding Index (BHI) were both significantly impaired in post-COVID-19 patients compared with controls (Table4).

Parameters	Control (n = 25)	Post-COVID (n = 50)	<i>p</i>
ΔSV (%) —Change in systolic velocity	35%	8%	< 0.01
ΔDV (%) — Change in diastolic velocity	50%	17%	< 0.01
ΔMV (%) — Change in mean velocity	39%	15%	< 0.01
BHI	1.41	0.55	< 0.01

Table 4: comparison of cerebral vasoreactivity and BHI between the 2 groups

Discussion:-

In our study CVR to CO₂ was assessed using TCD by measuring systolic, diastolic, and mean velocities in the middle cerebral arteries before and after BHT combined with the calculation of BHI. These recordings were performed in patients with moderate or severe COVID-19 and in a control group of non-COVID-19 patients. We were able to show that the various velocities were significantly lower in the post-COVID-19 group, both at rest and after BHT. In the post-COVID-19 group, the relatively slower accelerations of the various velocities after BHT resulted in a lower BHI in this group, indicating impaired CVR with a weak vasodilatory response to hypercapnia. Cerebral autoregulation is a homeostatic phenomenon that maintains constant cerebral blood flow despite fluctuations in cerebral perfusion pressure [16]. Changes in vascular tone play a key role in preserving cerebral hemodynamics. Cerebral blood flow is particularly sensitive to CO₂ fluctuations, such that hypercapnia induces cerebral vasodilation while hypocapnia induces cerebral vasoconstriction. The mechanisms of cerebral autoregulation remain poorly understood. It is estimated that three different mechanisms—metabolic, myogenic, and neurogenic—contribute to the phenomenon of cerebral autoregulation. These mechanisms affect cerebral blood flow, thereby ensuring regulation [17].

Portegies et al. showed that decreased CVR was associated with increased mortality [18]. Similarly, Ju et al. also reported that decreased CVR was an important prognostic factor for stroke [19]. Other authors have shown that in hypertensive patients, without neurological signs but with low CVR there is an increased risk of stroke and lacunar infarction compared to hypertensive patients of the same age with normal CVR [20]. The endothelium has been described as the “Achilles’ heel” of patients with COVID-19 [21]. Cytokines and pro-inflammatory mediators shift endothelial function from a state of homeostasis to a state of defense [22], and the microvascular lesions found in the brain and olfactory bulbs of patients who died from COVID-19 show that the virus attacks the endothelium of brain vessels and can cause disruptions in vasoreactivity [8]. Sonkaya et al assessed CVR in 20 hospitalized COVID-19 patients with neurological symptoms (headache, seizures, stroke, altered consciousness, ageusia, anosmia) and compared it with a control group. They found higher velocities and lower CVR—assessed by transcranial Doppler ultrasound—compared to the control group [23].

These results are consistent with ours, except that the participants in our study were assessed long after the episode of COVID-19 infection, having fully recovered, and did not have neurological symptoms. Marcic et al studied CVR using TCD and calculated the BHI in 25 patients who had recovered from mild COVID-19, and presented to neurology clinic for neurological symptoms 28 to 50 days after a negative SARS-CoV-2 RT-PCR test. These patients had lower cerebral velocities and lower BHI compared to a control group, which is also consistent with our findings [24]. Abdo-Cuza et al also included patients who presented with different clinical forms of COVID-19 several days after their recovery, and who did not present with neurological or cardiorespiratory symptoms at the time of inclusion in the study. They were able to show that the decrease in cerebral velocities and the BHI indicative of cerebral vasoreactivity disruption persisted after the acute phase of the disease. They also reported that these abnormalities could exist even in the absence of neurological manifestations, and that this endothelial damage could occur even after a mild form of COVID-19 [25]. Our study also focused on neurologically asymptomatic patients who presented with moderate or severe forms of COVID-19. CVR disruption is an expression of endothelial damage characteristic of SARS-CoV-2 infection. It could represent a warning sign in certain groups of patients without risk factors for cerebrovascular accidents and who are neurologically asymptomatic.

For clinicians in critical care and perioperative settings, these findings have several practical implications:

1. Persistent microvascular dysfunction may increase the risk of cerebrovascular events (ischemic stroke, hypoperfusion, or postoperative delirium) in patients recovering from COVID-19, even when neurological examination is normal.
2. Transcranial Doppler ultrasound (TCD) provides a noninvasive bedside tool for monitoring cerebral hemodynamics in the ICU or during anesthesia. Regular CVR assessment could help identify high-risk patients who may benefit from optimized hemodynamic management or endothelial-protective strategies.
3. In the context of neurocritical care, impaired CVR may contribute to poor neurological outcomes following secondary insults such as hypoxia, hypercapnia, or hypotension. Awareness of this vulnerability is crucial during mechanical ventilation or weaning in post-COVID-19 patients.

Furthermore, persistent endothelial dysfunction has been described in other organs—including the heart, kidneys, and lungs—suggesting a systemic microangiopathy that may underlie long-COVID manifestations such as fatigue, cognitive impairment, and exercise intolerance.

Study Limitations:-

This study has several limitations that should be acknowledged. First, the sample size was relatively small and drawn from a single center, which may limit generalizability. Second, we did not perform longitudinal follow-up, so the duration of cerebrovascular reactivity impairment over time remains unknown. Third, the Breath-holding Test relies on voluntary cooperation and may introduce variability, though we minimized this by averaging three consecutive measurements. Despite these limitations, the study's homogeneous methodology, single-operator TCD acquisition, and use of objective quantitative indices strengthen the reliability of the results.

Conclusion:-

In summary, this study demonstrates that patients recovered from moderate or severe COVID-19 exhibit significantly reduced Cerebral vasoreactivity to CO₂, as evidenced by lower CVR and BHI values compared with control group. These findings support the hypothesis that persistent cerebral endothelial dysfunction may represent a key pathophysiological mechanism in the post-COVID-19 period. The impairment appears proportional to the severity of the initial infection and may contribute to long-term neurological vulnerability. Routine bedside evaluation of CVR using transcranial Doppler could provide a valuable tool for early detection of subclinical microvascular injury in post-COVID-19 patients, especially those admitted to intensive care units or undergoing anesthesia. Further large-scale and longitudinal studies are needed to determine whether this dysfunction is reversible and to evaluate its impact on long-term cognitive and neurological outcomes.

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