Stroke

BRIEF REPORT

Transcranial Doppler in Acute COVID-19 Infection

Unexpected Associations

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BACKGROUND AND PURPOSE: Stroke may complicate coronavirus disease 2019 (COVID-19) infection based on clinical hypercoagulability. We investigated whether transcranial Doppler ultrasound has utility for identifying microemboli and clinically relevant cerebral blood flow velocities (CBFVs) in COVID-19.

METHODS: We performed transcranial Doppler for a consecutive series of patients with confirmed or suspected COVID-19 infection admitted to 2 intensive care units at a large academic center including evaluation for microembolic signals. Variables specific to hypercoagulability and blood flow including transthoracic echocardiography were analyzed as a part of routine care.

RESULTS: Twenty-six patients were included in this analysis, 16 with confirmed COVID-19 infection. Of those, 2 had acute ischemic stroke secondary to large vessel occlusion. Ten non-COVID stroke patients were included for comparison. Two COVID-negative patients had severe acute respiratory distress syndrome and stroke due to large vessel occlusion. In patients with COVID-19, relatively low CBFVs were observed diffusely at median hospital day 4 (interquartile range, 3–9) despite low hematocrit (29.5% [25.7%–31.6%]); CBFVs in comparable COVID-negative stroke patients were significantly higher compared with COVID-positive stroke patients. Microembolic signals were not detected in any patient. Median left ventricular ejection fraction was 60% (interquartile range, 60%–65%). CBFVs were correlated with arterial oxygen content, and C-reactive protein (Spearman ρ=0.28 [P=0.04]; 0.58 [P<0.001], respectively) but not with left ventricular ejection fraction (ρ=–0.18; P=0.42).

CONCLUSIONS: In this cohort of critically ill patients with COVID-19 infection, we observed lower than expected CBFVs in setting of low arterial oxygen content and low hematocrit but not associated with suppression of cardiac output.

Key Words: coronavirus ■ echocardiography ■ embolism ■ intensive care units ■ ischemic stroke

Encephalopathy and ischemic stroke, especially large vessel occlusion, are reported neurological complications of coronavirus disease 2019 (COVID-19) infection.[1,2] Hypothesized mechanisms include systemic hypercoagulability, vascular inflammation, and microvascular thrombosis.[3]

Transcranial Doppler ultrasound (TCD) is a portable, noninvasive technique that can detect circulating emboli and evaluate for cardiac embolism or vascular stenosis as potential stroke mechanisms.[4] This study investigated occurrence of microemboli and cerebral blood flow velocities (CBFVs) using TCD in patients with and without COVID-19 infection.

METHODS

We prospectively evaluated patients with confirmed and suspected COVID-19 infection hospitalized in 2 critical care units in an urban health system between April 4 and May 22, 2020, who underwent a TCD exam as standard of care for severe

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Nonstandard Abbreviations and Acronyms

CaO_2	arterial oxygen content
CBFV	cerebral blood flow velocity
COVID-19	severe acute respiratory syndrome coronavirus SARS-CoV-2
CRP	C-reactive protein
LVEF	left ventricular ejection fraction
MCA	middle cerebral artery
$PaCO_2$	partial pressure of carbon dioxide
TCD	transcranial Doppler

encephalopathy and suspicion of cerebral emboli. COVID-19 infection was confirmed using reverse transcription polymerase chain reaction. The study was approved by the Johns Hopkins Medicine institutional review board. Patient consent was waived. Data are available upon reasonable request and completion of a data use agreement at http://www.braininjury-outcomes.com/clear-about.

All patients underwent abbreviated 15-minute manual bilateral TCD monitoring to detect microembolic signals using a 7 dB threshold (Compumedics DWL, San Juan Capistrano, CA). The middle cerebral artery (MCA) was insonated bilaterally using a low-frequency probe (2 mHz), following a validated protocol.[5] All examinations were performed by a single experienced neurosonographer (B. Ergin) with the patient in supine position.

Patient characteristics and laboratory data were collected at admission and on day of TCD (±48 hours). Transthoracic echocardiography obtained closest to TCD were analyzed for markers of diastolic function and global longitudinal strain. Arterial oxygen content (CaO_2) was calculated from values of hemoglobin and fractional oxygen saturation at time of TCD, using the formula: CaO_2 (mL/100 mL)=hemoglobin (mmol/L)×(1.34 mL O2/g hemoglobin)×[(1.61 g hemoglobin/100 mL)/(mmol hemoglobin/L)]×saturation (%/100).

Data are reported as medians and interquartile range. We used Spearman ρ to correlate mean CBFVs in the MCA with markers of viscosity, inflammation, dehydration, and cardiac output: hematocrit, D-dimer, fibrinogen, CRP (C-reactive protein), blood urea nitrogen:creatinine ratio, left ventricular ejection fraction (LVEF), partial pressure of carbon dioxide ($PaCO_2$), and CaO_2. Two-sample *t* test compared differences in means. Statistical significance was determined by $P<0.05$. Statistical analysis was performed with Stata Version 14 (STATA Corp, College Station, TX).

RESULTS

Twenty-six patients were enrolled after undergoing TCD, 16 with COVID-19 pneumonia (Table 1). The other 10 patients had AIS and had negative reverse transcription polymerase chain reaction for COVID-19; of these, 2 had large vessel occlusion and severe acute respiratory distress syndrome.

TCD was performed at median 4 (2–5) days after admission. At time of TCD, all patients were afebrile; hematocrit was below normal in all but 4 patients (Table 2). In COVID-19 positive patients CRP, D-dimer, and fibrinogen (except one patient) were all elevated (Table I in the Data Supplement). Median CBFVs were at lower limit of normal relative to age-adjusted normative values in COVID-positive patients and lower relative to all COVID-negative stroke patients including 2 with acute respiratory distress syndrome (Figure). Microembolic signals were not detected in any patient. Mean CBFVs in the M1 division of the MCA were significantly correlated with CaO_2 (Spearman $\rho=0.28$; $P=0.04$) and CRP ($\rho=0.58$; $P<0.001$). Weak inverse correlations were found with blood urea nitrogen:creatinine ratio ($\rho=-0.26$; $P=0.06$) and $PaCO_2$ ($\rho=-0.31$; $P=0.09$) but not with other variables tested.

Twenty-two patients had transthoracic echocardiography with median LVEF of 60%. There were no significant differences when comparing LVEF between (1) COVID-19 negative stroke patients and COVID-19 positive patients (LVEF 60%) nor (2) COVID-positive versus COVID-negative stroke patients (LVEF 67.5% versus 65%, respectively). There was no significant correlation between LVEF and MCA CBFVs ($\rho=-0.18$; $P=0.42$). Eight patients had global longitudinal strain (median −19.75%, interquartile range, −20% to −15%), with 2 patients having mildly reduced strain (<14%). There was no association between CBFVs and global longitudinal strain. Four patients had smaller than normal left ventricle systolic diameters (<2.5 cm), 3 of whom were COVID-19 positive. Thirteen patients had abnormal mitral e/a ratios (<1 or >2), including 6 of 11 COVID-19 patients with mitral e/a data. Mean CBFVs were not different in those with diastolic dysfunction versus those without (58 versus 62 cm/s).

In this cohort, 8/16 of COVID-19 positive patients and 1/10 COVID-19 negative stroke patients died. Among the COVID-19 positive patients, venous thromboembolism was confirmed in 3 (1 with pulmonary embolism and 2 with deep venous thrombosis).

DISCUSSION

In this first study of TCD in critically ill COVID-19 patients, a short duration bilateral monitoring study did not demonstrate microembolic signals but could not also exclude potential for microembolic signals in these patients. We did observe relatively low CBFVs which appeared unrelated to cardiac ejection fraction and exhibited paradoxical associations with hematocrit, and with arterial oxygen content.

Abnormal hemostasis is a well-recognized complication in COVID-19, including elevated D-dimer, and markedly raised fibrinogen levels.[4,6] COVID-19-associated hemostasis abnormality in the lungs appears to result from localized thrombosis, rather than disseminated

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Table 1. Baseline and Laboratory Characteristics at Admission

Variables	Positive COVID-19 (n=16)	Positive COVID-19 with stroke (n=2)*	Negative COVID-19 with stroke and ARDS (n=2)	Negative COVID-19 with stroke/no ARDS (n=8)
Age	64 (53–73)	58 (53–63)	47 (38–55)	59 (48–66)
Male	9 (56.3)	1 (50)	1 (50)	3 (37.5)
Body mass index	28.8 (25.5–33.8)	33.4 (33–33.8)	22.5 (21.7–23.2)	24.8 (21.6–31.8)
Hypertension	8 (50)	2 (100)	0	4 (50)
Hyperlipidemia	5 (31.3)	0	0	2 (25)
Diabetes	4 (25)	1 (50)	0	2 (25)
Coronary artery disease	2 (13)	0	0	1 (12.5)
Atrial fibrillation	4 (25)	1 (50)	0	0
Pulmonary variables (first day of ventilation)				
Mechanical ventilation	12 (75)	2 (100)	2 (100)	1 (12.5)
PaO_2	86 (70–105)	234 (155–312)	72 (68–75)	149
FiO_2	80 (40–100)	50 (40–100)	50 (70–100)	30
PaO_2:FiO_2 ratio	148 (86–312)	337 (312–362)	88 (68–107)	497
ARDS: mild	1 (6.3)	0	0	
Moderate	5 (31.3)	0	0	
Severe	4 (25)	0	2 (100)	
No ARDS	6 (37.5)	2 (100)	0	8 (100)
Transthoracic echocardiogram	13 (81.3)	2 (100)	1 (50)	8 (100)
Ejection fraction (%)	60 (60–65)	68 (60–75)	70	65 (65–65)
Laboratory variables				
D-dimer, µg/mL	2.7 (1.1–4.7)	4.48 (4.2–4.8)	16.8 (3.5–30)	…
Fibrinogen, mg/dL	571 (413–747)	387	…	418 (406–438)
INR	1.1 (1.0–1.2)	1.1(1.05–1.1)	1.1 (1.0–1.2)	0.99 (0.98–1.00)
aPTT	28.5 (24.5–35.6)	23.2 (21.8–24.5)	24.8 (24.2–25.4)	25.3 (23.6–26.7)
Platelets ($\times 10^9$/L)	227 (176–314)	201 (172–230)	299 (255–343)	218 (187–233)
Hematocrit (%)	38 (32–41)	40.9 (40.7–41)	29 (27.1–30.8))	36.1 (33.7–37.8)
Ferritin, ng/mL	940 (622–1743)	402	876	…
C-reactive protein, mg/dL	11.1 (5.9–27)	9.6 (6.1–13.1)	…	…
Erythrocyte sedimentation rate	79 (59–121)	67 (11–123)	18 (10–26)	14 (8.5–26)
WBC ($\times 10^9$/L)	13.5 (7.5–17.8)	10.8 (8.3–13.3)	11.8 (6.4–17.2)	7.4 (5.9–8.6)
Lactate, mg/dL	2.4 (1.5–3.2)	3.8 (3.2–4.3)	1.8 (1.4–2.2)	1.1 (1.1–1.3)
BUN:creatinine ratio	19 (13–26)	11 (7–15)	26 (10–41)	14.5 (14–19.5)
Venovenous ECMO	4 (25)	0	0	0
SOFA (day 1)	6 (2.5–12)	5 (3–7)	9.5 (9–10)	5 (4–5)

aPTT indicates activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; SOFA, Sequential Organ Failure Assessment; and WBC, white blood cell.

*Subset of 16 subjects in the COVID-19 positive cohort.

intravascular coagulation or sepsis-induced coagulopathy.[3,6] If a similar microthrombotic pathology occurs in cerebral blood vessels, we would not expect to see embolic high-intensity transient signals on TCD, typically associated with cardiac emboli. Similarly, we did not find TCD signs of vasculitis, which is consistent with autopsy findings.[7] Reynolds et al[8] performed contrast-enhanced TCD in 18 mechanically ventilated patients with severe COVID-19 pneumonia and found that 83% of patients had detectable microbubbles; the number, which was inversely correlated with the PaO_2:FiO_2 ratio and with lung compliance, suggests that pulmonary vascular dilatation may be a significant cause of hypoxemia.[8]

Relatively low CBFVs diffusely in COVID-positive patients were unexpected given the low hematocrit. Hematocrit and viscosity are inversely related to CBFVs which increase by ≈20% with a drop in hematocrit from 40% to 30%.[9]

Fibrinogen also contributes to variance in CBFVs due to its direct association with plasma viscosity, which contributes to vascular resistance.[10] We found no correlation between fibrinogen and MCA velocities, which

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Table 2. Clinical Characteristics at Time of TCD

Variables	Positive COVID-19 (n=16)	Positive COVID-19 with stroke (n=2)*	Negative COVID-19 with stroke and ARDS (n=2)	Negative COVID-19 with stroke/no ARDS (n=8)
Blood pressure, mm Hg				
Systolic	123 (111–145)	152 (136–168)	119 (109–128)	126 (110–144)
Diastolic	55 (49–76)	85 (85–85)	71 (57–85)	69 (61–78)
Hematocrit (%)	29.5 (25.7–31.6)	36.5 (31.9–41.0)	24.2 (23.7–24.7)	32.1 (30.9–37.2)
Fibrinogen	545 (495–859)	387	571	418 (393–453)
BUN:creatinine ratio	28 (16–37)	13 (7–18)	18 (8–28)	18 (13–24)
PCO_2, mm Hg	55 (45–70)	40	39 (36–41)	34
spO_2 (%)	93.5 (91–97.5)	100	100	99.5 (95–100)
CaO_2 (mL/100mL)	10.4 (9.4–12.7)	15.5 (13.1–17.8)	10.2 (9.8–10.6)	14.7 (13.3–15.6)

ARDS indicates acute respiratory distress syndrome; BUN, blood urea nitrogen; CaO_2, arterial oxygen content; COVID-19, coronavirus disease 2019; spO_2, peripheral capillary oxygen saturation; and TCD, transcranial Doppler.
*Subset of 16 subjects in the COVID-19 positive cohort.

is contradictory to the described inverse and independent association of fibrinogen and CBFVs.[11] Changes in $PaCO_2$, owing to permissive hypercapnia resulted in $PaCO_2$ above normal in 8/15 patients; we observed a weak inverse correlation with MCA velocities. The expected result is vasodilation of resistance vessels and increased CBFVs, although with sustained hypercapnia, there is no adaptation.[10] Reduction of Doppler responsiveness to altered $PaCO_2$ has been associated with increased plasma viscosity and fibrinogen.[12]

At time of TCD, median oxygen saturation in COVID-19 patients was 93.5%. CaO_2 was significantly correlated with CBFVs in the MCA, but with a positive rather than inverse correlation which would be expected secondary to cerebral vasodilation. In studies of plasma viscosity manipulation in subjects without cerebrovascular disease, CaO_2 was found to be more important than viscosity in determining cerebral blood flow.[13] This reflects the importance of oxygen delivery to the brain and local mechanisms in CBF autoregulation, whereas viscosity is an important determinant of CBF when autoregulation is defective. In the latter case (eg, in ischemic tissue), resistance vessels are maximally dilated due to deficient O2 delivery and CBF passively follows perfusion pressure which is low in ischemic regions, where hematocrit may increase significantly, increasing blood viscosity and slowing blood flow.[14] This study did not evaluate autoregulation, but positive associations between relatively low CBFVs and low CaO_2 might suggest autoregulatory impairment in this cohort of patients experiencing relative hypoxia. Neuropathological findings from one COVID autopsy series included acute hypoxic injury in the cerebrum and cerebellum in all patients, but no thrombi or vasculitis.[7]

We considered that low CBFVs could be caused by a low flow state from cardiac systolic dysfunction; however, we observed a normal range of LVEF and global longitudinal strain. There was, however, a signal of diastolic dysfunction, measured by LV diameter and mitral e/a ratio. Acute myocarditis has been diagnosed in COVID-19 patients and could present with a normal LVEF and LV diastolic dysfunction.[15]

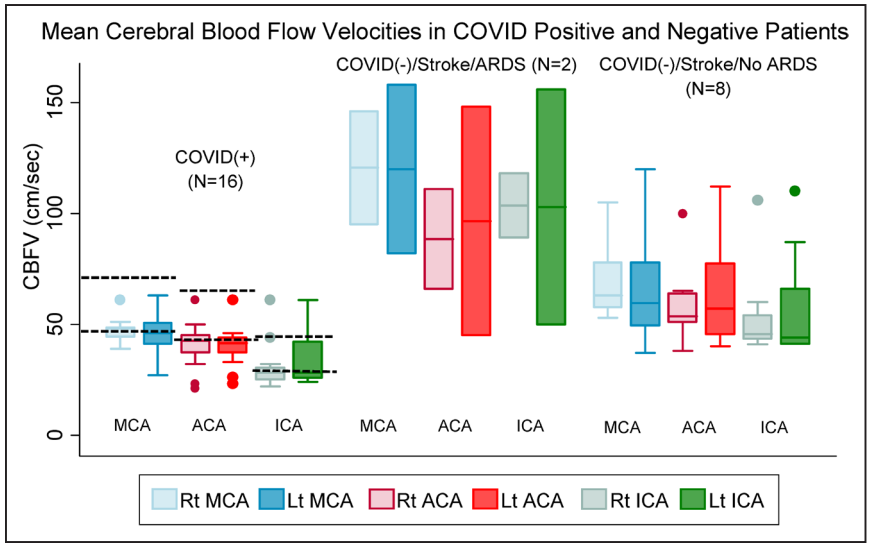

Figure. Mean cerebral blood flow velocities (CBFVs) in patients with and without coronavirus disease 2019 (COVID-19) infection.
Dashed lines indicate normative CBFV range for age group.

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Limitations of these data include small sample size, observational design, short duration of TCD monitoring for emboli detection, and lack of brain imaging which prevented us from assessing the association of TCD with neurological complications. However, inability to transport critically ill patients with COVID-19 was in fact the motivation for considering TCD as a diagnostic tool. This study is intended as hypotheses-generating where hypoxic ischemic injury may have important consequences for neurological recovery. We recommend that future evaluation of TCD in COVID-19 patients with pneumonia or neurological sequelae could include a bilateral TCD study supplemented by at least 30 min emboli detection and a TCD bubble test.

CONCLUSIONS

We cautiously suggest that TCD provides clinically useful information into mechanisms underlying COVID-19 neurological sequelae, although the significance of relatively low CBFVs in these critically ill patients requires further study.

ARTICLE INFORMATION

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Supplemental Materials

Online Table I

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