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Letter to the Editor

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Corresponding author:
Kenji Numata,
Email: kenjinumata777@hotmail.co.jp.

Respiratory Failure in COVID-19 with Awake Prone Positioning and HFNC Therapy: Aggravating Factors

Kenji Numata[1], Kentaro Sato[1], Shigeki Fujitani[1] and Daiki Kobayashi[2]

[1]Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan and [2]Division of General Internal Medicine, St. Luke's International Hospital, Tokyo, Japan

The combination of high-flow nasal cannula (HFNC) oxygen therapy and awake prone positioning (PP) was reported to improve the clinical outcome of patients with coronavirus disease 2019 (COVID-19) in respiratory failure.[1] However, delay in intubation among patients treated with HFNC and awake PP has been linked to mortality.[2] Our aim was to evaluate factors that indicated aggravation among patients with HFNC therapy and awake PP.

This cohort study was conducted from November 2020 to June 2021 at St. Marianna University School of Medicine, a tertiary facility with over 1000 beds. We included patients with COVID-19 who were treated with HFNC therapy and awake PP immediately after admission. The exclusion criteria were pregnancy, immunocompromisation (receiving chemotherapy, human immunodeficiency virus infection, etc.), or starting intubation or palliative care within 1 day after admission. We included patients who signed Do Not Resuscitate (DNR) or Do Not Intubate (DNI) orders after admission because the standard of care for COVID-19 was the same as patients without a DNR/DNI order. The final cohort of 65 patients was divided into 2 groups: those with an event (those who were intubated or died, $n = 18$) vs. without an event (those who were survived without intubation, $n = 47$).

HFNC therapy and awake PP were performed in patients requiring oxygen (saturation of percutaneous oxygen [SpO_2]/fraction of inspiratory oxygen [FiO_2] < 200) and whose chest images showed bilateral ground-glass opacities. The awake PP protocol involved asking patients to remain in the PP for 2 hours, 3 times a day.

Results were corrected for patients' characteristics, vital signs, blood test, treatment information, and clinical information. We compared between those with an event and those without an event using the Fisher exact test and Wilcoxon rank-sum test. We applied a strict cut-off p value of 0.005 due to the multiple comparisons. All analyses were performed using STATA/MP v15.1 (StataCorp LLC, College Station, TX, USA).

Table 1 shows the results. The median ROX index (with event, 6.02 vs. without event, 7.54), C-reactive protein (CRP) (with event, 12.7, vs. without event, 5.6), procalcitonin (with event 0.34, vs. without event, 0.09), and NT-pro-BNP (with event, 1108, vs. without event, 120) showed significant differences (all $P < 0.005$).

Our results showed a significantly lower ROX index in patients who had an event. The ROX index has been proposed as a tool to identify COVID-19 patients at high risk of intubation.[3] Our results suggest that the ROX index may be a useful tool to evaluate the risk of intubation among COVID-19 patients treated with HFNC therapy and awake PP.

CRP and procalcitonin were significantly elevated among patients with an event. The normal procalcitonin level is < 0.5 ng/ml, and high levels can predict bacterial infection.[4] Even though the procalcitonin levels were statistically significant between the 2 groups, it was almost within the normal range and clinically meaningless in the context of our study, however, CRP levels differed significantly between the 2 groups. NT-pro-BNP has been reported as independently associated with mortality among patients with COVID-19.[5] In our study, patients with an event had significantly higher NT-pro-BNP levels. These results suggest that higher CRP and NT-pro-BNP may predict events in COVID-19 patients treated with HFNC therapy and awake PP.

In conclusion, our study showed that ROX index, CRP, procalcitonin, and NT-pro-BNP might be related to an event. Further investigations using a larger sample size are necessary to confirm the effect of our regimen.

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Table 1. Comparison between coronavirus disease 2019 patients treated with HFNC[+] therapy and awake PP‡ who were intubated or died and patients who survived without intubation

Patient characteristic	With events (intubated or died) ($n = 18$)			Without events (survived without intubation) ($n = 47$)	*P* value
	Intubated ($n = 10$)	Died without intubation ($n = 8$)	Total		
Age (years), median (*IQR)	64.5 (61.0–75.0)	81 (78.5–88.5)	77 (64–82)	68 (52–74)	0.008
Male sex, No. (%)	8 (80.0)	6 (75.0)	14 (77.8)	33 (70.2)	0.542
Body mass index, median (IQR)	26.4 (23.3–28.7)	22.0 (19.9–26.3)	24.4 (22.4–28.6)	25.5 (22.8–28.0)	0.758
Smoking history, No. (%)	3 (30.0)	0 (0.0)	3 (16.7)	19 (40.4)	0.085
Comorbidities					
Chronic heart failure, No. (%)	1 (10.0)	0 (0.0)	1 (5.6)	3 (6.4)	1.000
Diabetes mellitus, No. (%)	5 (50.0)	2 (25.0)	7 (38.9)	20 (42.6)	0.788
Chronic obstructive pulmonary disease or asthma, No. (%)	3 (30.0)	2 (25.0)	5 (27.8)	7 (14.9)	0.288
Chronic kidney disease					
Without dialysis, No. (%)	0 (0.0)	1 (12.5)	1 (5.6)	6 (12.8)	0.663
With dialysis, No. (%)	3 (30.0)	1 (12.5)	4 (22.2)	1 (2.1)	0.018
Vital signs (after HFNC therapy)					
Heart rate (/min), median (IQR)	80 (74–90)	88 (79–117)	84 (77–103)	77 (64–89)	0.022
Systolic blood pressure (mmHg), median (IQR)	126.0 (18.0–142.0)	133.5 (112.5–151.5)	127.5 (108.0–145.0)	125.5 (118.0–135.0)	0.792
Diastolic blood pressure (mmHg), median (IQR)	67.0 (55.0–72.0)	63.5 (57.0–77.5)	65.5 (56.0–74.0)	64 (56.0–72.0)	0.587
Respiration rate (/min), median (IQR)	28 (16–28)	27 (22–29)	25.5 (20.0–28.0)	22.0 (20.0–25.0)	0.273
Body temperature (°C), median (IQR)	37.1 (36.4–37.3)	37.1 (36.8–37.7)	37.1 (36.6–37.4)	36.8 (36.5–37.1)	0.146
Saturation of percutaneous oxygen (%), median (IQR)	95.5 (92.0–97.0)	92.5 (91.0–97.0)	94 (91–97)	96 (94–97)	0.165
Partial pressure of arterial oxygen/fraction of inspiratory oxygen, median (IQR)	160.4 (139.5–174.4)	125.5 (104.1–200.7)	157 (117.1–183.8)	183.2 (160–228)	0.016
ROX index, median (IQR)	5.52 (4.79–7.19)	6.28 (5.17–7.82)	6.02 (4.79–7.22)	7.54 (6.67–10)	< 0.005
Blood test results					
White blood cell count ($\times 10^3/\mu L$), median (IQR)	6950 (5800–9400)	8950 (4900–12100)	7800 (5500–10400)	6600 (4000–9600)	0.189
C-reactive protein, mg/dL, median (IQR)	6.6 (4.1–12.8)	14.9 (12.6–19.3)	12.7 (6.9–16.7)	5.6 (3.0–8.3)	0.003
Procalcitonin (ng/mL), median (IQR)	0.34 (0.21–0.64)	0.43 (0.17–1.17)	0.34 (0.21–0.64)	0.09 (0.06–0.2)	< 0.001
D-dimer (μg/mL), median (IQR)	0.8 (0.4–1.5)	1.7 (0.9–3.3)	1.1 (0.6–1.9)	0.8 (0.6–1.9)	0.691
Ferritin (ng/mL), median (IQR)	650 (168–1440)	347 (157–1005)	470 (167–1272)	724 (370–1335)	0.291
Creatinine (mg/dL), median (IQR)	1.09 (0.87–6.21)	1.01 (0.73–2.28)	1.05 (0.85–2.67)	0.735 (0.6–1.08)	0.034
N-terminal pro-brain natriuretic peptide (pg/mL), median (IQR)	1275 (452–3994)	1275 (485–6584)	1108 (452–4510)	120 (38–310)	< 0.001
Interleukin-6 (pg/mL), median (IQR)	67.6 (42.4–112.2)	82 (22.2–91.2)	68.4 (34.6–91.2)	30.9 (9.6–83.4)	0.116
Arterial blood gas (after HFNC therapy)					
Partial pressure of arterial oxygen (mmHg), median (IQR)	99.8 (95.4–135.8)	80.2 (72.5–89.5)	94.8 (80.8–118.6)	99.8 (82–114.0)	0.655
Bicarbonate (mmol/L), median (IQR)	21.2 (20.2–22.1)	22.9 (19.9–24.7)	21.7 (19.9–23.5)	23.3 (21.7–25.5)	0.601
Treatment					
Antibiotic, No. (%)	4 (40.0)	8 (100.0)	12 (66.7)	29 (61.7)	0.780
Remdesivir, No. (%)	10 (100.0)	8 (100.0)	18 (100)	44 (93.6)	0.555
Dexamethasone, No. (%)	10 (100.0)	8 (100.0)	18 (100)	47 (100)	1.000
Heparin, No. (%)	10 (100.0)	8 (100.0)	18 (100)	47 (100)	1.000
Tocilizumab, No. (%)	3 (30.0)	6 (75.0)	9 (50.0)	11 (23.4)	0.069
Clinical information					
Time from symptom onset to admission (days), median (IQR)	7.5 (4.0–9.0)	6.5 (2.5–7.5)	7 (4–9)	8 (7–10)	0.070
Admission from another hospital, No. (%)	8 (80.0)	3 (37.5)	11 (61.1)	30 (63.8)	1.000

[+]High-flow nasal cannula
‡Prone positioning
*Interquartile range

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