Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Critical Care 69 (2022) 154020

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Feasibility of non-invasive respiratory drive and breathing pattern evaluation using CPAP in COVID-19 patients

Auguste Dargent, MD, PhD [a,b,*], Alexandra Hombreux, MD [a], Hugo Roccia, MD [a], Laurent Argaud, MD, PhD [a,c], Martin Cour, MD, PhD [a,c], Claude Guérin, MD, PhD [a,c]

[a] Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Médecine Intensive-Réanimation, F-69437 Lyon, France
[b] Université de Lyon, VetAgro Sup, Campus Vétérinaire de Lyon, UPSP 2016.A101, Pulmonary and Cardiovascular Aggression in Sepsis, F-69280 Marcy l'Étoile, France
[c] Université de Lyon, Université Claude Bernard Lyon 1, Faculté de médecine Lyon-Est, F-69373 Lyon, France

ARTICLE INFO

Keywords:
Acute respiratory failure
COVID-19
Respiratory drive
P0.1
Continuous positive airway pressure
High flow nasal cannula

ABSTRACT

Purpose: Increased respiratory drive and respiratory effort are major features of acute hypoxemic respiratory failure (AHRF) and might help to predict the need for intubation. We aimed to explore the feasibility of a non-invasive respiratory drive evaluation and describe how these parameters may help to predict the need for intubation.
Materials and methods: We conducted a prospective observational study. All consecutive patients with COVID-19-related AHRF requiring high-flow nasal cannula (HFNC) were screened for inclusion. Physiologic data (including: occlusion pressure (P0.1), tidal volume (Vt), inspiratory time (Ti), peak and mean inspiratory flow (Vt/Ti)) were collected during a short continuous positive airway pressure (CPAP) session. Measurements were repeated once, 12–24 h later.
Results: Measurements were completed in 31 patients after the screening of 45 patients (70%). P0.1 was high (4.4 [2.7–5.1]), but it was not significantly higher in patients who were intubated. The Vt ($p = .006$), Vt/Ti ($p = .019$), minute ventilation ($p = .006$), and Ti/Ttot ($p = .003$) were higher among intubated patients compared to non-intubated patients. Intubated patients had a significant increase in their diaphragm thickening fraction, Vt, and Vt/Ti over time.
Conclusions: Non-invasive assessment of respiratory drive was feasible in patients with AHRF and showed an increased P0.1, although it was not predictive of intubation.

1. Introduction

High flow nasal cannula (HFNC) and non-invasive ventilation (NIV) have been widely used as an alternative to invasive mechanical ventilation (IMV) [1], especially during the COVID-19 (coronavirus disease 2019) pandemic [2]. With acute hypoxemic respiratory failure (AHRF), the respiratory drive is commonly increased. When high inspiratory drive results in higher inspiratory effort, the latter can be deleterious due to large tidal volumes (Vt) and transpulmonary pressure swings, which can in turn aggravate lung injury [3]. This concept has been one tenet for advocating early IMV in COVID-19 patients [4]. In AHRF patients treated with NIV, higher Vt has been associated with NIV failure [5]. Furthermore, a recent study showed that higher inspiratory effort could predict NIV failure [6], suggesting that monitoring respiratory drive could assist the decision of intubation. Respiratory drive and effort can be investigated non-invasively by measuring diaphragm excursion and thickening fraction using ultrasound [7], Vt and inspiratory flow [8], or airway occlusion pressure after 100 ms after the initiation of inspiration (P0.1) [9]. These have been extensively studied in intubated patients as predictors of weaning outcome [10,11]. In contrast, data are scarce in non-intubated AHRF patients with COVID-19. As ventilators set in NIV-mode allow the collection of valid data [12], we reasoned that this could constitute a way of evaluating these variables in this setting.

The aim of the present study was to explore the feasibility of a non-invasive respiratory drive evaluation using ventilator-derived data and diaphragm ultrasound, and describe how these parameters may help to predict the need for IMV.

2. Materials and methods

A prospective observational study was conducted between November 2020 and February 2021 in our medical intensive care unit (ICU) in Lyon, France. The study was approved by our Institutional Review board

Abbreviation: AHRF, acute hypoxemic respiratory failure; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; FVC, forced vital capacity; HFNC, high flow nasal cannula; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; ROX index, index calculated by dividing SpO2/FiO2 ratio by respiratory rate; RR, respiratory rate; Ti, inspiratory time; Ttot, total respiratory cycle time; Vt, tidal volume.

* Corresponding author at: Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Médecine Intensive-Réanimation, F-69437 Lyon, France
E-mail address: auguste.dargent@chu-lyon.fr (A. Dargent).

https://doi.org/10.1016/j.jcrc.2022.154020
0883-9441/

(*Comité d'éthique des Hospices Civils de Lyon*, registration number: 20–42). Informed consent was obtained from all included patients. We screened all consecutive patients with COVID-19-related AHRF requiring HFNC for inclusion. In our center, HFNC was initiated in patients requiring more than 6 L/min of conventional oxygen therapy (administered *via* a facemask). A large bore cannula device was used (Optiflow®, Fisher Paykel Healthcare, Auckland, New Zealand) and set to a flow of 50 L/min.

First, while the patients were receiving HFNC, data regarding the inspired oxygen fraction (FiO2), peripheral oxygen saturation (SpO_2), respiratory rate (RR), the combined oxygenation index (ROX index) [13], presence of respiratory distress signs, and respiratory comfort scale were gathered. For the respiratory comfort scale an analogic rating was asked from the patient from 0, worst possible breathing comfort (choking), to 10, normal breathing comfort.

Then, a 20–30-minute continuous positive airway pressure (CPAP) session was performed *via* a face mask using an ICU ventilator (Evita, Draeger, Germany), set to a pressure of 5 cmH_2O. The mask was adjusted on the patient's face until the leaks were stable and strictly below 10 L/min. If this couldn't be achieved, the patient was excluded and the measurements were not performed. FiO_2 was set to match HFNC SpO2 ± 2%.

Ultrasound evaluation was performed during the CPAP session, with measurement of lung ultrasound score, diaphragmatic excursion, and thickening fraction. Diaphragm ultrasound was measured during tidal ventilation, and values were averaged over a minimum of 5 respiratory cycles. Measurements were taken on the right side, using a cutaneous marker for repeated observations. Diaphragmatic thickness was measured at end-expiration and peak inspiration, as the distance between the diaphragmatic pleura and the peritoneum using M-mode [7]. Diaphragm thickening fraction was defined as the percentage change in diaphragm thickness during inspiration.

Values of Vt, inspiratory time (Ti), peak, and mean inspiratory flow (Vt/Ti) were averaged over a 30 s period at the end of the CPAP session,

Table 1
Baseline clinical characteristics, physiologic measurements and outcomes in a cohort of COVID-19 patients treated with high-flow nasal cannula.

Variables	Coefficient of variation*	Total (n = 31)	Intubated (n = 13)	Non-Intubated (n = 18)	*p* value**
Demographics					
Age (years)		64 [58, 66]	66 [62, 72]	58 [53, 65]	0.042
Women		13 (42)	1 (8)	12 (67)	0.001
BMI (kg/m^2)		28 [28, 31]	31 [28, 33]	28 [27, 31]	0.373
COPD		3 (10)	2 (15)	1 (6)	0.361
SAPS II		29 [28, 34]	31 [30, 40]	28 [25, 32]	0.075
SOFA		2 [2,3]	3 [3, 5]	2 [2, 3]	0.097
Data at inclusion (on HFNC)					
Time since symptoms onset (days)		11 [10,12]	10 [9, 11]	11 [10, 12]	0.395
Time since ICU admission (hours)		13 [10,30]	13 [8, 32]	12 [6, 36]	0.859
PaO_2/FiO_2 ratio (mmHg)		97 [85, 118]	79 [66, 95]	109 [91, 140]	0.05
$PaCO_2$ (mmHg)		34 [32, 36]	35 [33, 38]	31 [30, 36]	0.231
FiO2 (%)		80 [65, 80]	90 [85, 96]	55 [52, 69]	<0.001
Respiratory rate (breaths/min)		25 [24, 28]	26 [23,30]	25 [22, 28]	0.798
ROX index		5.2 [4.6, 7.7]	4.6 [3.6, 5.1]	6.3 [5.1, 10]	0.006
Respiratory comfort scale score		7 [6, 7]	5 [5, 7]	8 [7, 8]	0.004
Signs of respiratory distress†		11 (35%)	4 (31%)	7 (39%)	0.641
CPAP data					
SpO_2/FiO_2 variation from HFNC (%)		40 [26, 53]	40 [21, 50]	41 [22, 63]	0.921
Air leaks (L/min)		5.1 [4.5, 6.3]	5.7 [4.2, 7.1]	5.0 [4.1, 6.4]	0.650
Respiratory rate (breaths/min)		30 [22,33]	29 [27, 33]	30 [22,31]	0.828
Minute ventilation (L/min)		12 [11, 14]	15 [13, 18]	11 [10, 12]	0.006
Minute ventilation (L/min/kg of PBW)		0.21 [0.19, 0.23]	0.22 [0.19, 0.27]	0.20 [0.17, 0.22]	0.293
P0.1 (cmH_2O)	19%	4.4 [3.4, 4.7]	3.5 [2.8, 5.4]	4.5 [3.3, 4.7]	0.916
Tidal volume (mL)	11%	418 [403, 532]	552 [464, 612]	383 [324, 507]	0.006
Tidal volume (mL/kg PBW)	11%	7.6 [6.8, 8.5]	8.2 [7.1, 8.9]	6.2 [6.1, 8.6]	0.196
Inspiratory duty cycle (Ti/Ttot)	10%	0.37 [0.35, 0.40]	0.42 [0.39, 0.45]	0.36 [0.32, 0.37]	0.003
Peak insp. flow (L/min)	9%	61 [58, 68]	61 [59, 79]	58 [54, 63]	0.135
Peak insp. flow (L/min/kg PBW)		1.0 [0.98, 1.1]	0.95 [0.89, 1.2]	1.0 [0.98, 1.2]	0.489
Vt/Ti (L/min)	12%	32 [31, 37]	38 [33, 43]	31 [28, 35]	0.019
Vt/Ti (L/min/kg PBW)		0.56 [0.53, 0.62]	0.55 [0.50, 0.64]	0.57 [0.51, 0.63]	0.662
FVC†† (% predicted value)		27 [24, 32]	30 [24, 36]	23 [21,33]	0.211
Ultrasound data (on CPAP)					
Lung ultrasound score		23 [21,23]	24 [20, 24]	23 [21, 23]	0.711
Diaphragm excursion (mm)		18 [17, 21]	20 [17, 24]	17 [15, 21]	0.349
Diaphragm thickening fraction (%)		20 [20, 41]	30 [17, 60]	20 [16, 36]	0.639
Outcomes					
Maximum HFNC FiO_2 (%)		100 [86, 96]	100 [100,100]	90 [78, 92]	0.003
HFNC treatment duration (days)		3 [3, 5]	2 [2, 4]	4 [4, 6]	0.010
Rescue NIV use		2 (6)	1 (8)	1 (6)	0.811
ICU length of stay (days)		9 [9, 23]	25 [19, 42]	5 [4, 7]	<0.001
Death during ICU stay		7 (23)	5 (38)	2 (11)	0.072

BMI: body mass index; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; FVC: forced vital capacity; HFNC: high flow nasal cannula; ICU: intensive care unit; NIV: non-invasive ventilation; PBW: predicted body weight; ROX index: index calculated by dividing SpO2/FiO2 ratio by respiratory rate; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; Ti: inspiratory time; Ttot: total respiratory cycle time; Vt: tidal volume.
Continuous variables are expressed as median with 95% confidence interval [lower limit, upper limit]. Discrete variables are expressed as count (percentage-point of group).

* The coefficient of variation was calculated for averaged physiological variables as mean/standard deviation.

** Intubated and non-intubated groups were compared using the Mann-Whitney test and Chi^2 test.

† Presence of supraclavicular or intercostal retraction, and/or nasal flaring.

†† FVC was expressed as % of predicted value according to the Global Lung Initiative 2012 reference equations.

after a stable and SpO2 and respiratory rate were obtained. P0.1 was then averaged over 5 measurements. Finally, forced vital capacity (FVC) was assessed from the volume given by the ventilator obtained after a maximum inspiration followed by a forced expiration [14]. CPAP was then discontinued.

Measurements were repeated once, 12–24 h later, when possible. The attending clinician was blinded to the results. The patients were followed-up until ICU discharge or death. Criteria used for intubation were: SpO2 < 90% with HFNC FiO_2 100%, and/or agitation, and/or altered consciousness.

The primary end-point was the study feasibility, assessed by the rate of failure of the measurements at the first time-point. The secondary end-point was the comparison of physiological variables between intubated and non-intubated patients.

Continuous and categorical variables were expressed as median [interquartile range], and count (percentage), respectively, and compared using non-parametrical tests. Correlations were assessed using the Spearman's coefficient test. The *p*-value for statistically significant threshold was set as <0.05. The statistical analysis was performed using Prism (GraphPad, USA).

3. Results

During the study period, 45 patients were screened, and 31 were included. Reasons for non-inclusion were: immediate intubation ($n = 5$), excessive leaks ($n = 3$), CPAP intolerance (n = 3), patient refusal ($n = 2$), inadequate ventilator for the measurements ($n = 1$). Thus, feasibility of the complete assessment amounted to 70% of the eligible patients.

The time from ICU admission to inclusion was 13 [5–25] hours. The median P0.1 was 4.4 [2.7–5.1] cmH_2O (Table 1), and was significantly correlated with the RR ($p = .001$, $r = 0.552$). There was no significant correlation between P0.1 and air leaks ($p = .310$, $r = -0.190$).

A total of 13 (42%) patients required intubation. The proportion of males ($p = .001$), the FiO_2 ($p < .001$), Vt ($p = .006$), Vt/Ti ($p = .019$), minute ventilation (MV) (p = .006), and Ti/Ttot ($p = .003$) were higher among intubated patients compared to non-intubated patients, whereas the ROX index (p = .006) and the respiratory comfort score ($p = .004$) were lower. However, when corrected for predicted body weight (PBW), the above-mentioned differences in Vt, Vt/Ti and MV where no longer significant. P0.1, diaphragm and lung ultrasound data were not significantly different between groups (Table 1).

A second evaluation was performed in 18 patients after a median time of 23 [17–25] hours. The second evaluation was not performed because of: intubation ($n = 7$, 54%), refusal ($n = 3$, 23%), CPAP intolerance ($n = 2$, 15%), pneumomediastinum ($n = 1$, 8%). Among the re-evaluated patients, 6 (33%) were eventually intubated. Intubated patients had a significant increase in the diaphragm thickening fraction, Vt, and Vt/Ti between the two assessments, whereas the ROX index, P0.1, and respiratory comfort score were unchanged (Fig. 1).

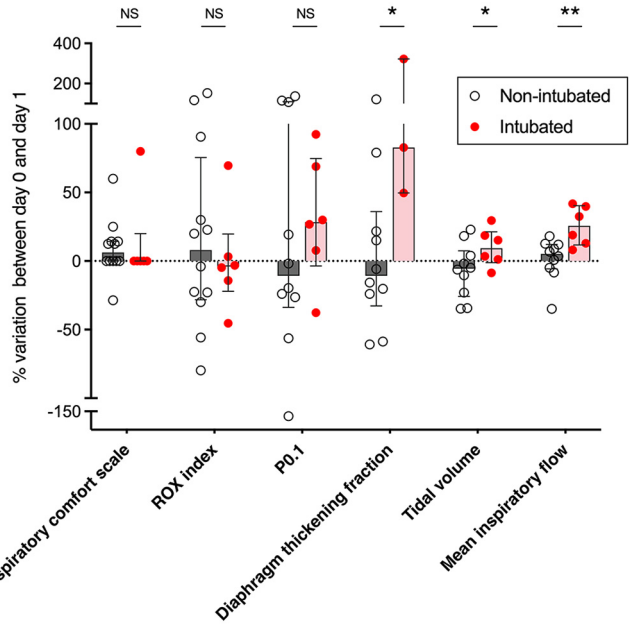

Fig. 1. Relative variations of respiratory variables recorded during spontaneous breathing in HFNC-treated COVID-19 patients.
Relative variations of respiratory variables are presented for the subset of patients in which two sets of measures were performed ($n = 18$, 58%), at a median interval of 23 h under continuous positive airway pressure by face mask. Relative variation is expressed as median percentage of baseline (day 0) value, in intubated ($n = 6$) (pink bars and red dots) and non-intubated patients ($n = 12$) (grey bars and white dots). Error bars represent interquartile range. A Mann-Whitney test was used to compare variations between groups.
HFNC: high flow nasal cannula; P0.1: airway occlusion pressure after 0.1 s; ROX index: index calculated by dividing SpO_2/FiO_2 ratio by respiratory rate.
* $p < .05$; ** $p < .01$ between intubated and non-intubated patients.

4. Discussion

Our results demonstrated that non-invasive assessment of respiratory drive was feasible in most COVID-19 patients with AHRF. To our knowledge, the present study is the first to describe P0.1 and breathing pattern in spontaneously breathing, non-intubated AHRF patients. P0.1 values have been measured on CPAP in chronic obstructive pulmonary disease patients with post-extubation respiratory distress [15], and were quite similar as the present ones. P0.1 was high in the present study, confirming that a high central respiratory drive is present. Nevertheless, it was not accurate at predicting the risk of intubation, in opposition with its performance to predict extubation failure [10].

Intubated patients had higher Vt, Vt/Ti, and minute ventilation values compared to non-intubated patients, but it was no longer significant when corrected for PBW. This might be explained by the higher proportion of men in intubated patients, as male gender was identified as a major risk factor for intubation during COVID-19 [16]. This excessive effort did even increase over time for intubated patients. This could be the result of the progression of COVID-19 lesions, but also of self-inflicted lung injury [5].

Finally, high peak and mean inspiratory flows were measured, exceeding the most commonly used flow rate of 50 L/min [1]. This challenges the common assumption that HFNC covers the inspiratory flow during AHRF, and suggests that FiO2 is overestimated by the HFNC setting in AHRF patients with high inspiratory flow. This could be one of the reasons for the dramatic SpO_2/FiO_2 improvement when switching from HFNC to CPAP. Of course, the improvement in oxygenation with CPAP may also be the result of PEEP itself. However, the increase in PEEP between HFNC and CPAP was probably modest, because HFNC is supposed to deliver 2–3 cmH_2O of PEEP and we used only 5 cmH_2O on our CPAP setting.

The present study has some limitations. First, even though it is appropriate for a feasibility study, it is limited by its small sample size and single-center design. With a higher number of patients, it might have been possible to explore more accurately the relationship between respiratory drive and outcome. As it is indeed, we cannot conclude regarding the potential predictive value of these data, and the clinical value of these physiologic parameters remain unclear. Second, the validity of P0.1 measurement using a non-invasive interface is questionable in the presence of leaks. We tried to overcome this limitation by minimizing leaks and excluding patients with excessive leaks. Although the residual leaks (5 [4-7] l/min) could underestimate P0.1, we measured high P0.1 values, indicating that it was related to an increased respiratory drive. Furthermore, there was no statistically significant correlation between P0.1 and air leaks. Third, we cannot rule out that respiratory drive during HFNC and during the CPAP session might be different. For this reason, we excluded patients with poor mask tolerance,

and we took the measurements with a SpO2 close to pre-CPAP SpO2 (PaO2 being a major determinant of respiratory drive). Lastly, respiratory variables are subject to great variations over time in spontaneously breathing subjects. More frequent measurements would have been necessary to overcome this variability, although it did not seem feasible due to the large amount of collected data.

5. Conclusions

Non-invasive assessment of respiratory drive was feasible in most COVID-19 patients with AHRF, and it confirmed that an increased respiratory drive was present. However, our data does not allow to conclude that a higher respiratory drive is associated with an increased risk of invasive mechanical ventilation. Therefore, the clinical value of these data remains unclear. Further studies are warranted to analyze the relationship between respiratory drive and outcome in AHRF patients, with or without COVID-19.

Ethics approval and consent to participate

The study was approved by our Institutional Review Board (*Comité d'éthique des Hospices Civils de Lyon*, registration number: 20–42). Informed consent was obtained from all included patients.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

AD conceived the study; AD and CG designed the study; AD, AH, HR contributed to data acquisition and analysis; AD, MC, LA and CG drafted and approved the manuscript.

CRediT authorship contribution statement

Auguste Dargent: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Alexandra Hombreux:** Investigation, Methodology. **Hugo Roccia:** Investigation, Methodology. **Laurent Argaud:** Resources, Supervision, Writing – review & editing. **Martin Cour:** Methodology, Writing – review & editing. **Claude Guérin:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interest.

References

[1] Besnier E, Hobeika S, Nseir S, Lambiotte F, Cheyron DD, Sauneuf B, et al. High-flow nasal cannula therapy: clinical practice in intensive care units. Ann Intensive Care. 2019;9:98.
[2] Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. Eur Respir J. 2020;56:2001935.
[3] Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Resp Crit Care. 2017;195:438–42.
[4] Battaglini D, Robba C, Ball L, Silva PL, Cruz FF, Pelosi P, et al. Non-invasive respiratory support and patient self-inflicted lung injury in COVID-19: a narrative review. Brit J Anaesth. 2021;127(3):353–64.
[5] Carteaux G, Millán-Guilarte T, Prost ND, Razazi K, Abid S, Thille AW, et al. Failure of noninvasive ventilation for De novo acute hypoxemic respiratory failure. Crit Care Med. 2016;44:282–90.
[6] Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, et al. Inspiratory effort assessment by esophageal manometry early predicts noninvasive ventilation outcome in de novo respiratory failure: a pilot study. Am J Resp Crit Care. 2019;0:558–67.
[7] Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med. 2015;41:642–9.
[8] Mortola JP. How to breathe? Respiratory mechanics and breathing pattern. Respir Physiol Neurobiol. 2018;261:48–54.
[9] Whitelaw WA, Derenne JP. Airway occlusion pressure. J Appl Physiol. 1993;74:1475–83.
[10] Fernandez R, Raurich JM, Mut T, Blanco J, Santos A, Villagra A. Extubation failure: diagnostic value of occlusion pressure (P0.1) and P0.1-derived parameters. Intensive Care Med. 2004;30:234–40.
[11] Esnault P, Cardinale M, Hraiech S, Goutorbe P, Baumstrack K, Prud'homme E, et al. High respiratory drive and excessive respiratory efforts predict relapse of respiratory failure in critically ill patients with COVID-19. Am J Resp Crit Care. 2020;202:1173–8.
[12] Lopez-Navas K, Brandt S, Strutz M, Gehring H, Wenkebach U. Non-invasive determination of respiratory effort in spontaneous breathing and support ventilation: a validation study with healthy volunteers. Biomed Eng Biomedizinische Technik. 2014;59:335–41.
[13] Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Resp Crit Care. 2018;199:1368–76.
[14] Gobert F, Yonis H, Tapponnier R, Fernandez R, Labaune M-A, Burle J-F, et al. Predicting Extubation outcome by cough peak flow measured using a built-in ventilator flow meter. Respir Care. 2017;62:1505–19.
[15] Hilbert G, Gruson D, Portel L, Vargas F, Gbikpi-Benissan G, Cardinaud JP. Airway occlusion pressure at 0.1 s (P0.1) after extubation: an early indicator of postextubation hypercapnic respiratory insufficiency. Intensive Care Med. 1998;24:1277–82.
[16] Jun T, Nirenberg S, Weinberger T, Sharma N, Pujadas E, Cordon-Cardo C, et al. Analysis of sex-specific risk factors and clinical outcomes in COVID-19. Commun Med. 2021;1:3.