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Worldwide Clinical Practice of High-Flow Nasal Cannula and Concomitant Aerosol Therapy among Adult Critical Care Subjects

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Conflict of interests

Dr. Li declares to receive research funding from Fisher & Paykel Healthcare Ltd, Aerogen Ltd, and Rice Foundation and lecture honorarium from AARC and Fisher & Paykel Healthcare Ltd outside the submitted work. Dr. Fink is Chief Science Officer for Aerogen Pharma Corp. Dr. Ehrmann reports consultancies from Aerogen Ltd, research support from Aerogen Ltd, Fisher & Paykel healthcare, Hamilton medical, travel reimbursements from Aerogen Ltd and Fisher & Paykel. The companies had no role in the study design, data collection, analysis, preparation of the manuscript, or the decision to publish the findings. Other authors have no conflicts to disclose.

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Abstracts

Background: Therapy with high-flow nasal cannula (HFNC) has been broadly utilized. However, no consensus has been achieved on practical implementation of HFNC and how to provide aerosol delivery during HFNC therapy in adult subjects.

Methods: An online anonymous questionnaire survey, endorsed by four academic societies from America, Europe, mainland China and Taiwan, was administered from May to December, 2019. Clinicians who had worked in adult intensive care unit for more than one year and had used HFNC to treat subjects within 30 days were included.

Results: 2,279 participants clicked on the survey link, 1358 respondents completed the HFNC section, while 1014 completed the whole survey. Post-extubation hypoxemia and moderate hypoxemia were major indications for HFNC. Initial flow was set mainly at 40-50 L/min. Aerosol delivery via HFNC was utilized by 24% (248/1014) of participants, 30% (74/248) of whom reported reducing flow during aerosol delivery. For subjects who required aerosol treatment during HFNC therapy, 40% (403/1014) of participants reported placing a nebulizer with a mask or mouthpiece while pursuing HFNC (a method shown to reduce inhaled dose) while 33% (331/1014) discontinued HFNC to use conventional aerosol devices. Vibrating mesh nebulizer (VMN) was the most commonly used nebulizer (40%) and was mainly placed at the inlet of the humidifier.

Conclusions: The clinical utilization of HFNC was variable, as were indications, flow settings, and criteria for adjustment. Many practices associated with concomitant aerosol therapy were not consistent with available evidence for optimal use. More efforts are warranted to close the knowledge gap.

Keywords: High-flow nasal cannula; aerosol therapy; survey; hypoxemia; trans-nasal pulmonary aerosol delivery**.**

Introduction

High-flow nasal cannula (HFNC) is a relatively new modality of oxygen therapy, which delivers oxygen at a warmed humidified flow, potentially exceeding subject's inspiratory flow demand. [1,2] Multiple randomized control trials and meta-analyses have demonstrated the superiority of HFNC over conventional oxygen and non-inferiority to noninvasive ventilation, as a method to improve oxygenation and ultimately avoid intubation or reintubation in hypoxemic patients. [3-10] Increasing evidence has supported the use of HFNC to reduce work of breathing, improve ventilation, alleviate hypercapnia including among chronic obstructive pulmonary disease (COPD) patients. [11-15]

Flow setting plays a critical role in HFNC utilization, as increased flow can reduce inspiratory effort, improve ventilation and dynamic lung compliance. [16,17] Carbon dioxide (CO_2) has been shown to decrease as the dead space in the upper airway is washed out by the high gas flow.[18] However, criteria for flow setting has not achieved consensus yet in clinical trials, and has varied from 10-15 L/min to 50-60 L/min (See online supplement), even in the same population (e.g., post-operative extubation).[19] Surveys from pediatric clinicians observed that the utilization of HFNC, including flow initiation and titration, subject's assessment, and HFNC weaning varied greatly.[20,21] A French nationwide survey of adult intensive care unit (ICU) subjects reported that the daily practice of HFNC, such as the criteria for HFNC initiation, weaning, and failure was heterogeneous among ICU physicians.[22] The practice in other countries/areas has not been reported. Clinically, no guideline has been established on how to apply HFNC.

Moreover, aerosol delivery via HFNC has attracted clinicians' interest in recent years,[23] due to its combined benefits from HFNC and aerosolized medication. A survey among American

pediatric respiratory therapists showed that 75% of them used HFNC to deliver aerosol therapy for pediatric subjects.[20] However, the utilization of aerosol therapy methods for adult subjects during HFNC therapy is still unknown.

Thus, to understand the current clinical practice, we implemented a worldwide survey among ICU clinicians who worked with adult subjects on the utilization of HFNC, with some focus on the concomitant delivery of aerosol therapy.

Methods

After a thorough literature review and discussion with six academic respiratory care experts, with ≥ 10years ICU experience and a university faculty position, we designed a questionnaire using an online survey platform (Surveymonkey, San Mateo, CA). This questionnaire included two main sections: the technical application of HFNC in ICU and aerosol delivery during HFNC therapy. De-identified demographic information was also collected (the questionnaire is available in online supplemental file). The questionnaire was sent to ten clinicians who worked at the bedside and used HFNC for ≥ 5 subjects/month and feedback was integrated. According to the local requirement, this study was approved by four major ethical committees in the US, France, mainland China and Taiwan. Need for informed consent was waived.

The survey was conducted from May 24th to December 31st 2019, the study was endorsed by the American Association for Respiratory Care, the European Society of Intensive Care Medicine, the Chinese Respiratory Disease Society and the Taiwan Respiratory Care Society. The survey's invitation was posted on their social media platforms, such as website, Facebook, Twitter, etc. Participants fulfilling all of the following three criteria were enrolled in the study: 1)

Provided care for adult ICU subjects; 2) Had more than one-year working experience in ICU; 3) Used HFNC for subjects in recent 30 days.

Data analysis

Questionnaires with incomplete responses, defined as >10% of questions in the first section of the questionnaire left unanswered, were not analysed. Continuous variables were reported as mean ± standard deviation or median (Inter-Quartile Range [IQR]), while categorical variables were reported as frequency and proportion. Two independent investigators reviewed answers to open questions. Chi-squared test or Fisher's exact test were utilized for comparing categorical variables. All the analyses were performed with SPSS 26.0 (SPSS Inc, SPSS, Chicago, IL, USA), and a two-sided p-value < 0.05 was considered as statistically significant.

Results

Among the 2,279 participants who clicked on the survey link, 755 were excluded due to the following reasons: 1) 242 were not working in adult ICU; 2) 114 worked in adult ICU for less than one year; 3) 362 had not used HFNC to treat subjects in the recent 30 days; 4) 37 had filled the survey before. Among the remaining 1,524 participants, 166 were excluded as they didn't complete the first section of the questionnaire. 1,358 participants from 61 countries/areas completed the HFNC section (Figure 1); of them 1014 continued to complete the aerosol therapy section, but only 988 offered their demographic information.

Among these 988 participants, 188 (19%) were from North America, and 92% of them were respiratory therapists (RTs); 428 (43%) were from mainland China and Taiwan, with 48% and 32% of them were nurses and RTs, respectively; 372 (38%) were from Europe and other areas, 76% of them were physicians. Overall, 72% worked in academic institutions, with 12.2 ±

9.2 years of ICU working experience; 53% (521/977) worked in leadership, including director, attending physician, manager, educator, and supervisor (Table 1).

The utilization of HFNC

The questions of this section were answered by 1,358 participants. According to them, 25% of participants' institutions had a HFNC protocol while others administrated HFNC empirically.

HFNC indications. Overall, the top four indications for HFNC were: post-extubation hypoxemia (78%), moderate hypoxemia with the ratio of partial pressure of oxygen to fraction of inspired oxygen (PaO_2/F_IO_2) at 100 to 200 mmHg (73%), mild hypoxemia with PaO_2/F_IO_2 at 200 to 300 mmHg (56%) and post-extubation of COPD (51%) (Figure 2). The former two indications were common among all the participants; however, HFNC to improve/maintain oxygenation peri-intubation was more commonly utilized in Europe than other areas (53% vs. 38%, $P < .001$), while HFNC for post-extubation of COPD was more commonly used in China than other areas (66% vs. 43%, $P < .001$).

Flow and temperature settings. 59% of the respondents set the same initial flow for all adult subjects, with 29%, 25%, and 20% of the participants set flow at 40, 50, and 60 L/min; while the remaining participants stated that they would set initial flow according to subjects' diseases, and 40 (35, 50) L/min was the most common flow setting. HFNC flow was adjusted primarily based on subjects' comfort (81%), oxygenation (77%), and breathing pattern (70%). 9% of the respondents deemed HFNC flow was set to match subject's inspiratory flow, 36% set the flow just exceeding the subject's inspiratory flow, while 28% set the flow much higher than subject's inspiratory flow. However, none of them reported measuring subject's inspiratory flow

147 before initiation. By their estimation, the inspiratory flow for subjects with mild, moderate, and
148 severe hypoxemia were 35 (25, 40), 40 (30, 50), and 50 (30, 60) L/min, respectively; while the
149 inspiratory flow for subjects with stable COPD and COPD exacerbation were 30 (20, 40) and 40
150 (30, 55) L/min, respectively. Regarding temperature settings during HFNC treatment, 52% set it
151 at 37 °C while 30% and 14% set it at 34 °C and 31 °C, respectively.

152 ***HFNC weaning***. When weaning from HFNC was considered, 52% and 13% of
153 respondents preferred first to reduce fraction of inspired oxygen (F_IO_2) vs. first to reduce the
154 flow, respectively, while 25% decreased flow and F_IO_2 alternately.

155 ***HFNC events***. Nasal cannula dislodgement and rainout were the top two complaints
156 during the utilization of HFNC. The incidence of ear or face skin breakdown > 6 cases/year was
157 also reported by 11% of the participants.

158 ***Aerosol delivery via HFNC***

159 The questions of this section were answered by 1,014 participants. When subjects
160 required aerosol treatment during HFNC therapy, 403 (40%) placed the nebulizer via a mask or
161 mouthpiece and pursued HFNC therapy with the cannula in place, 331 (33%) discontinued
162 HFNC treatment to use a conventional aerosol device, and 248 (24%) participants placed
163 nebulizer in-line within the HFNC circuit (Figure 3).

164 For the 248 respondents who administered aerosols this way, the use of a vibrating mesh
165 nebulizer (VMN), ultrasonic nebulizer, and small volume jet nebulizer (SVN) were 40%, 30%,
166 and 28%, respectively (Figure 3). Aerosol delivery via HFNC was more common in North
167 America than other areas (44% vs. 20%, $p<0.001$), and VMN was the preferred nebulizer (75%,

60/80) in North America. VMN was primarily placed at the inlet of the humidifier (57%) while SVN was primarily placed close to the subject (58%).

Among 248 respondents, 74 (30%) reduced flow during aerosol therapy, in order to increase aerosol deposition (68%) and to improve subject's comfort (34%); 27%, 26%, and 34% of these 74 participants reported to reduce flow to 10, 20, and 30 L/min, respectively.The top three medications that were frequently delivered (> 12 subjects/year) via HFNC were: albuterol (68%), ipratropium (66%), and budesonide (40%).

Compared to conventional aerosol therapy, 177 of 248 (71%) of participants preferred to place the nebulizer in-line within the HFNC circuit in order to maintain HFNC benefits; 50%, 49%, and 40% of participants claimed it was for better comfort, more efficiency, and more convenience, respectively.

45% of participants never used continuous nebulization; 20% of participants reported in-line placement of nebulizer via HFNC to deliver continuous aerosol, especially in North America (38%); while 23% placed a mask with the nebulizer on top of HFNC, and 9% discontinued HFNC to use conventional nebulizer continuously.

Among the 766 participants who didn't provide aerosol therapy via HFNC, 54% had never heard of this delivery route; 27% reported lack of evidence to support its utilization, while 17% deemed the aerosol deposition in the lung was low.

Discussion

To our knowledge, this is the first worldwide survey on the utilization of HFNC, and aerosol delivery during HFNC therapy in adult populations. HFNC was primarily utilized for hypoxemic subjects, specifically for subjects with moderate hypoxemia and post-extubation hypoxemia. HFNC was mainly implemented based on clinicians' experience, with only1/4 of participants' institutions having established a protocol. Participants agreed that HFNC flow should be set higher than subject's inspiratory flow, which was estimated to be variable based on subject's disease. One-fourth of participants delivered aerosol delivery via HFNC. For those participants who didn't use in-line nebulizer with HFNC, more than half of them placed a mask/mouthpiece with the nebulizer on top of the nasal cannula, while the remaining discontinued HFNC to deliver conventional aerosol therapy.

HFNC administrations

Predominant evidence has been established for subjects with acute hypoxemic respiratory failure to avoid intubation,[3,10] and for post-extubation, [4,7,8] and post-operative subjects [5,6] to reduce post-extubation respiratory failure or reintubation, compared to conventional oxygen therapy. A recent meta-analysis demonstrated that use of HFNC for preoxygenation before intubation of adult hypoxemic patients reduced the risk of intubation-related complications compared to conventional oxygen therapy, but subjects treated with HFNC still had a higher incidence of desaturation than noninvasive ventilation.[9]

The indications for HFNC in the present survey are aligned with the current evidence, except for the use of HFNC for pre-oxygenation before intubation, only 44% of participants considered it as an HFNC indication, especially in North America where only 27% of clinicians used HFNC for preoxygenation, compared with 53% in Europe. This difference might be due to the familiarity of this preoxygenation modality and the clinical urgency of intubation. So far, six

of seven randomized controlled trials using HFNC peri-intubation were completed in France,[9] which may explain the high percentage (84%) of French ICU physicians agreeing with the use of HFNC for pre-intubation oxygenation.[22]

Interestingly, participants preferred to use HFNC for subjects with moderate hypoxemia more than mild or severe hypoxemia (73% vs. 56%, 39%, respectively). However, Shen et al. performed a subgroup analysis in all the HFNC randomized controlled trials and found that trials with $PaO_2/F_IO_2 > 200$ mmHg had greater benefits than trials with $PaO_2/F_IO_2 \leq 200$ mmHg, specifically for post-extubation subjects. [24] Future studies are needed to clarify the role of HFNC in subjects with different severity and pathophysiology. Despite the insufficient evidence supporting HFNC for subjects with hypercapnia, one-fourth of participants used HFNC for COPD patients, whether stable or during exacerbation.

When the HFNC flow is set to match or exceed the subject's inspiratory flow, F_IO_2 begins to be stabilized, and an incremental increase of PEEP occurs linearly with an increase in HFNC flow.[25,26] Most authors suggest that the HFNC flow should be set higher than or equal to subject inspiratory flow. One should attempt to reach the inspiratory flow of the patient, not be lower, and eventually exceed it to have some safety as inspiratory flow may be variable from one breath to another. As inspiratory flow is not commonly measured at bedside, flow is commonly chosen based on observed response to changes in F_IO_2. Patient peak inspiratory flows can vary from 20 – 100 L/min, in some cases it may not be possible to meet patient peak inspiratory flow. Future studies are required to validate if the estimated flow by the respondents correlates to the actual inspiratory flow of subjects. Furthermore, from the summarization of the flow settings and adjustment in all the randomized controlled trials (See online supplement), the flow settings

varied in different diseases and countries; this is in agreement with our finding that more than 3/4 of the participants' institutions had not established an HFNC protocol.

Aerosol delivery during HFNC therapy

One-fourth of participants reported placing nebulizer in-line within the HFNC circuit to deliver aerosol, especially in North America; however, its utilization was lower than the previous survey among American pediatric respiratory therapists (47% vs. 75%), which might be explained by the difference in tolerance issue between the adult and pediatric populations with conventional aerosol devices, such as SVN with face masks/mouthpieces. Cold aerosol, mask on the face, and noise from the nebulizer have been reported to irritate small children, resulting in little to no inhaled dose.[27] This population was observed to tolerate in-line placement of nebulizer with HFNC better.[28-30] In adult subjects with stable asthma or COPD, three clinical trials reported similar efficacy of inhaling bronchodilator via HFNC at 15-35 L/min versus conventional aerosol device.[31-33] Likewise, for subjects with pulmonary hypertension and/or refractory hypoxemia, inhaled prostacyclin via HFNC at 30-50 L/min was reported to decrease mean pulmonary arterial pressure and/or improve oxygenation.[34-36] In all, increasing evidence supports the use of trans-nasal pulmonary aerosol delivery. In contrast, the evidence is against administering the nebulizer by mask or mouthpiece with concurrent HFNC, as it reduced inhaled dose to as low as 10% of the inhale dose achieved with trans-nasal aerosol delivery.[37] Consequently, the use of nebulizer with mask/mouthpiece concurrent with HFNC should be avoided.[23] Additionally, discontinuing HFNC to use conventional nebulizer interrupts HFNC therapy with no advantage in aerosol delivery efficiency.[23] More efforts are warranted to close the knowledge gap.

The inhaled dose has been reported to increase as HFNC gas flow decreases;[23,36,38,39] thus, flow reduction may be recommended during aerosol delivery via HFNC.[40] In the survey, only 30% of the participants reported decreasing the flow during aerosol delivery via HFNC.

In the survey, VMN was the most frequently used nebulizer during trans-nasal aerosol delivery, especially in North America, 75% of clinicians used VMN to deliver aerosol via HFNC, which is in agreement with the survey results among pediatric respiratory therapists (77%).[20] This finding might be due to the higher efficiency of trans-nasal aerosol delivery with VMN than SVN,[41] and that VMN does not add a secondary gas flow with different F_IO_2, temperature and humidity into the HFNC circuit.[23]

Limitations

Even though there were some incomplete responses, the overall results of the survey may be considered reliable due to the following reasons: 1) respondents were seasoned clinicians, with a mean ICU working experience of 10 years, and > 50% of them worked in leadership; 2) all respondents were required to use HFNC to treat subjects within 30 days, which ensures the answers reflect the current practice in their institutions.

Not all the participants who clicked on the survey and fulfilled the eligibility criteria completed the entire survey, especially the section of aerosol delivery via HFNC that only 2/3 provided the information, it might be due to the facts that the survey was lengthy or aerosol delivery via HFNC was not in their clinical practice. As such, the actual use of trans-nasal aerosol delivery might be lower than the reported rate.

Conclusion

HFNC is broadly utilized, particularly in hypoxemic patients. However, HFNC was mainly utilized empirically, and the detailed information about HFNC utilization, including flow settings and adjustments, varied largely. Consensus or guideline on HFNC utilization may be warranted. One-fourth of participants delivered aerosol via HFNC while the remaining participants provided aerosol therapy either via nebulizer with mask/mouthpiece on top of nasal cannula or discontinued HFNC to use conventional nebulization. The current practice represents a mismatch with available evidence suggesting the need for efforts to fill the knowledge gaps.

Abbreviations

HFNC: High flow nasal cannula; COPD: Chronic obstructive pulmonary disease; CO_2: Carbon dioxide; ICU: Intensive care unit; IQR: Inter-Quartile Range; RTs: Respiratory therapists; F_IO_2: Fraction of inspired oxygen; VMN: Vibrating mesh nebulizer; SVN: Small volume jet nebulizer

Declarations

Ethics approval

This study was approved by ethic committees in Rush University, Chicago, IL,USA (No. 18121305-IRB01-AM01), French Intensive Care Society, Paris, France (CE SRLF 19-18), Chang Gung Medical Foundation, Taiwan (201900250B0) and People's Liberation Army General Hospital, Beijing, China (S2019-047-01).

Consent for publication

Not applicable

297 ***Availability of Data and Materials***

298 The datasets analysed during the current study are available from the corresponding author on
299 reasonable request.

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302 ***Authors' contributions***

303 JL conceived and designed the study, analyzed the data, drafted and revised the manuscript. MT
304 implemented the study, interpreted the data and revised the manuscript, LY implemented the
305 study, interpreted the data and revised the manuscript , GJ analyzed the data and revised the
306 manuscript, JBF conceived the concept, interpreted the data and revised the manuscript, AD
307 implemented the study and revised the manuscript, LG implemented the study, analyzed the data
308 and revised the manuscript, LX supervised the study and revised the manuscript, and SE
309 implemented the study, interpreted the data and critically revised the manuscript.

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312 Association for Respiratory Care (AARC), European Society of Intensive Care Medicine,
313 Chinese Respiratory Disease Society and Taiwan Respiratory Care Society to endorse this survey
314 and post the questionnaire survey on their public media.

315

316 **Quick Look**

317 Current knowledge

318 High-flow nasal cannula (HFNC) has been broadly utilized to improve oxygenation and
319 avoid intubation /reintubation for hypoxemic patients. More recently, HFNC has been extended
320 to other patient populations, such as subjects with chronic obstructive pulmonary disease, to
321 assist endoscopy examination and intubation, etc. In the recent years, aerosol delivery via HFNC
322 has attracted clinicians' interest, due to its combined benefits from HFNC and aerosolized
323 medication.

324

325 What this paper contributes to our knowledge

326 This is the first worldwide survey on the utilization of HFNC and aerosol delivery via
327 HFNC in adult populations. It revealed a wide range of practices suggesting knowledge gaps
328 between the current practice and evidence. Clinical guidance on HFNC administration and
329 concomitant aerosol therapy are urgently needed, educational efforts or quality improvement
330 projects are warranted to close the knowledge gap.

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460 **Online supplement**

461 Summary of high flow nasal cannula utilization in published randomized controlled trials

462 **Figure legends**

463 **Figure 1**. Global distribution of the 1,358 respondents

464 Among these 1,358 participants, majority were from Mainland China (27%), Taiwan (8%), USA

465 (25%), and Europe (30%), including France, UK, Spain, et al.

466

Figure 2. HFNC indications

Overall (red bar), post-extubation hypoxemia was the top HFNC indication, followed by moderate hypoxemia, mild hypoxemia and post-extubation COPD. In North America, more clinicians preferred to use HFNC to treat severe hypoxemia than other areas, while in China, more clinicians used HFNC to facilitate extubation for COPD patients, and more European clinicians used HFNC to improve/maintain oxygenation peri-intubation.

HFNC, high-flow nasal cannula; COPD, chronic pulmonary obstructive disease; EU, Europe.

Figure 3. Aerosol therapy during HFNC treatment

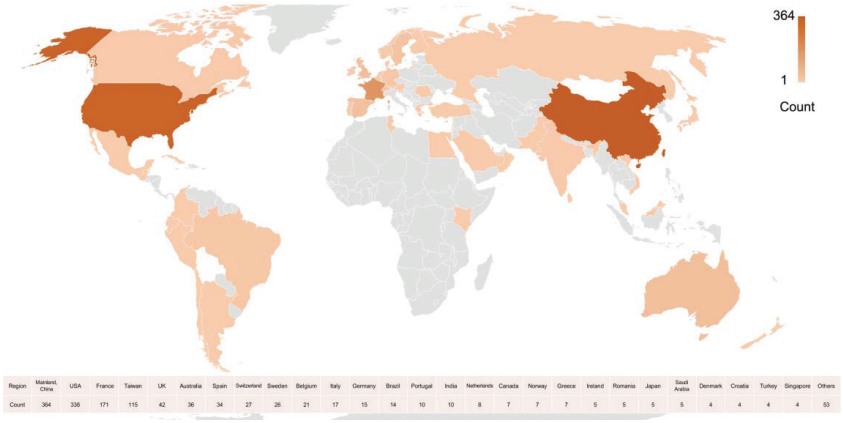
When patients required short-term aerosol treatment during HFNC therapy, 33% (331/1014) of participants discontinued HFNC treatment to use a conventional aerosol device, 40% (403/1014) placed the nebulizer with a mask over the nasal cannula, and 24% (248/1014) placed nebulizer in-line within the HFNC circuit. Of the 248 participants who delivered aerosol via HFNC, 40% used vibrating mesh nebu lizer, 30% used ultrasonic nebulizer and 28% used small volume jet nebulizer .

HFNC, high-flow nasal cannula

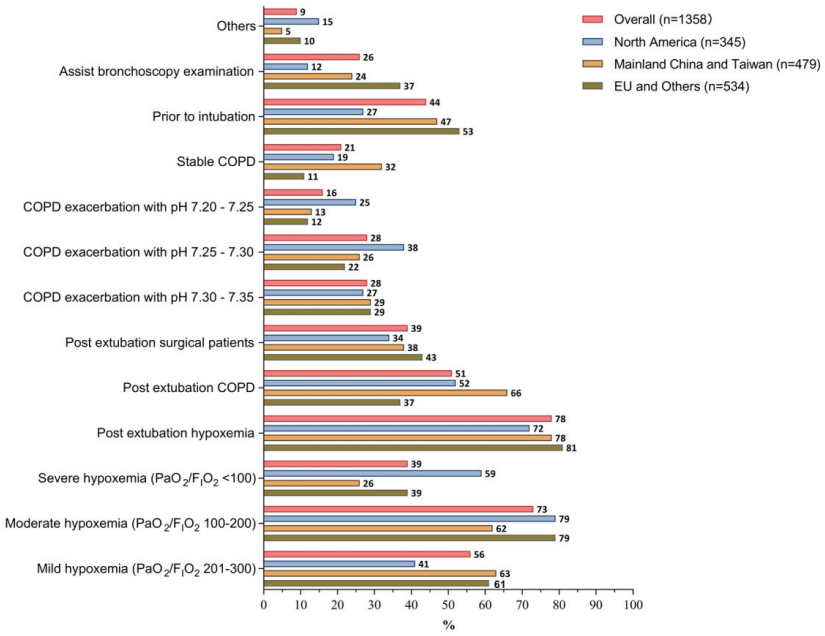
Table 1. Participants' Demographic Information

		Overall	North America	Mainland China and Taiwan	EU and Others
No. of participants		**988**	**188**	**428**	**372**
Profession (n=988)	MD	375(38%)	13(7%)	80(19%)	282(76%)
	RT	323(33%)	173(92%)	138(32%)	12(3%)
	RN	224(23%)	2(1%)	204(48%)	18(5%)
	PT	60(6%)	0	2(0%)	58(16%)
	Others	6(1%)	0(0%)	4(1%)	2(1%)
Hospital (n=984)	Community	209(21%)	87(47%)	10(2%)	112(30%)
	Academic	713(72%)	100(53%)	356(83%)	257(70%)
	Others	62(6%)	0	62(14%)	0
Job title (n=977)	Attending MD or RN/RT/PT director/ manager	280(29%)	47(25%)	58(14%)	175(48%)
	RT/RN educator	110(11%)	17(9%)	90(21%)	3(1%)
	Fellow MD or RT /PT supervisor	131(13%)	28(15%)	63(15%)	40(11%)
	Resident or RN/ RT/ PT staff	394(40%)	92(49%)	199(47%)	103(28%)
	Others	62(6%)	2(1%)	15(4%)	45(12%)
Degree (n= 978)	Associate	116(12%)	66(35%)	31(7%)	19(16%)
	Bachelor	442(45%)	86(46%)	313(73%)	43(10%)
	Master	178(18%)	23(12%)	65(15%)	90(51%)
	Doctorate	231(24%)	11(6%)	16(4%)	204(88%)
	Others	11(1%)	0	3(1%)	8(73%)
Years of ICU working experience (n=965)		12.2±9.2	19.2±11.5	8.6±5.6	13.3±9.0

MD, medical doctor; RT, respiratory therapist; RN, registered nurse; PT, physical therapist; EU, Europe; ICU, intensive care



Region	Mainland, China	USA	France	Taiwan	UK	Australia	Spain	Switzerland	Sweden	Belgium	Italy	Germany	Brazil	Portugal	India	Netherlands	Canada	Norway	Greece	Ireland	Romania	Japan	Saudi Arabia	Denmark	Croatia	Turkey	Singapore	Others
Count	364	338	171	115	42	36	34	27	26	21	17	15	14	10	10	8	7	7	7	5	5	5	5	4	4	4	4	53



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