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BRIEF RESEARCH REPORT

Infectious Disease

Aerosol risk with noninvasive respiratory support in patients with COVID-19

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Abstract

Objectives: This study evaluates aerosol production with high-flow nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV) compared to 6 L/min by low-flow nasal cannula.

Methods: Two healthy volunteers were randomized to control (6 L/min by low-flow nasal cannula), NIPPV, or HFNC using block randomization. NIPPV conditions were studied using continuous positive airway pressures of 5, 10, and 15 cm H_2O with an FiO_2 of 1.0 delivered via full-face mask. HFNC conditions included flow rates of 30 and 40 L/min with an FiO_2 of 1.0 with and without coughing. HFNC and low-flow nasal cannula conditions were repeated with and without participants wearing a surgical mask. Six aerosol sizes (0.3, 1.0, 2.5, 5, and 10 μm) and total aerosol mass were measured at 2 and 6 ft from the participant's nasopharynx.

Results: There was no significant difference in aerosol production between either HFNC or NIPPV and control. There was also no significant difference with the use of a procedural mask over the HFNC. There was significant variation between the 2 participants, but in neither case was there a difference compared to control. There was an aerosol-time trend, but there does not appear to be a difference between either flow

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rate, pressure, or control. Furthermore, there was no accumulation of total aerosol particles over the total duration of the experiment in both HFNC and NIPPV conditions.
Conclusions: HFNC and NIPPV did not increase aerosol production compared to 6 L/min by low-flow nasal cannula in this experiment involving healthy volunteers.

1 | INTRODUCTION

The COVID-19 pandemic pushed the healthcare system beyond its capacity to care for critically ill patients in many locations across the world. While the spread of infections began to decline in May 2020, the likelihood of a second wave of the disease warrants continued discussion on potential therapies especially for those patients with acute hypoxemic respiratory failure. Given the highly infectious nature and aerosol stability of the SARS-CoV-2 virus,[1,2] all major societies currently recommend against aerosol-generating interventions when possible. Aerosols include both liquid and solid particles of any size in air, and thus encompass both respiratory droplets and the residual solid components after droplet evaporation.

Non-invasive positive pressure ventilation (NIPPV) is considered aerosol-generating and is relatively contraindicated. The Society for Critical Care Medicine recommends the use of heated humidified high-flow nasal cannula (HFNC) with a surgical mask to mitigate aerosolization risk in COVID-19 patients,[3] but many hospitals continue to withhold HFNC use due to the presumed aerosolization risk.[4] Early experimental studies, however, show that there is limited dispersion of exhaled air when NIPPV and HFNC are used with good mask interface,[5] yet dispersion distances increase significantly with coughing on HFNC.[6] Additionally, while studies have evaluated dispersion *distances* of varying oxygen delivery devices using laser visualization of smoke on a high fidelity simulator,[7] no studies to our knowledge have evaluated the aerosols *produced* during use of each of these oxygen delivery modalities. We convened an interdisciplinary team to assess the aerosol production with NIPPV and HFNC.

2 | METHODS

We enrolled 2 healthy volunteers to participate in this study. The study was conducted in an intensive care unit room at Banner University Medical Center–Tucson, with the room ventilation set at standard pressure (not isolation/negative pressure) over 2 days (March 28 and 29, 2020). The participants were randomized to Participant 1 and Participant 2, and Intervention 1 (HFNC) and Intervention 2 (NIPPV). The comparator was wall oxygen at 6 LPM by low flow nasal cannula, as this is widely considered non-aerosol generating.

For the HFNC arm, we utilized the Vapotherm (Vapotherm, Exeter, NH, USA) set to a heater temperature of 34°C, an FiO_2 of 1.0, and a flow rate based on the assigned treatment condition. For HFNC conditions, we had 2 separate periods—mask or no mask, and cough or no cough. For the NIPPV conditions, we utilized the Respironics V60 (Philips Respironics, Murrysville, PA, USA) with an FiO_2 of 1.0 and continuous positive airway pressure (CPAP) based on the assigned treatment conditions delivered via oronasal mask with a standard single limb exhalation circuit and HEPA filter. We tested the following conditions, each repeated 3 times for each participant, using block randomization: 6 LPM by nasal cannula (control); HFNC: 30 LPM, 40 LPM; NIPPV: CPAP 5 cm H_2O, CPAP 10 cm H_2O, CPAP 15 cm H_2O.

We took several baseline readings of the room each day with no interventions. The standard hospital bed was placed in a 90° seated position. The detectors were placed at the height of the participant's mouth at distances of 0.6 m (2 ft) and 1.8 m (6 ft) from the participant. The 0.6 m distance detector was placed slightly off center of the participant, as our hypothesis was that any aerosols produced while wearing a mask (either surgical with HFNC or face mask with NIPPV) would be exhaled around the side of the mask with HFNC or the exhalation port with NIPPV, both pointed directly at the detector. The 1.6 m distance detector was placed directly in the midline.

We used the Particles Plus 8306 handheld particle counter (Particles Plus, Inc, Stoughton, MA, USA), which measures ambient temperature and humidity and uses a laser diode to count aerosols in 6 different channels at the following sizes: 0.30, 0.50, 1.0, 2.5, 5, 10 μm. Each sample run was 150 seconds with the average concentration logged every 10 seconds. We further evaluated aerosol sizes between 5 and 10 μm based on recent data from the World Health Organization that SARS-CoV-2 is transmitted most commonly by respiratory droplets in that range (WHO reference number: WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.2). Statistical analysis used analysis of variance to evaluate experimental factors associated with variation in aerosol amounts (mass or counts of 5–10 μm droplets), and was performed separately for each intervention. Graphical analyses were used extensively to understand data structure, while ANOVA results (eg, the magnitude of *F* statistics) were used to corroborate the relative importance of experimental factors.

This study was approved by the Human Subjects Protection Program of the University of Arizona (IRB #2003513875).

3 | RESULTS

3.1 | Main results

Summary statistics for aerosols produced by treatment modality are presented in Table 1. We found no significant difference in aerosol production between either HFNC or NIPPV and control (6 LPM by nasal cannula) or among the levels of support with each device (Figure 1). We

TABLE 1 Summary statistics for concentration (counts/m^3) of aerosols 5–10 μm in diameter by the different conditions

High flow nasal cannula—particle sizes 5–10 μm				
Flow (LPM)	Cough condition	Distance	Mean	SD
Control	Cough	2 ft	2378	677
Control	Cough	6 ft	2425	776
Control	No cough	2 ft	1483	636
Control	No cough	6 ft	3720	1,534
30L	Cough	2 ft	1942	529
30L	Cough	6 ft	2413	961
30L	No cough	2 ft	1706	675
30L	No cough	6 ft	3590	1,436
40L	Cough	2 ft	1977	1,163
40L	Cough	6 ft	2672	1,005
40L	No cough	2 ft	1542	388
40L	No cough	6 ft	1977	952
Noninvasive positive pressure ventilation—particle sizes 5–10 μm				
CPAP conditions (cm H_2O)		Distance	Mean	SD
Control		2 ft	2189	827
Control		6 ft	2260	871
5		2 ft	1860	647
5		6 ft	2072	648
10		2 ft	1836	828
10		6 ft	1930	470
15		2 ft	1812	589
15		6 ft	2425	835

Baseline conditions mean (SD): Day 1–1130 (503); Day 2–644 (705).
Abbreviation: CPAP, continuous positive airway pressure.

also found that the use of procedural mask over the HFNC made no significant difference. We did find variation between the 2 participants, but in neither case was there a difference compared to control. There was an aerosol-time trend, but there does not appear to be a difference between either flow rate, pressure, or control. There was also no accumulation over the total duration of the experiment in both HFNC and NIPPV conditions in either the <0.3 μm or respiratory droplet 5–10 μm ranges (Figure 2).

3.2 | High flow nasal cannula

The total aerosol mass measured among all sizes of measured aerosols, including those >10 μm, differed significantly between the 2 and 6 ft distances (*F* statistic, $F_{1,99} = 34.9$, $P < 0.0001$), with the 6 ft. distance exhibiting greater mass (mean 15 μg/m^3 vs 10 μg/m^3). Aerosol mass

TABLE 2 Analysis of variance by treatment modality

High flow nasal cannula—aerosol sizes 5–10 μm					
	DF	Sum Sq	MeanSq	*F*	Pr (>*F*)
Participant	1	190.4	190.37	1.87	0.18
Groups	4	650.6	162.66	1.59	0.18
Cough	1	19.5	19.49	0.19	0.66
Distance	1	2493.6	2493.64	24.43	<2e-16
Groups:Cough	4	757.6	189.39	1.86	0.12
Groups:Distance	4	305.7	76.42	0.75	0.56
Cough:Distance	1	532.9	532.85	5.22	0.02
Groups:Cough: Distance	4	884	221.02	2.17	0.08
Residuals	99	10104.4	102.06		
Noninvasive positive pressure ventilation—aerosol sizes 5–10 μm					
	DF	Sum Sq	MeanSq	*F*	Pr (>*F*)
Participant	1	424.79	424.79	7.61	0.01
Flow rate	3	95.55	31.8	0.57	0.64
Distance	1	102.06	102.06	1.83	0.18
Flow:Distance	3	56.12	18.7	0.34	0.80
Residuals	39	2175.60	55.78		

DF, degrees of freedom; Sum Sq, sum of squares; Mean Sq, mean squares.

did not differ significantly with flow rate ($F_{2,99} = 2.6$, $p = 0.08$) or with flow x distance interaction ($F_{2,99} = 1.6$, $p = 0.2$). There was a difference in total aerosol mass between the 2 participants ($F_{1,99} = 4.8$, $p = 0.03$), but neither appeared to differ by flow rate. Lastly, there was no difference between either flow rate and control in either the cough or no cough and mask or no mask conditions. Analysis of variance shows a significant difference in measurements based on distance from the participant and between participant variability; the latter of which is not significant when limiting the analysis to droplets 5–10 μm in size (Table 2). The difference by distance may be due to the differing orientation of the monitor and indicative of a difference in the trajectory of the large aerosols as emitted from the participant. There is some evidence that the effect of coughing may differ by distance ($F_{1,99} = 7.1$, $P = 0.01$); at 2 ft the no cough condition has a lower mean, while at 6 ft the no cough condition is slightly greater (at some flow rates). Interestingly this appears to be associated with only Participant 2.

3.3 | Noninvasive positive pressure ventilation

The total aerosol mass measured with NIPPV also does not appear to be significantly different from control at any of the 3 levels of support ($F_{3,39} = 3.8$, $P = 0.79$), although there were differences between the 2 participants ($F_{1,39} = 7.9$, $P = 0.01$). The analysis of variance for NIPPV shows significant differences in total aerosol mass between the 2 participants and the 2 distances (Table 2).

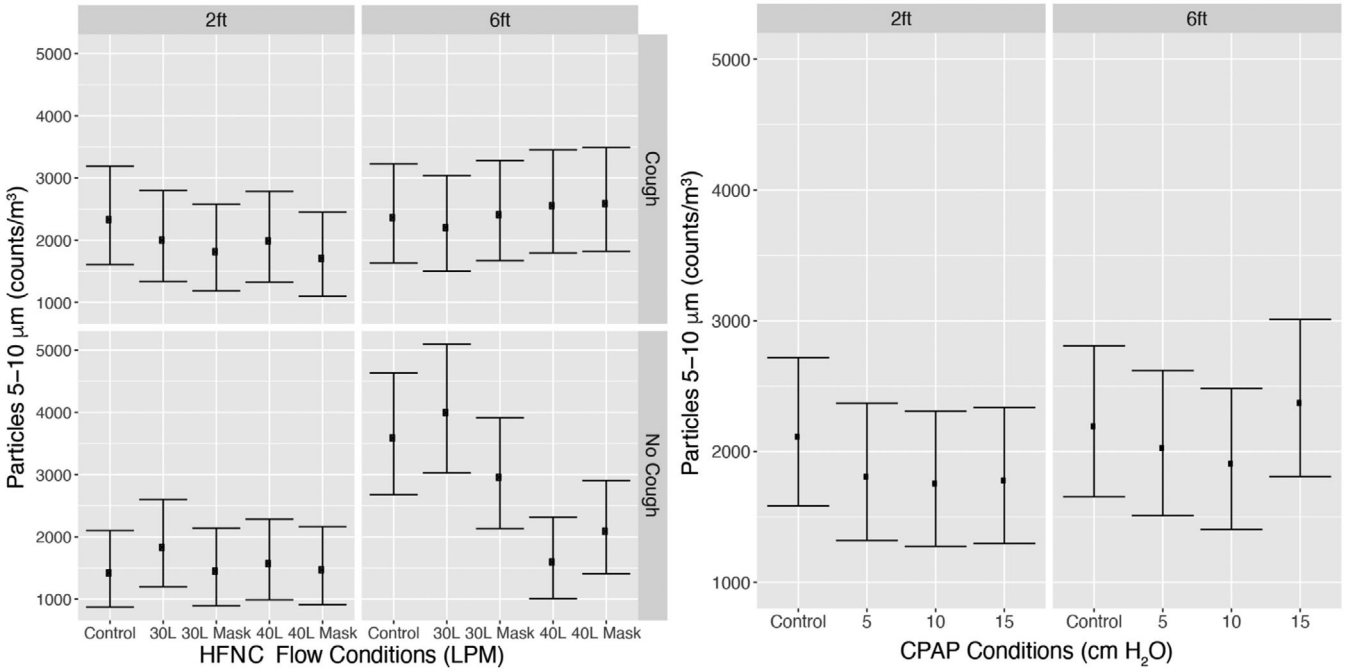

FIGURE 1 Main results. Concentration (count/m^3) of particles 5–10 µm in diameter under control (low flow nasal cannula at 6 LPM), HFNC (at 30 and 40 LPM with and without a surgical mask), and NIPPV (at 5, 10, and 15 cm H_2O) measured at 2 and 6 ft from each participant's nasopharynx. We used particle sizes between 5–10 µm based on recent data from the World Health Organization that SARS-CoV-2 is transmitted most commonly by respiratory droplets in that range (WHO reference number: WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.2). Values represent means and 95% confidence intervals of 2 participants performing each condition in triplicate

3.4 | Aerosol-time trend

Interestingly, an aerosol-time trend was most pronounced in the submicrometer size range (<1.0 µm) in contrast to no significant temporal trend for aerosols between 5 and 10 µm (Figure 2). Given the periodicity of the trend, it is possible that the ventilation in the room contributed to this finding. Furthermore, coagulation of smaller aerosols to larger ones can plausibly explain the increased sensitivity of number concentration as a function of time for the smaller aerosols. We performed the experiment in a negative pressure room set to "standard" rather than "isolation/airborne," which when activated increases the cycles per hour of negative pressure. However, when looking at all aerosols <5 µm, there are some outlying and potentially influential measurements, which may indicate that total aerosol mass could accumulate over time on these therapies. Considering aerosols <0.3 µm, there does not appear to be a difference between either flow rate or control, or an accumulation over the total duration of the experiment in both HFNC and NIPPV conditions. However, the number of participants is small and this should be replicated with more people and different rooms to account for differing ventilation conditions. For HFNC conditions, there was still a difference in particle counts by distance; however, there was no difference based on flow rates or mask use (Table 2). For the NIPPV conditions, there was not a significant difference between distances or pressures, but there is significant intersubject variability (Table 2).

4 | DISCUSSION

Any column of air passing over a liquid surface, such as exhaled air over the mucosal surfaces of the respiratory tract, produces aerosols. This, in turn, increases the risk of transmission of viral aerosols via respiratory droplets. Previous studies have used laser visualization of smoke to measure dispersion distances of various oxygenation modalities on simulators,[5] but to our knowledge this is the first study to evaluate the actual aerosols produced with each modality. We found no increase in aerosols produced compared to control, neither between modalities nor among levels of support within each modality. Additionally, there is little evidence that the use of a mask or the flow conditions have an effect on total aerosol mass.

Our findings regarding NIPPV are similar to an earlier study that demonstrated no significant aerosol production with the use of NIPPV.[8] Additionally, HFNC has been shown to not increase bacterial environmental contamination.[9] HFNC and NIPPV have become central for advanced preoxygenation prior to intubation in patients with hypoxemic respiratory failure,[10,11] and in the noninvasive respiratory treatment of patients not requiring intubation and/or after extubation. The health care system is facing a deluge of patients with respiratory failure with a need for mechanical ventilators that exceeds current available supply. Without these modalities, providers are faced with extremely dangerous peri-intubation desaturation events, and very difficult choices including rationing health care, premature transition

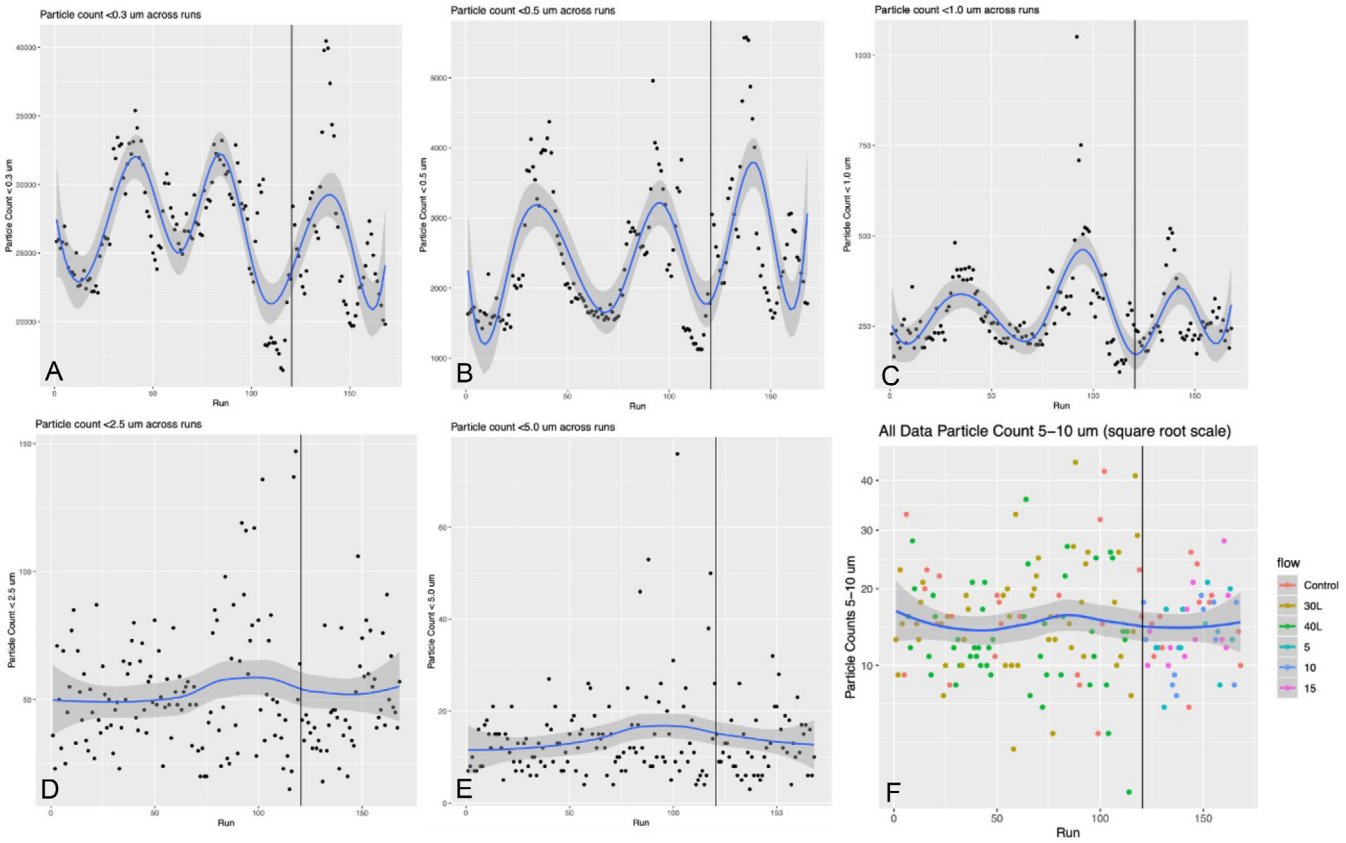

FIGURE 2 Aerosol-time trend. Concentration (count/m^3) of particles versus time (indicated by run order) by aerosol size (A-E). There was an aerosol-time trend that was most pronounced in the submicrometer aerosol size range (<1.0 μm) in contrast to the supermicrometer size range (panels D and E). Each experimental run has average particle count, and is reflected on the x-axis in the order they were completed. Runs were randomized by experimental condition. The vertical line represents the transition from HFNC and control conditions to NiPPV and control conditions. For all conditions, there is not a significant temporal trend (f)

to comfort measures, cohorting on a single ventilator, and using crowd-sourced or homemade ventilators. If our findings are confirmed, these therapies can potentially be safely used in patients with COVID-19 when combined with adequate personal protective equipment and a high air exchange rate through the ventilation system.

Our study has limitations including using healthy controls and a small sample size with inter-participant variability. However, block randomization and 3 repetitions of each condition resulted in 168 total measurements. We also acknowledge that aerosolization of respiratory secretions in healthy volunteers may be different than in critically ill COVID-19 patients. However, our results merit immediate replication to further assess the risk of aerosolization with the use of HFNC and NIPPV in critically ill patients with increased respiratory secretions.

Aerosolization risk in COVID-19 patients remains a concern in the emergency medicine and critical care communities. Our results suggest that we may be able to safely offer these non-invasive respiratory failure treatment strategies during the COVID-19 pandemic. Limiting their use may be unwarranted.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jarrod M. Mosier and David C. Miller conceived the study idea. Jarrod M. Mosier, David C. Miller, Paloma Beamer, Dean Billheimer, Vignesh Subbian designed the experiment. Jarrod M. Mosier and David C. Miller collected the data. Dean Billheimer performed the statistical analysis. All authors interpreted the results. Jarrod M. Mosier and David C. Miller drafted the initial manuscript and all authors contributed significantly to the revisions. Jarrod M. Mosier takes responsibility for the project as a whole.

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