Anaesthesia 2021, 76, 1465–1474 doi:10.1111/anae.15475

Original Article

The effect of respiratory activity, non-invasive respiratory support and facemasks on aerosol generation and its relevance to COVID-19

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Summary

Respirable aerosols (< 5 μm in diameter) present a high risk of SARS-CoV-2 transmission. Guidelines recommend using aerosol precautions during aerosol-generating procedures, and droplet (> 5 μm) precautions at other times. However, emerging evidence indicates respiratory activities may be a more important source of aerosols than clinical procedures such as tracheal intubation. We aimed to measure the size, total number and volume of all human aerosols exhaled during respiratory activities and therapies. We used a novel chamber with an optical particle counter sampling at 100 $l.min^{-1}$ to count and size-fractionate close to all exhaled particles (0.5–25 μm). We compared emissions from ten healthy subjects during six respiratory activities (quiet breathing; talking; shouting; forced expiratory manoeuvres; exercise; and coughing) with three respiratory therapies (high-flow nasal oxygen and single or dual circuit non-invasive positive pressure ventilation). Activities were repeated while wearing facemasks. When compared with quiet breathing, exertional respiratory activities increased particle counts 34.6-fold during talking and 370.8-fold during coughing ($p < 0.001$). High-flow nasal oxygen 60 at $l.min^{-1}$ increased particle counts 2.3-fold ($p = 0.031$) during quiet breathing. Single and dual circuit non-invasive respiratory therapy at 25/10 $cm.H_2O$ with quiet breathing increased counts by 2.6-fold and 7.8-fold, respectively (both $p < 0.001$). During exertional activities, respiratory therapies and facemasks reduced emissions compared with activities alone. Respiratory activities (including exertional breathing and coughing) which mimic respiratory patterns during illness generate substantially more aerosols than non-invasive respiratory therapies, which conversely can reduce total emissions. We argue the risk of aerosol exposure is underappreciated and warrants widespread, targeted interventions.

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Accepted: 18 March 2021
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Introduction

Infection with SARS-CoV-2 and consequent COVID-19 are a significant cause of mortality and morbidity among patients, healthcare workers and the general population [1, 2]. Many international COVID-19 guidelines state that SARS-CoV-2 transmission is primarily through larger respiratory fluid 'droplets' (> 5 μm diameter), while aerosols (< 5 μm) are only of significant risk during aerosol-generating procedures [3, 4]. Therefore, standard protection against COVID-19 is based on preventing droplet transmission, which includes surgical facemasks, whereas, fit-tested N95/FFP3 respirators and enhanced environmental ventilation are recommended only during aerosol-generating procedures [3, 4]. Aerosols are of concern as they may: contain replication-competent virus; travel on airflows; better evade surgical masks; and deposit on the alveolar epithelium, potentially increasing disease severity [5–9].

Concerningly, a higher prevalence of infection has been observed in healthcare workers caring for COVID-19 patients using droplet compared with aerosol measures [10–12].

The special status accorded to aerosol-generating procedures is based on weak epidemiological evidence from the severe acute respiratory syndrome (SARS) 2003 epidemic, where increased disease transmission occurred in healthcare workers exposed to patients requiring acute respiratory therapies [13]. Aerosols were not measured in these studies [13]. Respiratory therapies such as high-flow nasal oxygen (HFNO) and non-invasive positive pressure ventilation (NIPPV) are universally designated as aerosol-generating procedures [14]. However, these therapies may suppress aerosol emissions by altering pulmonary mechanics or filtering exhaled gases [15]. Earlier studies quantifying aerosols during therapies suggest both increased and decreased emissions [16–19]. A recent study [20] and preprint (Hamilton et al., preprint, https://www.medrxiv.org/content/10.1101/2021.01.29.21250552v1) suggest coughing may generate up to 3-10 times more aerosols than HFNO and NIPPV. However, the methods used in these studies may have underestimated total emissions and exposure risk.

Classification of HFNO and NIPPV as aerosol-generating procedures may have two serious adverse consequences. First, the risk from common respiratory activities may be underestimated, so effective precautions will not be used widely and second, patients may have delayed or restricted access to beneficial therapies [3, 14, 21]. Based on the established mechanisms of physiological aerosol generation, we hypothesised total emissions will be increased by exertional respiratory activity and decreased by clinically indicated therapies [9, 15]. To provide better quantification of risk, we developed a novel chamber aiming to measure total human aerosol emissions during six respiratory activities, and made comparisons with emissions during HFNO, NIPPV and the wearing of surgical facemasks.

Methods

Our protocol was approved by the South Eastern Sydney Ethics Committee and written consent was obtained from all participants. We recruited healthy, non-smoking, healthcare workers using a screening questionnaire and physiological measurements. The chamber was designed combining clean airflow concepts based on the expiratory droplet investigation system (EDIS) as designed by Morawska (Queensland University of Technology, Brisbane, Australia) and the Gesundheitt-II, which employs a large sampling cone as developed by Milton (University of Maryland, Baltimore, MD, USA) (Fig. 1) [22, 23]. The cone was connected to an optical particle counter (OPC) sampling at 100 $l.min^{-1}$ (Aerotrak 9500, TSI Instruments, Shoreview, MN, USA). The optical particle counter counts particles into six size categories or 'bins': 0.5–0.7; 0.7–1; 1–3; 3–5; 5–10; and 10–25 μm.

Subjects wore hooded polypropylene coveralls and were positioned with their heads within the cone. The chamber was purged during quiet breathing, whereby counts fell from ambient (approximately 50,000–70,000 per 100 l) to < 120 total counts per 100 l (0.0012 $particles.ml^{-1}$) and were stable (change < 2 $counts.s^{-1}$). Each sample required a 1 min prior purge, followed by 1 min of activity and sampling, and ended with a sustained purge. Exercise was an exception, where pedalling began 1 min before sampling. The entire protocol lasted approximately 4 h per subject. To minimise potential order effects, six subjects performed the protocol in the order described and four in reverse order.

Ten subjects performed six respiratory activities with and without surgical facemasks and then repeated selected activities whist receiving three respiratory therapies designated as aerosol-generating procedures (online Supporting Information Table S1). The six respiratory activities were chosen because they represent common aerosol-generating activities or were proxies for respiratory symptoms associated with acute infections, such as increased work of breathing and atelectasis. The combinations of activities and therapies were based on practical feasibility and clinical relevance. These were: quiet breathing through either the nose or mouth; repeating the

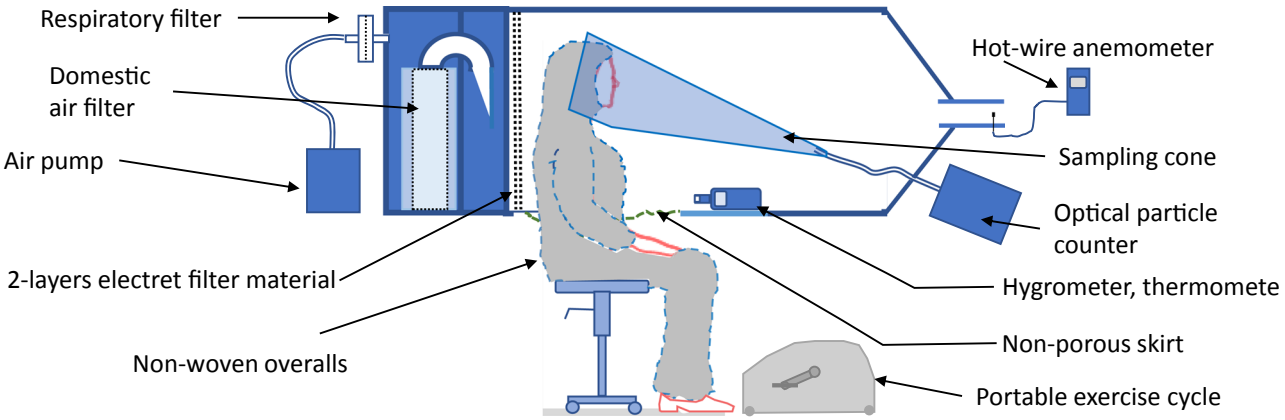

Figure 1 The sampling chamber consists of a rear section containing filters, which supplies clean air through a wall composed of air-filter media, and a clear-walled forward section which accommodates the torso of the subject. A flexible non-porous skirt allows entry of the subject and the tubing of non-invasive devices. The subject's head is positioned within a cut-away section of a large cone, which is attached to an optical particle counter, sampling at 100 $l.min^{-1}$ and mounted outside the chamber. Airflow in the 100-mm diameter tube at the distal end in the chamber is monitored via an anemometer probe. Humidity and temperature were monitored using a hygrometer and thermometer positioned in front of the subject, on the chamber floor. A moveable pedal exerciser was mounted so the subject could exercise in their seated position.

alphabet while talking loudly; repeating a short sentence as loud as can be sustained; six forced expiratory volume (FEV) manoeuvres; six volitional coughs of moderate intensity; and exercise with a pedal exerciser (PhysioRoom, Padiham, UK) set to mid-load (to achieve ~ 70% of maximal estimated heart rate). The six activities were repeated wearing a surgical mask with ties (Med-Con, item 170515, Shepparton, Australia). The timing of the FEVs and volitional coughs was every 7-8 s, finishing at 45 s.

We used three respiratory therapies. First, a C6 ventilator (Hamilton, Bonaduz, Switzerland) delivered humidified HFNO at a temperature of 33°C and FiO_2 of 0.25 via an Optiflow plus circuit and an MR850 humidifier (Fisher and Paykel, Auckland, New Zealand). Flows were delivered at 20, 40 and 60 $l.min^{-1}$ during quiet breathing, and 60 $l.min^{-1}$ during talking, FEVs, coughing and exercise. We then used two types of NIPPV: NIPPV-S with a single circuit in which all exhaled gas directly enters the sampling cone via an unfiltered outlet; and NIPPV-D in which gas leaves the circuit at a distant location and gases sampled in the cone represent leakage from the skin-mask interface or the anti-asphyxia valve. For NIPPV-S, a V60 ventilator (Phillips, Eindhoven, Holland) delivered humidified gas at 33°C, FiO_2 of 0.25 via a Nivairo facemask (RT045, Fisher and Paykel, Milton Keynes, UK) with the open expiratory port positioned inside the sampling cone. For NIPPV-D, the Hamilton-C6 ventilator was used with a high-efficiency air particulate (HEPA) filter on the expiratory limb. For both types of NIPPV, pressures delivered were (peak inspiratory/peak expiratory): 5/5; 10/10; 15/10; 20/10; and 25/10 $cm.H_2O$ during quiet breathing, and 20/10 $cm.H_2O$ during exercise.

Subjects' perception of air deflecting backwards across their face during certain higher velocity exertional activities and when using surgical facemasks prompted an observational study of the behaviour of visible expired plumes using e-cigarette aerosols, a replica transparent cone and two subjects. An unexpected difference in aerosol emissions between NIPPV-S and NIPPV-D prompted a detailed comparison of ventilator performance in two subjects. Both experiments are detailed in online Supporting Information Appendix S1.

Sample size was based on pilot data obtained during protocol development and previous studies [24]. As particle counts were skewed positively, the counts were log-transformed before analysis. To accommodate zero values (which cannot be logged), the transformation included a zero offset, as follows: log-count = $\log_{10}$ (count + 0.3). To compare differences in particle counts between activities and respiratory therapies, a mixed effects linear regression model was used to take account of repeated measures across particle bin sizes and within participants (Proc Mixed, SAS version 9.4, Cary, NC, USA). In all models, the dependent variable was log-count. The main fixed effect was activity or therapy (or both). Reference values were quiet breathing (for activity) and no therapy. To assess the impact of wearing a facemask, the models were repeated with the main fixed effect terms of activity, with and without a facemask. Results are reported as fold differences between

the geometric means of activities and/or therapy with 95% CIs. Particle counts in the six size bins were transformed to estimated particle volumes using the formula, volume = 4/3 × π × radius^3. Further details of data analysis and volume conversion are provided in online Supporting Information Table S2.

Results

The respiratory fluid particles between 0.5 and 25 μm exhaled by 10 healthy subjects during 31 different physiological and therapeutic conditions were counted and size fractionated. Four females and six males of mean (SD) age 29 (2.8) y were recruited. Detailed subject and environmental data are provided in online Supporting Information Tables S3 and S4. When compared with quiet breathing, each of the exertional respiratory activities was associated with a large increase in emissions (Table 1, Figs. 2 and 3, online Supporting Information Table S5). This ranged from a 34.6-fold increase during talking up to a 370.8-fold increase during six coughs (all $p < 0.001$). The emissions are also presented as average total number of particles and as estimated total volumes per particle bin size (Fig. 3, online Supporting Information Table S5).

The three respiratory therapies showed slight increases in total particle counts at higher flows and pressures (Table 1; Fig. 2, online Supporting Information Table S5; Fig. S1) relative to the quiet breathing benchmark. Particle counts reduced when HFNO was used during respiratory activities, and significantly during coughing where emissions were halved ($p = 0.028$). During exercise, the three respiratory therapies reduced particle counts by 30-60%, though only significantly during NIPPV-S ($p = 0.002$) (Table 1, online Supporting Information Fig. S1). The effect of surgical facemasks varied with activity, generally decreasing total emissions with apparent larger reductions observed in activities with higher particle counts (Table 1, online Supporting Information Fig. S1). The 1.2-fold increase in emissions wearing a mask during quiet breathing was not significant ($p = 0.616$).

The majority (> 92%) of particles produced (by number) across all activities and procedures were respirable aerosols (≤ 5 μm) (Fig. 3, online Supporting Information Table S5). The proportion of the total volume of particles that were aerosols ranged between 5.9% and 34.9% for all respiratory activities alone, with coughing producing the greatest proportion, and between 7.1% and 22.4% during HFNO and NIPPV with quiet breathing (Figure 3, online Supporting Information Table S5 and S6).

The intraclass correlation of subjects for all activities with and without devices was 0.065 and 0.068, respectively, indicating substantial variation between subjects in the total number of exhaled particles and the effect of activities and respiratory therapies. Although breathing was consistently a minor contributor to the total volume of particles, the ranking of other activities varied between subjects (online Supporting Information Fig. S2). The removal of the highest contributor had negligible effect on the relative magnitude of changes in particle emissions between activities and therapies (online Supporting Information Table S7).

The qualitative viewing of exhaled e-cigarette aerosols is illustrated in online Supporting Information Fig. S3 and Video S1. This suggests minor incomplete sampling may have occurred with all activities and substantial under-sampling during coughing, FEVs and wearing of surgical masks. The assessment of ventilator performance demonstrated NIPPV-D was associated with 30% more asynchronous respiratory cycles than NIPPV-S (online Supporting Information Table S8).

Discussion

This study is the first to explore near-complete exhaled respiratory emissions and the most detailed in comparing emissions (counts, size distributions and estimated volumes) across a broad range of respiratory activities with three non-invasive respiratory therapies. We have shown that the emissions per min during common exertional respiratory activities are often one to two orders of magnitude greater than during HFNO and NIPPV, which are currently classified as aerosol-generating procedures. Importantly, when these therapies were used during exertional respiratory activities that mimic respiratory illness, emissions were reduced compared with activities alone.

Our study advances and compliments two recent landmark studies which also compared respiratory activities and therapies. Gaeckle et al. found that NIPPV and HFNO did not generate significantly more aerosols compared with other respiratory activities, while coughing increased emissions 3-fold [20]. Hamilton et al. (preprint, https://www.medrxiv.org/content/10.1101/2021.01.29.21250552v1) reported that coughing produces a 10-fold rise in emissions whilst NIPPV-S was associated with fewer emissions than three respiratory activities and HFNO did not increase respiratory-generated aerosols. While comparisons are complicated by their different measures of peak and average counts, they too concluded that coughs were the most likely source of hazardous aerosols irrespective of therapies.

These and other recent studies to quantify respiratory aerosols have collected particles at a short distance from the

Table 1 Fold changes in average total particle counts (geometric mean per size bin) relative to reference activity using log particle counts.

During respiratory activities compared with quiet breathing				
Respiratory activity	**Fold change**	**95%CI**		**p value**
Talking	34.6	15.2–79.1		< 0.001
Exercise	58.0	25.4–132.5		< 0.001
Shouting	163.6	71.6–373.9		<0.001
Forced expirations	227.6	99.6–520.0		<0.001
Coughing	370.8	162.3–847.1		<0.001
During quiet breathing with respiratory therapy compared with quiet breathing alone				
Therapy	**Flow; l.min^{-1}**	**Fold change**	**95%CI**	**p value**
HFNO	20	1.3	0.6–2.4	0.472
	40	1.7	0.9–3.3	0.101
	60	2.3	1.2–4.4	0.031
Therapy	**Airway pressure; cm.H_2O**			
NIPPV-S	5/5	1.5	0.9–2.3	0.079
	10/10	1.3	0.9–2.1	0.185
	15/10	2.1	1.4–3.3	< 0.001
	20/10	2.4	1.5–3.8	< 0.001
	25/10	2.6	1.7–4.1	< 0.001
NIPPV-D	5/5	1.9	1.1–3.3	0.031
	10/10	2.9	1.6–5.0	< 0.001
	15/10	3.1	1.7–5.4	< 0.001
	20/10	4.6	2.6–8.0	< 0.001
	25/10	7.8	4.4–13.6	< 0.001
During exercise with respiratory therapy compared with exercise alone				
Therapy	**Fold change**	**95%CI**		**p value**
HFNO at 60 l.min^{-1}	0.7	0.4–1.3		0.215
NIPPV-S 20/10	0.4	0.2–0.7		0.002
NIPPV-D 20/10	0.7	0.4–1.3		0.214
During breathing activities with HFNO 60 l.min^{-1} compared with activities alone				
Respiratory activity	**Fold change**	**95%CI**		**p value**
Quiet breathing	2.3	1.1–4.9		0.032
Talking	0.9	0.6–1.5		0.728
Forced expirations	0.7	0.4–1.3		0.194
Coughing	0.5	0.3–0.9		0.028
While wearing a surgical facemask compared with without a facemask				
Respiratory activity	**Fold change**	**95%CI**		**p value**
Overall	0.4	0.3–0.6		< 0.001
Quiet breathing	1.2	0.6–2.2		0.616
Talking	0.4	0.2–0.9		0.032
Exercise	0.7	0.4–1.1		0.079
Shouting	0.3	0.1–0.6		0.005
Forced expirations	0.3	0.1–0.8		0.020
Coughing	0.2	0.1–0.6		0.011

HFNO, high-flow nasal cannula therapy with flow in l.min^{-1}; NIPPV-S and NIPPV-D, non-invasive positive pressure ventilation (single and dual circuits, respectively) with inspiratory/expiratory airway pressures shown in cm.H_2O.

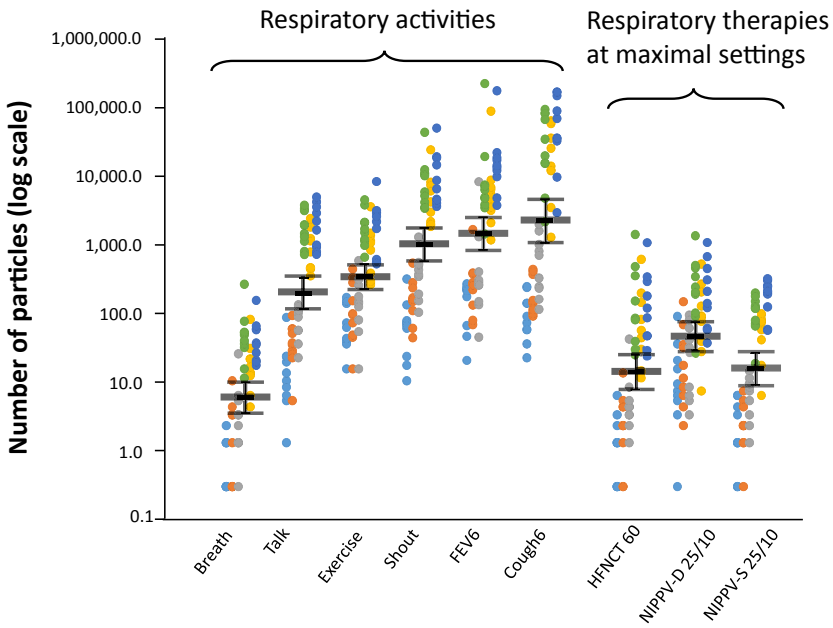

Figure 2 The total number of exhaled respiratory particles sampled from ten subjects. Samples were measured over a period of 1 min during six respiratory activities and when breathing quietly while three respiratory therapies, designated as aerosol-generating procedures, were applied. The therapies were high-flow nasal oxygen (HFNO) and non-invasive positive pressure ventilation with a single (NIPPV-S) or dual (NIPPV-D) circuit. All respiratory therapies shown were recorded at the highest settings used: HFNO at a flow of 60 $l.min^{-1}$ and both NIPPV-S and NIPPV-D at inspiratory/expiratory airway pressures of 25/10 $cm.H_2O$. The geometric mean and upper and lower 95% confidence intervals are shown by the black bars (⧧). The size range in the six particle bins as measured by the optical particle counter are: 10–25 μm (light blue); 5–10 μm (orange); 3–5 μm (grey); 1–3 μm (green); 0.7–1 μm (yellow); and 0.5–0.7 μm (dark blue). A value of 0.3 was added to all counts to facilitate analysis after log transformation, so zero particle counts are shown as 0.3. Overlapping dot points are not shown. Both the forced expiratory volume (FEV) manoeuvre and cough were repeated six times in the sampling min.

subject, using a small sampling inlet positioned in free space with very low air sampling rates, typically of 1-5 $l.min^{-1}$ [20, 25–28]. Accurately sampling exhaled aerosols is made challenging by airflows in excess of 600 $l.min^{-1}$, nebulous plumes travelling up to 60 $m.s^{-1}$, downward directed exhalations during certain phonetic phonemes and the addition of high volumes of ventilator gases [26, 27]. To minimise incomplete sampling by an unknown degree, we positioned the subjects' heads within a large cone and sampled at 100 $l.min^{-1}$, attempting to capture as close to total emissions as possible. This novel approach could explain why our study demonstrates such markedly increased overall fold differences compared with previous studies of both respiratory activities and respiratory therapies [20, 25–28].

Our study is consistent with several others in demonstrating exertional respiratory activities dramatically generate aerosols, which increase with speech loudness, greater breathing rate and volume and particularly during coughing [24–26, 29–31]. From the perspective of the physiological factors involved, the increases with activities are associated with rises in subglottic pressure, aerodynamic shear stresses and vocal fold and terminal airway open-closure frequency [9, 25, 28, 31–33].

In contrast, we saw modest rises in emissions during respiratory therapies and these were restricted to non-exertional respiratory activities. Of note, the pressure changes and flow velocities generated during respiratory therapies are far less than during respiratory exertion [34–36]. During quiet breathing with HFNO, the slight increase in emissions as flow rises may be due to turbulence within the upper airways. During NIPPV, rising pressure may generate increases through greater tidal volumes and subsequent airway open-closure. The increase in emissions with NIPPV-D may be explained by a greater degree of ventilator-subject desynchrony, which could create pressure spikes within the facemask, causing leaks and aerosol generation at the mask-skin interface [9, 37, 38]. All the increases in emissions with respiratory therapies were small compared with those with exertional respiratory activities and are likely only detectable because of our sampling system and very low background counts. Our study suggests the physiological benefits of positive airway pressure, which splints open airways and reduces the

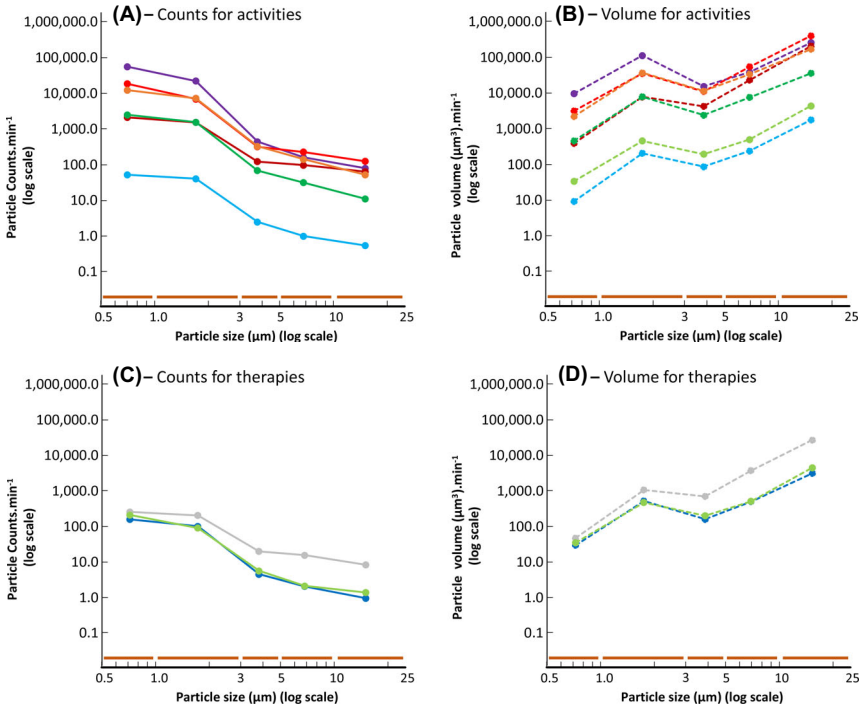

Figure 3 A and C show the geometric mean of the total number of particles for 10 subjects, for six respiratory activities (A) and three respiratory therapies (C) by particle size. B and D show the geometric mean of the total estimated respiratory fluid volume for 10 subjects, for six respiratory activities (B) and three respiratory activities (D) by particle size. The therapies were: high flow nasal oxygen (HFNO) (light blue) and single (NIPPV-S) (green) or dual (NIPPV-D) (grey) circuit non-invasive positive pressure ventilation. All respiratory therapies shown were recorded at the highest settings used: HFNO at a flow of 60 $l.min^{-1}$ and both NIPPV-S and NIPPV-D at inspiratory/expiratory airway pressures of 25/10 $cm.H_2O$. Both forced expiratory reserve volume manoeuvres and cough were repeated six times in the sampling min. Particle size bin boundaries are indicated above the x-axis (orange line). The log centre of each bin is used as the particle size value. The numbers and volumes from the 0.5–0.7 µm and 0.7–1 µm size bins have been combined. The respiratory activities and therapies are: quiet breathing (light blue); exercise (dark red); talking (green); shouting (orange); forced expiratory volumes (light red); and coughing (blue). Particle number is indicated by a solid line, volume by a dashed line.

pressure changes required to breath efficiently, may reduce aerosols [15, 35, 36]. The inclusion of exercise and forced expiratory manoeuvres, as proxies for symptomatic laboured breathing and atelectasis, suggests an aerosol-suppressing role for such therapies in patients with respiratory distress. Total aerosol emissions during non-invasive respiratory therapy reflect a balance between the aerosol-generating effects of gas flow and pressure detectable during quiet breathing, and aerosol-suppressing effects which predominate during exertional respiratory activities.

When a surgical mask was worn, the apparent filtration increased during higher velocity activities. However, our video study suggests this was partly due to masks deflecting gas away from the collecting cone. This is consistent with other studies showing sideways leakage with surgical masks [39, 40]. While this deflection may blunt the forward plume and remove large droplets, reducing direct person-to-person exposure, aerosols could still accumulate in poorly ventilated spaces [15].

Our study's strengths are that we were able to capture almost all of the particles emitted over the relevant size range of 0.5–25 µm during both respiratory activities and therapies, with negligible background contamination. By viewing the complex exhaled airflow patterns, we demonstrated that our method captures most respiratory aerosols during several of the activities and all the therapies. Our analysis model separately considered different-sized particles and their estimated volumes as opposed to only total particle counts as in some other studies. The estimations of total volume serve as a unifying comparator between activities, therapies and subjects and enables future exposure risk modelling during numerous scenarios.

There are several limitations to our study. We recruited 10 healthy subjects who performed a single protocol run. There may have been some differences in how subjects performed activities, which may contribute to the previously observed wide inter-subject variation [25, 29]. We estimated the average residence time for particles in the cone should have been sufficient for them to reach equilibrium diameter [41]. However, given wide variation between activity airflows, volumes and the addition of humidified therapy gases, we are unsure exactly what proportion of variation in size distributions is physiological or methodological. Our video study shows cough and FEV are incompletely sampled, highlighting that the most aerosol-generating activities are also the most challenging to comprehensively measure due to high airflow velocities. We have not modelled NIPPV aerosol emissions during mask removal but have quantified the aerosol content in unfiltered exhaled gas by using NIPPV-S. Hamilton et al. (preprint, https://www.medrxiv.org/content/10.1101/2021.01.29.21250552v1) did examine both mask leak and removal and found little evidence of increased aerosol emission. Our attempts to model acute respiratory physiology and symptoms with volitional activities are likely to differ from patients with COVID-19. However, Hamilton et al. reported a comparable skew in particle size distribution in both COVID-19 patients and healthy controls, suggesting potential similarity. Crucially, all studies measuring aerosols are limited by not quantifying viable virus. Acquiring high-quality data outside of controlled laboratory conditions is challenging, but these are needed to establish if physiological exertion and respiratory symptoms increase total viral and aerosol emissions in infected patients, as our study suggests.

Our data suggest aerosol generation from the gas flows and pressures delivered by respiratory therapies were unlikely to be the primary cause of the observed association between their use and transmission of disease during the SARS-CoV-1 epidemic, which underpins the current 'aerosol-generating procedure' model [13]. The therapies were indicated for worsening acute respiratory failure, suggesting patients' respiratory activities will have included fast, deep breathing, coughing and terminal airway closure. Our study suggests these exertional respiratory activities result in a high output of aerosols. This could expose staff to the risk of disease transmission during any periods of close care, irrespective of use of specific respiratory therapies. Indeed, the use of respiratory therapies may suppress aerosol emissions in this setting (though emission levels are likely to be considerably greater than during quiet breathing). It seems plausible, if aerosols were responsible for disease transmission in this historic setting, they were physiologically and not procedurally generated. This distinction is important as protective measures targeting aerosol-based transmission are currently prioritised based solely on procedure, regardless of clinical, physiological and environmental context [3, 4].

In summary, our data add to a small but growing number of quantitative studies that challenge the rationale for describing certain respiratory therapies as aerosol-generating procedures [17–20]. Patients acutely requiring HFNO or NIPPV are likely to present a high disease transmission risk due to their propensity to produce aerosols, but we find no basis for withholding or delaying access to these therapies. We conclude instead that exertional respiratory activities themselves are the primary modes of aerosol generation and represent a greater transmission risk than is widely recognised currently. Therefore, increased measures targeting physiologically generated aerosols could protect patients, healthcare workers and the public from respiratory pathogens, including SARS-CoV-2.

Acknowledgements

This study was supported by a Prince of Wales Hospital Foundation research grant. We acknowledge the subject volunteers for their participation and the Intensive Care Department at the Prince of Wales Hospital for their support. For providing comments on our manuscript, we thank: M. Jermy; A. McNarry; K. Brohi; J. Morgenstern; D. Waters; D. Bihari; M. Johns; M. Theaghlach; D. Carruthers; P. Dwan; R. McCusker; R. Rowley; and A. Thaventhiran. No other external funding or competing interests declared.

References

1. Amnesty International. Mapping health worker deaths from COVID-19. 2020. https://www.amnesty.org/en/latest/news/2020/09/mapping-covid19-health-worker-deaths/ (accessed 04/01/2021).
2. Heneghan C, Howdon D, Oke J, Jefferson T. The ongoing problem of UK hospital acquired infections - the centre for evidence-based medicine. The Centre for Evidence-Based Medicine - University of Oxford. 2020. https://www.cebm.net/covid-19/the-ongoing-problem-of-hospital-acquired-infections-across-the-uk/ (accessed 04/01/2021).
3. The World Health Organisation (WHO). Scientific brief. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions (accessed 21/01/2021).
4. Public Health England. COVID-19: infection prevention and control (IPC). 2021. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control (accessed 30/01/2021).
5. Fennelly KP. Particle sizes of infectious aerosols: implications for infection control. *Lancet Respiratory Medicine* 2020; **8**: 914–24.

6. Lednicky JA, Lauzard M, Fan ZH, et al. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. *International Journal of Infectious Diseases* 2020; **100**: 476–82.
7. Nissen K, Krambrich J, Akaberi D, et al. Long-distance airborne dispersal of SARS-CoV-2 in COVID-19 wards. *Scientific Reports* 2020; **10**: 19589.
8. Tellier R, Li Y, Cowling BJ, Tang JW. Recognition of aerosol transmission of infectious agents: a commentary. *BMC Infectious Diseases* 2019; **19**: 101.
9. Mittal R, Ni R, Seo JH. The flow physics of COVID-19. *Journal of Fluid Mechanics* 2020; **894**: F2.
10. Lai X, Wang M, Qin C, et al. Coronavirus Disease 2019 (COVID-2019) infection among Health care workers and implications for prevention measures in a tertiary hospital in Wuhan, China. *Journal of the American Medical Association: Network Open* 2020; **3**: e209666.
11. Zhong Q, Liu YY, Luo Q, et al. Spinal anaesthesia for patients with coronavirus disease 2019 and possible transmission rates in anaesthetists: retrospective, single-centre, observational cohort study. *British Journal of Anaesthesia* 2020; **124**: 670–5.
12. Cook TM, Lennane S. Occupational COVID-19 risk for anaesthesia and intensive care staff – low-risk specialties in a high-risk setting. *Anaesthesia* 2020; **76**: 295–300.
13. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012; **7**: e35797.
14. Jackson T, Deibert D, Wyatt G, et al. Classification of aerosol-generating procedures: a rapid systematic review. *British Medical Journal: Open Respiratory Research* 2020; **7**: 730.
15. Wilson NM, Norton A, Young FP, Collins DW. Airborne transmission of severe acute respiratory syndrome coronavirus-2 to healthcare workers: a narrative review. *Anaesthesia* 2020; **75**: 1086–95.
16. Dhillon RS, Rowin WA, Humphries RS, et al. Aerosolisation during tracheal intubation and extubation in an operating theatre setting. *Anaesthesia* 2020; **76**: 182–8.
17. Thompson KA, Pappachan JV, Bennett AM, et al. Influenza aerosols in UK hospitals during the H1N1 (2009) pandemic - the risk of aerosol generation during medical procedures. *PLoS One* 2013; **8**: e56278.
18. Brown J, Gregson FKA, Shrimpton A, et al. A quantitative evaluation of aerosol generation during tracheal intubation and extubation. *Anaesthesia* 2020; **76**: 174–81.
19. Jermy MC, Spence CJT, Kirton R, et al. Assessment of dispersion of airborne particles of oral/nasal fluid by high flow nasal cannula therapy. *PLoS One* 2021; **16**: e0246123.
20. Gaeckle NT, Lee J, Park Y, Kreykes G, Evans MD, Hogan CJ. Aerosol generation from the respiratory tract with various modes of oxygen delivery. *American Journal of Respiratory and Critical Care Medicine* 2020; **202**: 1115–24.
21. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: Guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetist. *Anaesthesia* 2020; **75**: 785–99.
22. Yan J, Grantham M, Pantelic J, et al. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. *Proceedings of the National Academy of Sciences of the United States of America* 2018; **115**: 1081–6.
23. Morawska L, Johnson GR, Ristovski ZD, et al. Size distribution and sites of origin of droplets expelled from the human respiratory tract during expiratory activities. *Journal of Aerosol Science* 2009; **40**: 256–69.
24. Larsson P, Bake B, Wallin A, et al. The effect of exhalation flow on endogenous particle emission and phospholipid composition. *Respiratory Physiology and Neurobiology* 2017; **243**: 39–46.
25. Asadi S, Wexler AS, Cappa CD, Barreda S, Bouvier NM, Ristenpart WD. Aerosol emission and superemission during human speech increase with voice loudness. *Scientific Reports* 2019; **9**: 1–10.
26. Bake B, Larsson P, Ljungkvist G, Ljungström E, Olin A-C. Exhaled particles and small airways. *Respiratory Research* 2019; **20**: 8.
27. Johnson GR, Morawska L. The mechanism of breath aerosol formation. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2009; **22**: 229–37.
28. Gregson FKA, Watson NA, Orton CM, et al. Comparing aerosol concentrations and particle size distributions generated by singing, speaking and breathing. *Aerosol Science and Technology* 2021 Epub 26 February. https://doi.org/10.1080/02786826.2021.1883544.
29. Bake B, Ljungström E, Claesson A, Carlsen HK, Holm M, Olin AC. Exhaled particles after a standardized breathing maneuver. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2017; **30**: 267–73.
30. Almstrand AC, Bake B, Ljungström E, et al. Effect of airway opening on production of exhaled particles. *Journal of Applied Physiology* 2010; **108**: 584–8.
31. Johnson GR, Morawska L, Ristovski ZD, et al. Modality of human expired aerosol size distributions. *Journal of Aerosol Science* 2011; **42**: 839–51.
32. Kwon SB, Park J, Jang J, et al. Study on the initial velocity distribution of exhaled air from coughing and speaking. *Chemosphere* 2012; **87**: 1260–4.
33. Lagier A, Legou T, Galant C, Amy de La Bretèque B, Meynadier Y, Giovanni A. The shouted voice: a pilot study of laryngeal physiology under extreme aerodynamic pressure. *Logopedics Phoniatrics Vocology* 2017; **42**: 141–5.
34. Gupta JK, Lin CH, Chen Q. Flow dynamics and characterization of a cough. *Indoor Air* 2009; **19**: 517–25.
35. Ricard J-D, Roca O, Lemiale V, et al. Use of nasal high flow oxygen during acute respiratory failure. *Intensive Care Medicine* 2020; **46**: 2238–47.
36. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *The Lancet* 2009; **375**: 250–9.
37. Hess DR. Patient-ventilator interaction during noninvasive ventilation. *Respiratory Care* 2011; **56**: 153–67.
38. Schettino G, Tucci M, Sousa R, Barbas C, Amato M, Carvalho C. Mask mechanics and leak dynamics during noninvasive pressure support ventilation: a bench study. *Intensive Care Medicine* 2001; **27**: 1887–91.
39. Verma S, Dhanak M, Frankenfield J. Visualizing the effectiveness of face masks in obstructing respiratory jets. *Physics of Fluids* 2020; **32**: 61708.
40. Tang JW, Liebner TJ, Craven BA, Settles GS. A schlieren optical study of the human cough with and without wearing masks for aerosol infection control. *Journal of the Royal Society Interface* 2009; **6**(S6): 727–36.
41. Nicas M, Nazaroff WW, Hubbard A. Toward understanding the risk of secondary airborne infection: emission of respirable pathogens. *Journal of Occupational and Environmental Hygiene* 2005; **2**: 143–54.

Supporting Information

Additional supporting information may be found online via the journal website.

Figure S1. Fold changes in particle numbers and 95% CIs plotted on a log scale with different aerosol-generating procedures and masks.

Figure S2. Total volumes of particles generated by six different activities by each subject.

Figure S3.1-3.10. Series of photographs from Video S1 to illustrate specific exhaled gas sampling behaviour.

Table S1. Activities are shown in columns and devices in rows.

Table S2. Particle size to volume conversion table used to convert particle number to particle volume.

Table S3. Subject baseline demographic data.

Table S4. Recordings of temperature and relative humidity from within the chamber during the title experiment.

Table S5. The distribution of particle number and total sum of particle volumes.

Table S6. Physiological data during exercise while receiving non-invasive positive pressure ventilation.

Table S7. Recorded ventilator variables in a two-subject study.

Table S8. Fold difference in particle counts for respiratory activities and respiratory therapies all compared with quiet breath, for all subjects (n = 10) and with the subject contributing highest emission is removed (n = 9).

Video S1. Study establishing exhaled gas sampling efficiency during different respiratory therapies and activities using replica apparatus.

Appendix S1. Further description of the methods used for these experiments.