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PRECLINICAL VALIDATION OF OCCUPATIONAL AND ENVIRONMENTAL SAFETY OF AN ISOLATION SYSTEM FOR NON-INVASIVE VENTILATION IN COVID-19 AND OTHER AEROSOL-TRANSMITTED INFECTIONS.

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Contributorship statement.

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Preclinical validation of occupational and environmental safety of an isolation system for non-invasive ventilation in COVID-19 and other aerosol-transmitted infections

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Abstract

Background: Current SARS-CoV-2 pandemic has provoked the collapse of some health systems due to insufficient intensive care unit capacity. The use of continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO) therapies have been limited in consideration of the risk of occupational infection in healthcare professionals.

Aims: In preclinical experimental simulations, evaluate occupational and environmental safety of the newly developed isolation system for aerosol transmitted infections (ISATI).

Method: Simulations were conducted to test ISATI's capability to isolate aerosolized molecular (caffeine), and biological (SARS-CoV-2 synthetic RNA) markers. Caffeine deposition was analyzed on nitrocellulose sensor discs by proton nuclear magnetic resonance spectroscopy. Synthetic SARS-CoV-2 detection was performed by reverse transcription polymerase chain reaction.

Results: ISATI demonstrated efficacy in isolating molecular and biological markers within the enclosed environment in simulated conditions of CPAP, HFNO and mechanical ventilation therapy. Neither the molecular marker nor substantial amounts of synthetic SARS-CoV-2 RNA were detected in the surrounding environment, outside ISATI, indicating appropriate occupational safety for healthcare professionals.

Conclusion: Aerosolized markers were successfully contained within ISATI in all experimental simulations, offering occupational and environmental protection against the dissemination of aerosolized microparticles under CPAP or HFNO therapy conditions, which are indicated for patients with acute respiratory infections.

Keywords: Occupational respiratory infection; isolation devices respiratory infection; COVID-19; influenza; high-flow oxygen; continuous positive airway pressure

1. Introduction

Respiratory viruses can be highly infectious, mainly due to person-to-person transmission through respiratory droplets produced by expiration, coughing or sneezing [1]. Infected individuals present a range of clinical manifestations, from flu-like symptoms to severe pneumonia, in some cases necessitating oxygen support and/or hospitalization [1,2]. Reports of viral aerosol transmission, notably in hospital environments, presents a challenge to the occupational safety of health professionals [1,3-5]. In the SARS-CoV-1 outbreak in Canada in 2003, half of all cases resulted from the nosocomial contamination of health professionals [6]. Studies indicate that coronavirus particles can remain viable in external environments for hours, supporting the notion of high rates of incidence with regard to occupational contamination [7-9].

As health care professionals face a greater risk of transmission during aerosol-generating procedures performed in patients infected with respiratory viruses, strict requirements have been implemented with regard to the use of non-invasive ventilation (NIV), continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO) therapies [5,6,10-12]. The isolation of rooms by laminar air flow and negative pressure has made the widespread use of NIV and HFNO infeasible in the face of the COVID-19 pandemic [6,10-12]. In an effort to avoid hospital airflow system contamination by aerosolized viral particles generated when performing HFNO and CPAP therapies, these procedures are often not performed even when indicated [6,10-12].

The COVID-19 pandemic has demonstrated the capacity of respiratory viruses to collapse healthcare systems worldwide [11,13]. COVID-19 patients who progress to respiratory failure, necessitating orotracheal intubation and prolonged periods of mechanical ventilation during hospitalization, have placed high demands on intensive care units (ICU) [6,11,13]. Treatment guidelines designed to limit aerosol transmission by COVID-19 patients have recommended early orotracheal intubation with mechanical ventilation, further exacerbating pressure on hospital ICUs [6]. In several countries, baseline ICU bed capacity has been exceeded [11,13]. In this scenario, emergency temporary measures, including treating hypoxemic COVID-19 patients with CPAP or HFNO, were not possible due to occupational contamination risk, despite these oxygen support therapies being appropriate therapeutic alternatives for affected patients [6,10,14,15].

This manuscript describes preclinical experiments for validation of an easily implementable system for the isolation of patients with respiratory virus infection, denominated Isolation System for Aerosol Transmitted Infections (ISATI). The objective is to safely enable an alternative for oxygen delivery via NIV or HFNO for patients with mild or moderate hypoxemia, especially in hospital environments challenged by infectious aerosol transmission with deficient ICU capacity. ISATI has been designed to prevent viral contamination in hospital environments, and thus increase the occupational protection of health professionals and other hospitalized patients. The present report aims to evaluate the effectiveness of the proposed system in retraining the dissemination of aerosolized molecular and biological markers in simulated CPAP, HFNO and mechanical ventilation procedures.

2. Methods

2.1 Description of the Isolation System for Aerosol Transmitted Infections (ISATI)

ISATI possesses two distinct security features: a physical barrier between the patient and the external environment, and a microparticle filter for connection to hospital vacuum pump systems. The physical barrier consists of a transparent polyethylene plastic cover (measuring 5x4x0.001m) manufactured by Bhiosupply®. To maintain the plastic cover elevated over the patient, a sterilizable, stainless steel structure was designed (Bhiosupply®), which allows the system to dynamically adapt to any type of hospital bed and also enables the hospital bed to be fully elevated. The sizeable plastic cover surrounds the entire hospital bed and is fixed to the inferior part of the bed via a polyester and elastane elastic band (Figure 1). A 0.1-0.2μ porous membrane microparticle filter (Bhiosupply®) enables connection to a hospital vacuum pump system or can be connected to another vacuum pump at a suction pressure outflow rate of 40 L/min. The air suction system connected to the microparticle filter aspirates continuously the air under the plastic cover. The disposable components of ISATI are the plastic cover and microparticle filter. Non-disposable autoclavable components are fabricated from stainless steel.

2.2 Molecular marker analysis by proton nuclear magnetic resonance spectroscopy

Chemical monitoring (internal and external) was performed using strategically positioned pairs of nitrocellulose discs (NC 47mm 8.0µ) used as sensors to detect the molecular marker (Figure 2), caffeine (1,3,7-trimethylpurine-2,6-dione), which was dispersed (1% w/v solution) within the ISATI via either pressurized aerosolization or nebulization. The air suction system under the plastic cover was activated during all experiments. Upon conclusion of each experiment, all sensor discs were removed and placed inside 5 mL Eppendorf tubes protected from light for posterior analysis.

All sensor discs were sonicated in their respective Eppendorf flasks for 5 minutes in a 0.6 mL D_2O solution containing 0.2% TSP-d4 [3- (trimethylsilyl) propionate-2,2,3,3 -d4 sodium]. The extracted solution was then analyzed by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR).

All ^{1}H-NMR analysis was performed using a 14.1 Tesla (600 MHz for hydrogen frequency) Bruker AVANCE III HD 600 MHz nuclear magnetic resonance spectrometer, using a 5 mm proton-optimized triple cryo-probe, with the sampling temperature maintained at 298K during the entire analysis using a pulse sequence with a continuous wave pre-saturation and gradient field. The following acquisition parameters were utilized: acquisition time (AQ=4.18s), relaxation delay (d1=1s), spectral width (SWH=7837 Hz), number of scans (ns=128), received gain (rg=128) and pulse duration (p1=7.7 µs). The obtained readings were processed using TopSpin® software (Bruker version 3.5 pl7) without apodization. For detection limit determination of 1 ppm, a water 1% caffeine solution was used, using identical acquisition and processing conditions as described above.

2.3 Production of synthetic SARS-CoV-2 RNA and reverse transcription polymerase chain reaction amplification

Sequences of the amplification sites of SARS-CoV-2 genes E, RdRp and N, along with the T7 promoter sequence, were synthetized as duplex DNA oligonucleotides; in vitro transcription was performed using a T7 RiboMAX™ Express Large Scale RNA Production System (Promega, Madison, WI, USA) in accordance with the manufacturer's instructions. The generated synthetic RNA transcripts were mixed in 15 mL of 0.9% NaCL solution at the following concentrations: 10^{10} RNA copies/mL for the E gene and 10^7 RNA copies/mL for genes N and RdRp. Detection was performed by reverse transcription polymerase chain reaction (RT-PCR) using a commercially available multiplex kit (Allplex™ 2019-nCoV Assay - Seegene, Seoul, South Korea), following the manufacturer's instructions. RT-PCR was performed on a 7500 Fast Real Time PCR system (ThermoFisher Scientific, Waltham, MA, USA) using a total of 45 amplification cycles for each tested sample. Amplification of the nucleic acid was detected by accumulation of a fluorescent signal, giving a cycle threshold (Ct) value, which is inversely proportional to the amount of target nucleic acid in the sample

2.4 NIV with CPAP simulation

In all experimental simulations, an Airway Management Trainer manikin (Laerdal®) was placed on a hospital bed inside the ISATI enclosure. To simulate hypoxic conditions associated with respiratory viruses, a tube was attached to the manikin to simulate intravenous therapy, in addition to multiparameter patient monitoring cables and respirator tubes. CPAP was performed using an orofacial mask set at a continuous positive pressure of 15 cm H_20, programmed to 14 breaths/minute. In the two initial CPAP simulations, 15 mL of caffeine solution (1% in D_2O) was sprayed inside the ISATI using a BhioQap® spraying device under high-pressure aerosolization (average pressure of 200 psi) at a flow rate of 2 mL/s for a period of 90 minutes. A vacuum pump was activated to remove air from inside the ISATI at flow rate of 40 L/min throughout the duration of the experiment. In a third CPAP simulation scenario, 15 mL of caffeine solution was aerosolized using a medical nebulizer, with the hospital's vacuum pump system again used to remove air from inside the ISATI. In a fourth CPAP experiment, a 15 mL suspension of 0.9% NaCL containing 10^{10} RNA copies/mL of the E gene, as well as 10^7 RNA copies/mL of N and RdRp genes, was sprayed inside the ISATI using a nebulizer with internal suction maintained via the hospital's vacuum pump system for 60 minutes. Samples were collected using swabs inside and outside the ISATI for RT-PCR analysis; three samples were collected for each position used for the sensor disks used to detect the molecular marker. Importantly, sensors for molecular marker identification were only removed, and samples for RT-PCR analysis were only collected, including those on the health

professional's chest (figure 2), following the complete disassembly of the ISATI, including disposal of the plastic cover and all disposable items.

2.5 HFNO simulation

To simulate HFNO, the same experimental setting was established as described above. A nasal cannula was positioned in the airway of the manikin (Laerdal®) with an oxygen flow setting of 80 L/minute. A nebulizer was used to spray 15 mL of a 0.9% NaCL solution containing 10^{10} RNA copies/ml of the E gene, in addition to 10^7 RNA copies/mL of genes N and RdRp, inside the ISATI, with air suction via a hospital vacuum pump system maintained during the entire 60-minute experimental period. Samples were collected from inside and outside the ISATI for RT-PCR analysis at the same positions as described for NIV with CPAP simulation. Samples for RT-PCR analysis were only collected, including those on the health professional's chest (figure 2), following the complete disassembly of the ISATI, including disposal of the plastic cover and all disposable items.

2.6 Mechanical ventilation simulation

The ISATI was assembled using the same configuration described in the previous sections. Over a 6-hour period, three aerosolizations, at 120-minute intervals, of 10 mL of the 1% caffeine solution were achieved using a pump delivering 200 psi of pressure (BhioQap®) at a flow rate of 2 mL/s. Again airflow exhaust was performed by connecting the ISATI to the hospital vacuum pump system at a flow rate of 40 L/min. Another simulation conducted over a 6-hour period was performed using continuous nebulization while connected to the hospital vacuum pump system. In both experiments, nitrocellulose sensor discs were collected every two hours. At the end of the 6-hour period, sensors for molecular marker identification were only removed, including those on the health professional's chest (figure 2), following the complete disassembly of the ISATI, including disposal of the plastic cover and all disposable items.

3. Results

Similar results were obtained using high pressure aerosolization (average pressure of 200 psi) versus aerosolization with a nebulizer. In both simulation scenarios the internal environment of the ISATI was saturated with droplets. ISATI's internal air suction method, when connected to hospital's vacuum system or using a pump machine with suction pressure of 40 L/min, did not interfere in the results. No traces of the molecular marker were detected on any of the sensor discs positioned outside the ISATI.

The standard ^{1}H-NMR spectra analysis of the caffeine solution, depicting a typical signature for this molecule, is shown in Figure 3, Spectrum A. The chemical shifts (δ) of the methyl groups (δ = 3.28; 3.45; 3.91 ppm) and of the purine hydrogen (δ 7.88 ppm) are evident. A similar pattern is observed in spectrum D (yellow line), which corresponds to the sensor discs positioned inside the ISATI (positive control sensors) (figure 2, position 4) during the NIV with CPAP simulation. However, this signature is not evidenced in either spectrum B, the sensor disc positioned at the entrance of the patient monitoring cables and respiratory tubes (figure 2, position 1), or spectrum C, the disc placed just below the point where intravenous therapy tube was positioned (figure 2, position 2), indicating the absence of caffeine molecules, and thus the efficiency of the ISATI.

Figure 4 presents the ^{1}H-NMR spectra analysis of sensor discs following a 6-hour mechanical ventilation simulation with a caffeine solution sprayed at 120-minute intervals inside the ISATI. Caffeine molecules were not found on any of the sensor discs except position 4 (spectrum E), the control sensor located inside the ISATI.

After determining the isolation efficacy of the ISATI through ^{1}H NMR analysis using caffeine as a molecular marker, we next evaluated its efficacy using synthetic viral particles to better emulate a clinical scenario involving infected patients.

Figure 5A illustrates that undetectable levels of synthetic viral RNA (10^7 SARS-CoV-2 RNA copies/mL) were found in samples collected from the external environment of the ISATI following simulated aerosolization experiments. The N gene of the synthetic viral RNA was only detected in samples collected from positions inside the ISATI, identified as number 10 (internal surface #2, the inner surface

of the plastic cover), position 11 (manikin) and 12 (HEPA filter, the air inflow side of the microparticle filter used to connect to the hospital vacuum system, located inside the ISATI). The RdRp gene was also only detected in the samples collected from inside the contaminated ISATI environment, at positions 11 and 12 (figure 5A).

To simulate a more extreme viral particle concentration environment, the E gene (10^{10} synthetic SARS-CoV-2 viral RNA per mL, 15 mL of solution) was found to be detectable in all analyzed samples. Here a scattering gradient was observed, with much higher concentrations identified inside the ISATI with gradually reduced levels found in the external environment (figure 5B).

4. Discussion

Experimental testing under all simulated conditions indicated that ISATI effectively contained the molecular marker evaluated, 1 ppm of caffeine, without leading to contamination in the surrounding external environment during and after the performed simulations, as determined by ^{1}H-NMR analysis of sensor discs.

The simulated conditions in this study were designed to be more critical than actual medical situations. For 900 minutes in the simulations, the caffeine solution was aerosolized under high pressure (average pressure of 200 psi), equivalent to approximately 14,000 cm H_2O, which is much higher than that used in NIV with CPAP (max. 30 cm H_2O). All experimental simulations resulted in the internal environment of ISATI becoming saturated with the aerosolized solution, with clearly visible droplet formation inside the plastic cover.

Experimental simulations also involved concentrations of synthetic RNA particles aerosolized inside the ISATI that simulated much more infectious conditions than the virus concentrations described in clinical settings [4,9,16]. The aerosolization of Synthetic RNA virus at a concentration of 10^7 copies/mL was equivalent to 150 million virus particles, considering that 15 mL of solution was aerosolized inside ISATI. It simulated a condition with extremely high virus air concentration, not identified in publications describing virus air concentrations in clinical settings [4,9]. The concentration of 10^{10} synthetic RNA copies/mL aerosolized 150 billion viral particles in 15 mL of solution, simulating an inconceivable clinical condition not described in scientific publications in the context of respiratory airborne virus conditions [4,9,16]. This extreme viral particle concentration was intentionally used to certify that small amounts of synthetic virus particles could be detected outside the ISATI, and was not designed to evaluate the system's efficacy.

Sars-CoV-2 concentrations in throat and sputum samples of infected patients have reportedly ranged from 641 copies per mL to $1.34x10^{11}$ copies per mL, with a median of $7.99x10^{\square}$/mL in throat samples and $7.52x10^{\square}$/mL in sputum samples [15]. Studies identify lower environmental concentrations of SARS-CoV-2 particles than levels found in infected patients' throats and saliva [4,9,16]. Studies have also indicated that airborne virus concentrations near hospitalized COVID-19 patients present maximum concentrations of $4.82x10^4$/mL in the air next to patients receiving oxygen by nasal cannula [4,9]. Mean air virus concentrations in patient rooms had the highest values at $2.86x10^3$/mL [4].

SARS-CoV-1 infected patients were reported to present saliva concentrations of $7.08x10^3$ to $6.38x10^8$ copies per mL (median: $9.92x10^4$ copies/mL) [17]. Data on SARS-CoV-1 nasopharyngeal concentrations ranges from $1.7x10^3$/mL to $3.4x10^7$/mL [17,18]. Airborne SARS-CoV-1 concentrations near infected patients ranged from $1.1x10^1$ to $1.3x10^5$ copies/mL [19]. The number of SARS-CoV-1 particles expelled per cough in infected patients was shown to be less than that found in nasopharynx [18-20]. SARS-CoV-1 cough concentrations ranged from 900 particles to $3.02x10^5$ particles/mL/cough [20].

Average air concentrations of viral load in influenza were found to be $4x10^5$ copies/mL up to 0.3 meters away from infected patients, while higher numbers of particles ($1.9x10^6$) were identified closer to patients [21].

Published data on virus concentrations in the air near infected patients with influenza virus, SARS-CoV-1 and Sars-CoV-2 indicate that total viral concentrations do not exceed 10^6 particles/mL even in the presence of aerosol-producing medical procedures [4,9,19-21]. These data confirm that the synthetic virus concentration used in the present study (10^7 copies/mL) to evaluate the efficacy of the ISATI is considerably higher than the expected air concentrations found near patients infected with respiratory viruses [4,9,19-21].

Airborne viral concentrations of SARS-CoV-1 and Sars-CoV-2 have been reported to be similar [4,9,19,20]. Considering the concentration of synthetic RNA particles used in the present experimental simulations (10^7 copies/mL, equivalent to 150 million viral particles) compared to the maximum reported concentration of SARS-CoV-1 per cough ($30.2x10^4$ particles/mL/cough) [20], an equivalent measure would be a patient coughing no less than 496 times in a 60-minute period in order to achieve the virus concentration established in the present study.

Considering all experimental simulations conducted herein, a total of 160 external sensor discs were analyzed, with no caffeine detected on any of the external sensors analyzed. In addition, synthetic SARS-CoV-2 RNA particles were used as an additional method of evaluating the ability of ISATI to isolate virus particles and protect the surrounding environment. The efficacy of the ISATI was confirmed by the detection and quantification of synthetic RNA by RT-PCR amplification.

The molecular size of caffeine is on the order of Angstroms (10^{-10}m), while viral particles are measured in nanometers (10^{-9}m). Importantly, SARS-CoV-2 dissemination occurs through the aerosolization of larger particles measuring in submicrons (0.25 to 1.0 μm) or supermicrons (> 2.5 μm) [9]. It follows that ISATI was shown to inhibit the dissemination of caffeine molecules, which are smaller than viral particles, and also to prevent the spread of larger-sized synthetic SARS-CoV-2 RNA. Regardless of the size of the marker used in experimentation, our results indicate the environmental safety of ISATI as an isolation system capable of proving occupational protection to health professionals treating patients with aerosol transmitted infections.

The data in the literature is controversial regarding the use of CPAP in the treatment of virus-related respiratory failure. Publications indicate that this procedure does not decrease the need for intubation and should be avoided due to high failure rates in patients with acute respiratory distress syndrome and H1N1 [12,22]. However, clinical reports have also indicated that patients affected by acute respiratory syndrome during the 2003 (SARS) and 2009 (H1N1 virus) epidemics who were submitted to CPAP had shorter hospital stays and lower mortality rates than patients treated with mechanical ventilation, obtaining results similar to hospitalized patients who did not need ventilation support [23,24], with a CPAP effectiveness rate of 40.6% [24]. Benefits with regard to NIV also reveal that similar rates of mortality were found in patients for whom CPAP support was ineffective, thus requiring further mechanical ventilation, as those necessitating intubation as the initial treatment of acute respiratory failure [23,24. Guidelines have been published suggesting the use of CPAP and HFNO [25,26] and publications provide evidence of benefits of these therapies in COVID-19 patients [27-29].

Regardless of the controversy as to whether early intubation, CPAP or HFNO represent the best initial treatment option for respiratory virus-related hypoxemia, it is important to recognize that ICU availability has been lacking in some countries during the COVID-19 pandemic, thus necessitating alternative measures for the mechanical ventilation of hypoxemic patients, even if performed as a temporary stopgap measure. Insufficient amounts of ICU beds during respiratory viral outbreaks can lead to the collapse of health systems, and NIV could offer a solution to provide oxygen to patients, thus keeping them alive, until achieving stability in ICU capacity. However, the conduct of NIV in the context of aerosol-transmitted infections must be performed in hospital environments that can ensure occupational safety for healthcare professionals.

Considering the experimental data presented herein, we conclude that ISATI represents an efficient system to prevent the dissemination of microparticles under the simulated conditions described. ISATI could be a useful tool to boost occupational and environmental safety in cases where NIV or HFNO are indicated for hypoxemic patients with respiratory viral infections, dispensing the need to isolate these patients exclusively in laminar airflow and negative pressure environs. The system can also be used to promote environmental protection by isolating infected patients under mechanical ventilation for up to 6 hours, and offers protection to health care professionals by lowering airborne contamination within hospitals.

The results of this experimental study provide convincing evidence of ISATI's efficacy in the simulations described in this publication. Considering the demands placed by the Sars-CoV-2 pandemic on the Brazilian health system, the clinical use of ISATI was approved by national health authorities under the brand of BhioCOVID®, manufactured by Bhiosupply®.

The process required to assemble ISATI is simple and can be accomplished in just a few minutes. With the patient lying on a hospital bed, the non-disposable stainless steel components are installed. Part of this structure houses the microparticle filter connected to a plastic tube that is attached to the hospital's vacuum system, establishing an air suction system once activated. A CPAP face mask or nasal catheter

for HFNO are attached to the patient. The plastic cover is then positioned over the patient and the hospital bed. An elastic band secures the inferior part of the plastic cover to the hospital bed. Oxygen flow for CPAP or HFNO is then initiated.

As ISATI resembles a chamber, CO_2 buildup represents a plausible concern. However, as the patients inside are being treated with oxygen, high oxygen concentrations are produced. In addition, ISATI does not constitute a fully enclosed chamber; rather, it promotes isolation. The air under the plastic cover is continuously aspirated, thereby creating a preferential air flow. The elastic band that fixes the inferior part of the plastic cover to the bed has been intentionally designed to allow air to enter, which results in the establishment of a negative pressure environment. Our experiments demonstrate that the air inside the ISATI does not exit the chamber through its inferior section, as no markers were detected by sensors/sample collection.

The plastic that covers the entire hospital bed is transparent. There have been no COVID-19 infected patients reports of feelings of claustrophobia, in clinical settings, when treated with CPAP or HFNO using ISATI.

Once non-invasive ventilation is started, provoking aerosolized particle dissemination, lifting the plastic cover of ISATI's chamber to access to the patient is inadvisable, as this would promote contamination. If there is any need to gain access to the patient, the entire plastic cover with its disposable items would need to be completely discarded.

Removal of the plastic cover can be accomplished in seconds. Oxygen flow is first turned off or lowered to 2L per minute, after which the elastic band underneath the cover is removed. Two health personnel positioned on the sides of the bed remove the plastic cover by rolling it up with the external surface outward for eventual disposal. The microparticle filter and air suction tube are also retrieved and discarded. All non-disposable items are cleaned with antiseptic solutions in the case of reuse by the same patient. Non-disposable items, such as the stainless steel structure, are autoclaved prior to being used for another patient.

Our experimental tests did not detect any occupational risk in the removal and discard of the plastic cover when the suction system remained connected to the microparticle filter under aspiration. Swabbing to identify synthetic virus particles and sensors for the detection of caffeine placed on the garments of the personnel who removed the plastic cover did not reveal the presence of any markers.

5. Conclusions

The present experiments indicate that ISATI is effective in microparticle containment under simulated conditions of CPAP, HFNO and mechanical ventilation. In all simulation scenarios, the molecular marker aerosolized inside the ISATI was undetectable at the exterior sampling positions evaluated. The use of a synthetic SARS-CoV-2 RNA gradient both inside and outside the ISATI demonstrated its efficacy in viral isolation capability. This tool should be considered in an effort to guarantee the environmental and occupational safety of health professionals when performing CPAP and HFNO in eligible respiratory virus-infected patients to diminish the risk of contamination.

Authorship contributions

Authors that participated in the process of planning, conception of the study design, conducting experiments, acquisition, interpretation and analysis of data: Quadros CA, Leal MB, Baptista-Sobrinho Cd, Nonaka CK, Souza BS, Ferreira AG. Authors that participated in conducting experiments and data acquisition: Milan-Mattos JC, Catai AM, Pires Di Lorenzo VA. All authors participated in writing the manuscript.

Data sharing

The data, analytic methods, and study materials will be made available to other researchers by request to the corresponding author.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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*Papers of special note have been highlighted as: * of interest, ** of considerable interest*

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Figure 1

Figure 2

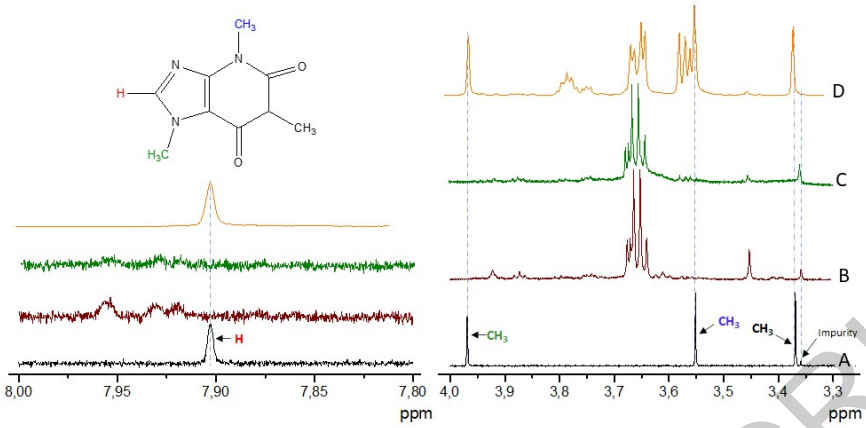

Figure 3

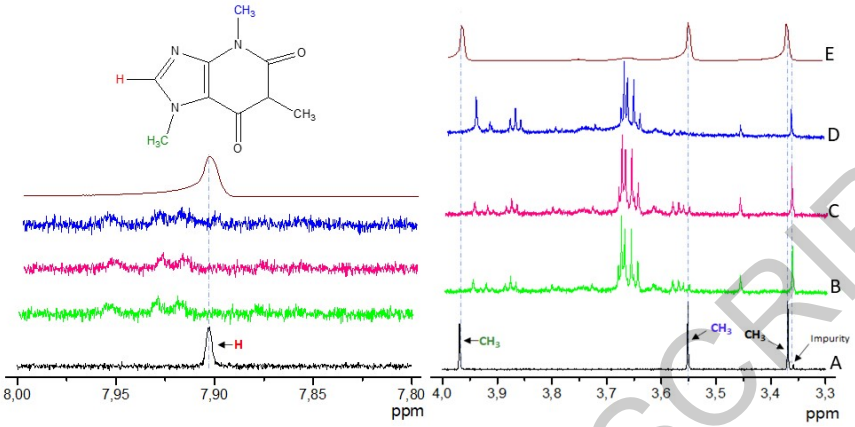

Figure 4

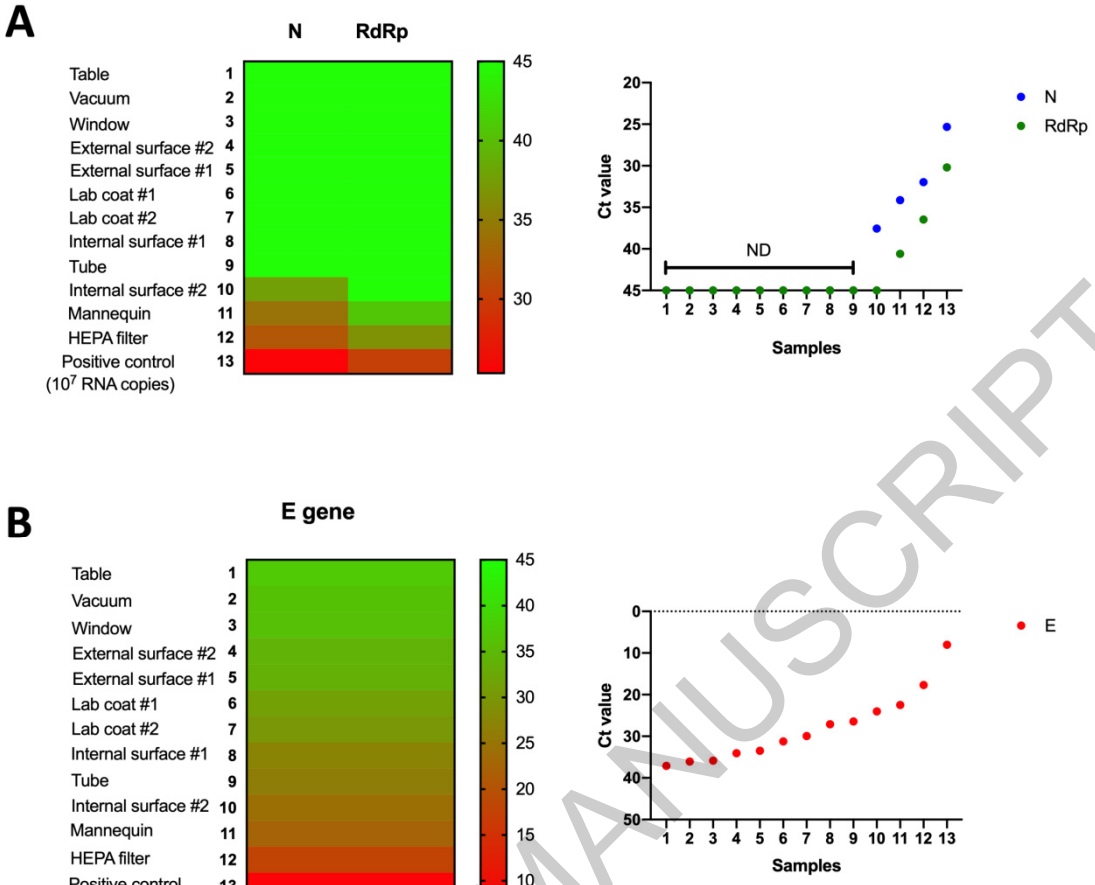

Figure 5