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Overnight delivery of hypertonic saline by nasal cannula aerosol for cystic fibrosis

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Abstract

AIM—Inhaled hypertonic saline increases mucociliary clearance, improves pulmonary function, and decreases exacerbations in cystic fibrosis (CF) but contributes to the already significant treatment burden of CF. Overnight delivery of inhaled medications via a specially designed nasal cannula-aerosol device (Trans-nasal Pulmonary Aerosol Delivery (tPAD)) is an alternative approach. Here we test whether overnight inhalation of hypertonic saline via tPAD improves mucociliary clearance and assess the tolerability of the device.

METHOD—In this study, 12 CF subjects inhaled 7% hypertonic saline (HS) for 8 hours overnight using the tPAD system. Safety and tolerability were assessed and measurements of mucociliary and absorptive clearance (MCC/ABS) were performed after the treatment. Comparisons were made versus sham treatment where the same subjects wore the nasal cannula overnight but did not receive aerosol.

RESULTS—Both the HS and sham treatments were well-tolerated. Only one subject did not complete the overnight HS treatment. There were no significant differences in MCC associated with HS inhalation at any time point (90 min, 3hr, 6hr) in any lung zone. Changes in FEV₁ on both study days were similar. There were no differences in quality of sleep between HS and sham nights as assessed with the modified Leeds Sleep Evaluation Questionnaire (mLSEQ). Sino-Nasal Outcome Test (SNOT-14) questionnaires demonstrated significant increases (worsening) in 2/14 symptom categories with HS.

CONCLUSIONS—The most likely cause for the failure to accelerate MCC was under-dosing of HS relative to the active transport of salt from the airways.

Keywords

cystic fibrosis; imaging; mucus disorders; mucociliary clearance; nasal cannula; hypertonic saline

Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease associated with a single gene, the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which encodes an anion channel on epithelial surfaces. In CF, the absence or dysfunction of CFTR causes airway surface liquid (ASL) dehydration which impairs mucociliary clearance (MCC). CF lung disease is associated with chronic infection and inflammation, lung damage, loss of respiratory function, and premature mortality^{1–6}.

Nebulized hypertonic saline (HS) is used extensively as a therapy in CF based on seminal studies that demonstrated increased pulmonary function and decreased exacerbation rates with its use⁷⁸. HS is thought to reverse the osmotic gradients in the ASL, rehydrating mucus and improving MCC⁷⁹. In current clinical use, HS is inhaled two to four times daily using a nebulizer.

The treatment burden of CF is significant. Patients perform daily, time-consuming airway clearance therapies and nebulize multiple medications. One option for easing this treatment burden is delivery of inhaled medications during sleep using the Transnasal Pulmonary Aerosol Delivery or tPAD device (Parion Sciences, Durham NC) – a device that allows for aerosolization of liquid medication for administration via a modified nasal cannula designed to be worn at night. It includes a liquid reservoir system that allows for extended operation and an air delivery and mixing system that sizes the aerosol for transnasal delivery to the lungs and transports the aerosol through the cannula and into the nares where it is inhaled. Delivery of HS to the airways via tPAD offers a “slow infusion” alternative to traditional nebulizer delivery that may provide prolonged exposure to osmotic gradients when compared to oral inhalation using a standard nebulizer.

In pre-clinical studies, aerosol size at the cannula prongs was 1.81 – 2.04 μm , volume median diameter (VMD), as measured by laser diffraction. The total saline dose delivered over 8hrs was 1,371–2,047 mg with a 7% HS solution. Pulmonary deposition efficiency of the tPAD device was assessed via deposition scintigraphy. Lung dose was 38 $\pm$ 9% of emitted dose, similar to oral inhalation from the Pari LC Star nebulizer¹⁰. Other more recent studies of tPAD performance are also now available¹¹.

Here, we utilized a functional imaging technique to measure MCC and absorptive clearance (ABS) after overnight delivery of 7% HS from the tPAD device and compared the measurements to a sham treatment night. MCC measurements have been used as a biomarker of therapeutic efficacy in several studies^{712–15}. The technique measures the clearance of non-absorbable radiolabeled particles from the airways, providing a marker of mucus clearance. ABS is a developmental biomarker that measures the paracellular

absorption of a small molecule radiopharmaceutical from the airways. ABS is increased in the CF lung⁹ and is proportional to ASL absorption *in vitro*¹⁶. We also assessed safety and tolerability of tPAD therapy for overnight use.

Materials and Methods

The tPAD device

The tPAD device includes a 2 LPM air pump, an Aeroneb Pro Nebulizer (Aerogen, Galway, Ireland), a 250 ml liquid reservoir, a liquid collection chamber, and an integrated nebulization chamber (INC) where the aerosol is combined with the flow from the air pump. It also includes electronics allowing for timed device operation for up to 8 hours. A system-specific nasal cannula is attached to the INC and used to deliver the aerosol. For this study the cannula was secured to the subject using a Wisp nasal mask frame and headgear (Philips Respironics, Murrysville, PA).

Hypertonic saline solutions (HS)

Pulmosal 7% (pH+) sodium chloride inhalation solution was used for all studies except one where it was not available. *Pulmosal* is sterile, non-pyrogenic, preservative-free, and balanced to a pH of 7.4. In one study another 7% HS product for inhalation was utilized (subject 9).

Study design

The study was approved by the University of Pittsburgh Institutional (ethics) Review Board (clinicaltrials.gov NCT02141191, U of P PRO14010272). All subjects signed informed consent. Adult subjects with CF were enrolled if they had one second forced expiratory volumes (FEV₁) of 40–110% of predicted and a BMI < 30 kg/m². Subjects were excluded if they had an acute upper or lower respiratory tract infection or required treatment with antibiotics or systemic corticosteroids within 28 days of study enrollment (not including normal maintenance antibiotics), had a diagnosis of sleep apnea, symptoms of allergic rhinitis, previous diagnosis of *Burkholderia cepacia*, smoked, or were pregnant or nursing. All subjects performed a 30 minute tolerance test of *Pulmosal* inhalation from the tPAD device prior to the overnight visits and were excluded if they demonstrated a 10% reduction from pre-dose value in FEV₁, measured 30 minutes after completion.

A randomized, balanced, crossover design was utilized that included two overnight visits, one dosing HS and the other sham. Subjects discontinued use of HS for 72 hours prior to each study visit. Long-acting beta agonists were halted for 12 hours and short-acting beta agonists for 6 hours prior. Inhaled antibiotics were allowed prior to, or after tPAD use. During the overnight HS visit, subjects received inhaled HS from the tPAD device from 11:30pm–7:30am while domiciled in the clinical research unit. The tPAD was loaded with an initial HS dose of 240 ml. The device was reloaded 5.5 hours later with 60–80 ml of HS. Pulse oximetry was monitored throughout the night while the subjects slept and the tPAD operated continuously. During the sham visit, subjects wore the cannula as they did during the HS visit and the tPAD was powered on, but the nebulizer and the air pump were non-operational and no air flowed through the cannula. Subjects who did not complete both

nights were not included in the analysis and were replaced until a total of 12 subjects had completed both visits.

MCC measurement – Radiopharmaceutical delivery and imaging

After a 4 minute background scan, subjects were seated for inhalation of the radiopharmaceutical aerosol. Inhalation of tracer was initiated within 30 minutes of the end of tPAD administration when possible. The radiopharmaceutical aerosol was delivered from a DeVilbiss 646 nebulizer which was controlled by a Spira dosimeter which triggered the nebulizer to deliver aerosol for 0.7s after the first 100 ml of inhaled volume. A metronome was used to maintain a breathing rate of 30 breaths per minute during delivery. The nebulizer was loaded with 296 MBq (8 mCi) of Technetium 99m sulfur colloid (Tc-SC) and 55.5 MBq (1.5 mCi) Indium 111-DTPA (In-DTPA). Tc-SC is a non-absorbable particle with a mean diameter of approximately 300 nm¹⁷. In-DTPA is a hydrophilic small molecule (545.29 Daltons)¹⁸. Aerosol delivery was performed for approximately 5 minutes. Afterwards, a dynamic scan including 45 sequential two-minute images was performed followed by a Cobalt 57 transmission scan. Follow-up images were collected at t=3hr (10 minute image) and t=6hr (30 minute image). Three energy windows were recorded for each image (140, 210, and 245 keV). These correspond respectively to Tc99m, a mid-window between the lower and upper energy peaks of In111, and the upper peak of In111. Two different gamma cameras were used during the course of the study: a Siemens Symbia (7 studies) and a GE Discovery NM630 gamma camera (3 studies). Two subjects used the Siemens camera on day 1 and the GE camera on day 2. All imaging was performed with subjects recumbent.

The primary outcome of the study was MCC as compared between HS and sham visits. Secondary outcomes included safety assessments, ABS, and results from Sino-Nasal Symptoms (SNOT-14) and modified Leeds Sleep Evaluation Questionnaires (mLSEQ). Questionnaires were presented to the study subjects at screening and on the mornings after HS and sham administration.

MCC measurement – Image analysis

Semi-automated imaged analysis was performed using a MATLAB script. Posterior images of the right lung were used. The left lung was not used to avoid interference from the stomach. The Co57 transmission scan was used to trace the right lung boundary which was then applied to the dynamic clearance scan sequence enabling “whole lung” radioactive counts to be measured in each energy window. Counts were adjusted for background, decay, and isotope spillover, as previously described⁹. The data were then normalized by starting counts and retention vs. time curves were produced. Tc-SC counts were used to assess MCC. In-DTPA is cleared by both MCC and absorption. We calculated the absorption rate of DTPA (ABS) by subtracting the MCC rate measured using Tc-SC from the total clearance rate of In-DTPA. Previous studies have related ABS to ASL absorption¹⁶, and ABS responses to inhaled HS have been previously demonstrated *in vivo*⁹. A central right lung zone, defined as a rectangular area that had one-half the height and one-half the width of a rectangle that surrounded the lung perimeter, was placed on the medial border of the right lung at approximately mid-height to determine central lung counts.

Assessments of Safety and Tolerability

Spirometry was assessed during screening, prior to tPAD use, and again after tPAD use and imaging. Pulse oximetry was measured every 2 hours during tPAD use. A modified version of the Leeds Sleep Evaluation Questionnaire was administered at screening and on the morning after sham and HS treatments. It includes 10 questions about sleep quality. Subjects were administered a portion of the Sino-Nasal Outcome Test (SNOT) which included 14/20 usual categories relevant to overnight tPAD use (SNOT-14). Categories were ranked (1-no problem, 2- very mild problem, 3-mild or slight problem, 4-severe problem, 5-problem as bad as it can be).

Results

Table 1 includes subjects who completed the study. Two subjects failed screening after experiencing 10% reduction from pre-dose FEV₁, measured 30 minutes after completion of a 30 minute HS screening treatment from the tPAD. One later rescreened and entered the study after treatment for a previously undiagnosed infection. One subject successfully completed the HS night but then did not return to complete the sham night. One subject experienced acute nasal irritation during first two hours of tPAD use during the HS night and treatment was discontinued. Both the HS and sham treatments were well-tolerated. There were no serious adverse events. There were 11 adverse events considered possibly or probably related to treatment: cough (3), fatigue, headache (3), increased mucus, nasal congestion, nasal pain, and oral pain. All adverse events were of mild or moderate intensity. There was no difference in pre-study FEV₁ between the study days ($p=0.76$ by paired t-test.)

Table 2 and Figure 1 include the results of whole lung MCC measurements made after the HS and sham nights. There were no significant differences in whole lung MCC associated with the HS therapy at any time point (for comparisons at $t=90\text{min}$, 3hr, and 6hr, $p=0.75$, 0.38, and 0.64 respectively, by paired t-test). Figure 2 includes the average retention curves for the HS and sham treatment nights. Tables S1 and S2 list the values for central and peripheral lung MCC respectively. There were no significant differences when comparing HS and sham nights (central lung, $p=0.67$, 0.20, and 0.17; peripheral lung, $p=0.98$, 0.97, 0.89). Measurements of MCC were more tightly distributed after HS vs. sham. The standard deviation of MCC within the group was smaller in every zone (whole, central, peripheral) at every time point (90 min, 3hr, 6hr), after HS inhalation.

Table 3 and Figure 3 compare whole lung ABS as measured the morning after the HS and sham nights. There were no significant differences in whole lung ABS associated with the HS therapy at $t=90\text{ min}$ or 6hrs ($p=0.45$, and 0.37 respectively, by paired t-test). At $t=3\text{hrs}$, study day differences approached significance with HS being associated with increased ABS ($p=0.09$). Tables S3 and S4 list the values for central and peripheral lung ABS respectively. Central lung ABS was increased with HS for the 3hr and 6hr time points ($p=0.04$, 0.03) while the 90min time point did not demonstrate any significant differences by study day ($p=0.30$). The measured ABS effects are opposite of what would be anticipated with HS inhalation, as demonstrated in previous studies⁹, though measurements in those studies were conducted immediately after oral inhalation of HS. Peripheral lung ABS was similar between study days at all time points ($p=0.78$, 0.63, 0.44).

We considered the effect of radiopharmaceutical aerosol distribution on measurements of MCC and ABS using central to peripheral deposition ratio (C/P) as a gauge. Deposition was generally repeatable between test days (comparing C/P by paired t-test, $p=0.23$). Values are included in Table 1. The average intrasubject difference in C/P between test days was 0.3 ± 0.2 (range 0–0.8). Intersubject differences were higher and the range of C/P values was 0.8–3.5. Subject 9 had highly central deposition on both testing days (C/P=3.4, 3.5) and demonstrated higher MCC and lower ABS when compared to the other subjects. Linear relationships were indicated for both MCC and ABS vs. C/P (MCC $R^2=0.24$, $p=0.01$; ABS $R^2=0.41$, $p=0.001$). These comparisons did not vary significantly if subject 9 was removed. The slopes of these relationships are approximately 10(C/P) for MCC and $-11(C/P)$ for ABS, thus a 0.5 increase in C/P would be associated with a 5% increase in MCC and a 5.5% decrease in ABS. The time between the end of treatment and the beginning of radiopharmaceutical aerosol delivery was similar for HS: 32 ± 6 min (range: 22–45 min) and sham: 31 ± 4 min (range: 27–40 min), $p=0.43$, by paired t-test.

As shown in Table S5, average FEV_1 decreased slightly on average during both sham and HS visits, as assessed before the beginning of the overnight treatment and during the next day in the afternoon after the completion of the imaging study (FEV_1 HS: $-48 \text{ ml} \pm 108$ vs. Sham: -110 ± 147 ml, $p=0.14$). These differences are not clinically significant. Average pulse oximetry readings were similar by subject during sham and HS nights ($p=0.21$, paired t-test).

Table S6 includes the average results from the modified Leeds Sleep Evaluation Questionnaires (mLSEQs). There was no difference between the average self-assessed quality of sleep between the sham and the HS nights (sham= 48.6 ± 13.0 , HS= 47.2 ± 9.7 ; $p=0.66$ by paired t-test). Quality of sleep was decreased during both sham and HS nights when compared to the screening day questionnaire (screening= 57.2 ± 11.9 ; vs sham $p=0.09$, vs HS $p=0.04$).

Table S7 includes the total scores from the modified Sino-Nasal Outcome Test (SNOT-14) for the screening and testing days. Differences between sham and HS approached significance $p=0.06$. Other comparisons were not significantly different (screen vs. HS, $p=0.18$; screen vs. sham $p=0.96$). Figure 4 includes individual average category scores. Comparisons of HS vs. sham demonstrated significant increases for “need to blow nose” ($p=0.02$) and “runny nose” ($p=0.01$) with HS. “Runny nose” was also significantly increased when comparing HS to screen ($p=0.02$).

Discussion

Overnight inhalation of HS by nasal cannula using the tPAD device did not significantly increase mucociliary clearance as assessed 30 minutes after the conclusion of delivery to subjects with CF. HS inhalation did narrow the range of MCC values measured within the group. Specifically, MCC standard deviation was lower in every zone at every time point after HS inhalation. This could be indicative of therapeutic regulation of MCC that brought subjects with initially lower rates closer to the population mean. Though no trends indicating

therapeutic response are apparent in the outcomes, a type 2 error could of course still be possible especially given the small number of enrolled subjects.

Our previous studies have demonstrated consistent MCC increases with inhaled HS in measurements made during and immediately after oral HS inhalation⁹. In explaining the outcomes here we must first consider the NaCl dose delivered to the airways by both tPAD and oral inhalation. Pre-clinical studies indicate that the tPAD emits 3.47 ± 0.41 mg of NaCl per minute or $1,665 \pm 196$ mg NaCl over eight hours. Pulmonary deposition efficiency of the tPAD device was measured in awake healthy subjects using deposition scintigraphy techniques and was similar to that of the Pari LC Star nebulizer used for oral inhalation ($38 \pm 9\%$ of emitted dose)¹⁰. The delivery rate for the tPAD over an 8hr dosing interval is estimated at 632 mg or 1.31 mg/min. Oral aerosol delivery typically utilizes 4 ml loaded doses (280 mg of NaCl). Assuming that the emitted dose for oral delivery is 70% of loaded dose (30% losses within the nebulizer), with 38% pulmonary delivery efficiency and a 15 minute delivery time, the total lung dose and delivery rate is 74.5 mg and 5 mg/min, respectively. Thus NaCl delivery to the lung during a typical oral inhalation treatment occurs at a rate 3–4 times that provided by tPAD. Later studies of tPAD performance describe lower NaCl dosing rates¹¹.

To better understand the relationship between tPAD dosing and ASL hydration in the CF airways, we utilized a computational model of ASL volume developed from human bronchial epithelial (HBE) cell culture data¹⁹. Predictions from the model are presented in terms of the liquid volume found on the surface of HBE cell cultures and can be evaluated relative to the dotted line on figure 5a which represents the “normal” non-CF (periciliary) liquid volume ($12 \mu\text{L}$). We modeled ASL hydration assuming uniform aerosol deposition over the areas of either the first 10 or first 16 Weibel airway generations²⁰, using 7 and 14% saline concentrations, and fast and slow transepithelial Na^+ absorption rates (fast: $1.2 \mu\text{eq/hr/cm}^2$ from²¹, slow: $0.65 \mu\text{eq/hr/cm}^2$ ¹⁹). The model (Figure 5a) indicates that the aerosol deposition area is the primary model factor determining increased hydration. With uniform deposition over 10 generations, an increase of ASL height to normal levels is attained in 1–5hrs with 14% and 7% HS, respectively, but normal ASL height is never attained at either concentration if deposition over 16 generations is assumed. In Figure 5b, we incorporated previously published models of aerosol deposition within specific airway generations^{22,23} into the model, and considered hypertonic saline delivery by nasal (tPad, 8hr delivery, $1 \mu\text{m}$ aerosol diameter) and oral (Pari LC Star, 15 min, $4 \mu\text{m}$) routes. Airway obstruction has been reported from generation 6 in CF²⁴. Oral delivery rapidly increases ASL height in all 3 generations considered (7 through 9) and the effect was sustained for several hours. Nasal delivery produces durable increases in ASL height in generation 7, but not in the smaller airway generations, unless 14% saline is modeled.

Though our ability to accurately estimate airway dose is limited, these results indicate that dosing rates from the tPAD for airways distal to generations 8–10 may well be less than what is required to overcome active Na^+ absorption by the airway epithelium, preventing the development of osmotic gradients across the ASL. Deposition scintigraphy studies also indicated increased peripheral deposition with tPAD which may mean even less of the dose was delivered to the large airways which are most likely to dominate the MCC

measurement¹⁰¹¹. Peripheral deposition was likely driven by the small delivered droplet sizes and the slower respiration patterns that occur during sleep²⁵. Both general and model-driven considerations of dosing rate indicate that efficacy of the tPAD treatments is limited by the airway delivery rate of NaCl obtainable with a 7% saline solution. Higher concentrations of hypertonic saline may provide an improved effect. There is history of human use of concentrations as high as 14.4% though at low delivered volumes²⁶.

ABS is a developmental biomarker that measures the absorption rate of the small molecule DTPA which is thought to occur exclusively through paracellular routes. Its absorption could be influenced by deposition location (airways vs. alveoli), elements of airway permeability such as tight junction diameter, and ASL convection through paracellular paths. Our previous *in vitro* studies have demonstrated that ABS is proportional to ASL volume absorption and increased in airway cell cultures from CF lungs. Our previous *in vivo* imaging studies have demonstrated increased ABS in CF at baseline and decreased ABS absorption after HS inhalation⁹¹⁶. Here there was no consistent ABS response to the HS.

The tPAD device was safe and well tolerated during overnight use. There were no serious adverse events and all adverse events reported were of mild or moderate intensity. Only one subject discontinued overnight use. All other subjects who began the study nights completed the 8 hour treatment. There were no significant differences in overnight pulse oximetry and changes in study day FEV1 were small and similar between HS and sham. There was no difference between the average self-assessed quality of sleep between the sham and the HS nights. Results of the modified SNOT-14 indicated significant worsening in two symptom categories with HS (need to blow nose and runny nose). Other categories were similar.

In summary, the overnight delivery of inhaled 7% HS via nasal cannula using the tPAD device was safe and well tolerated but did not alter measurements of MCC or ABS made the morning after delivery. Given that acute increases in MCC and decreases in ABS have been previously demonstrated after oral inhalation, the most likely cause for the negative result is under-dosing relative to the rate of active transport of salt from the airways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hirsh AJ. Altering airway surface liquid volume: inhalation therapy with amiloride and hyperosmotic agents. *Adv Drug Deliv Rev.* 2002; 54(11):1445–62. [PubMed: 12458154]
2. Knowles MR, Boucher RC. Mucus clearance as a primary innate defense mechanism for mammalian airways. *J Clin Invest.* 2002; 109(5):571–7. [PubMed: 11877463]

3. Mall M, Grubb BR, Harkema JR, et al. Increased airway epithelial Na⁺ absorption produces cystic fibrosis-like lung disease in mice. *Nat Med.* 2004; 10(5):487–93. [PubMed: 15077107]
4. Matsui H, Grubb BR, Tarran R, et al. Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. *Cell.* 1998; 95(7):1005–15. [PubMed: 9875854]
5. Frizzell RA, Pilewski JM. Finally, mice with CF lung disease. *Nat Med.* 2004; 10(5):452–4. [PubMed: 15122239]
6. Pilewski JM, Frizzell RA. Role of CFTR in airway disease. *Physiological reviews.* 1999; 79(1 Suppl):S215–55. [PubMed: 9922383]
7. Donaldson SH, Bennett WD, Zeman KL, et al. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med.* 2006; 354(3):241–50. [PubMed: 16421365]
8. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med.* 2006; 354(3):229–40. [PubMed: 16421364]
9. Locke LW, Myerburg MM, Markovetz MR, et al. Quantitative imaging of airway liquid absorption in cystic fibrosis. *Eur Respir J.* 2014; 44(3):675–84. [PubMed: 24743971]
10. Parion Sciences, Investigator's Brochure tPAD – trans-Nasal Pulmonary Aerosol Delivery of Hypertonic Saline. First Edition ed2013
11. Zeman KL, Rojas Balcazar J, Fuller F, et al. A Trans-Nasal Aerosol Delivery Device for Efficient Pulmonary Deposition. *Journal of aerosol medicine and pulmonary drug delivery.* 2017; doi: 10.1089/jamp.2016.1333
12. Daviskas E, Anderson SD, Eberl S, et al. Effect of increasing doses of mannitol on mucus clearance in patients with bronchiectasis. *Eur Respir J.* 2008; 31(4):765–72. [PubMed: 18057051]
13. Donaldson SH, Corcoran TE, Laube BL, et al. Mucociliary clearance as an outcome measure for cystic fibrosis clinical research. *Proc Am Thorac Soc.* 2007; 4(4):399–405. [PubMed: 17652507]
14. Bennett WD, Laube BL, Corcoran T, et al. Multisite comparison of mucociliary and cough clearance measures using standardized methods. *Journal of aerosol medicine and pulmonary drug delivery.* 2013; 26(3):157–64. [PubMed: 23517172]
15. Rowe SM, Heltshe SL, Gonska T, et al. Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis. *Am J Respir Crit Care Med.* 2014; 190(2):175–84. [PubMed: 24927234]
16. Corcoran TE, Thomas KM, Brown S, et al. Liquid hyper-absorption as a cause of increased DTPA clearance in the cystic fibrosis airway. *EJNMMI research.* 2013; 3(1):14. [PubMed: 23446051]
17. Saha, G. *Fundamentals of Nuclear Pharmacy.* Fifth. Springer; 2004.
18. GE-Healthcare. Drug label for INDIUM DTPA In 111 Pentetate Indium Disodium In 111
19. Markovetz MR, Corcoran TE, Locke LW, et al. A Mathematical Model of Thin Film Liquid and Ion Transport in Human Bronchial Epithelial Cells (poster abstract). *Pediatr Pulmonol.* 2014; 49(S38):258.
20. Weibel, ER. *Morphometry of the human lung* Berlin. Springer; 1963.
21. Boucher RC. Human airway ion transport. Part one. *Am J Respir Crit Care Med.* 1994; 150(1): 271–81. DOI: 10.1164/ajrcm.150.1.8025763 [PubMed: 8025763]
22. Sood N, Bennett WD, Zeman K, et al. Increasing concentration of inhaled saline with or without amiloride: effect on mucociliary clearance in normal subjects. *Am J Respir Crit Care Med.* 2003; 167(2):158–63. [PubMed: 12411282]
23. Gerrity TR, Lee PS, Hass FJ, et al. Calculated deposition of inhaled particles in the airway generations of normal subjects. *J Appl Physiol Respir Environ Exerc Physiol.* 1979; 47(4):867–73. [PubMed: 511695]
24. Boon M, Verleden SE, Bosch B, et al. Morphometric Analysis of Explant Lungs in Cystic Fibrosis. *Am J Respir Crit Care Med.* 2016; 193(5):516–26. DOI: 10.1164/rccm.201507-1281OC [PubMed: 26551917]
25. Douglas NJ, White DP, Pickett CK, et al. Respiration during sleep in normal man. *Thorax.* 1982; 37(11):840–4. [PubMed: 7164002]

26. Daviskas E, Anderson SD, Gonda I, et al. Inhalation of hypertonic saline aerosol enhances mucociliary clearance in asthmatic and healthy subjects. *Eur Respir J*. 1996; 9(4):725–32. [PubMed: 8726937]

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FIGURE 1.

Mucociliary clearance (MCC) rate measured after overnight inhalation of 7% HS from the tPAD device or sham delivery. (A) 90 minute measurement, (B) 3 hr, (C) 6hr. Gray symbols indicate values that decreased from sham to HS and white symbols indicate increases. Error bars are $\pm$ SD.

FIGURE 2.

Retention curve of Tc-SC (mucociliary clearance=100-retention) shown over 90 minutes and measured after overnight inhalation of 7% HS from the tPAD device or sham delivery. Error bars are $\pm$ SEM.

FIGURE 4.

Individual category results from the Sino-Nasal Outcome Test (SNOT-14). HS vs. sham – need to blow nose ($p=0.02$), runny nose ($p=0.01$). “Runny nose” was also increased when comparing HS to screen ($p=0.02$). For other comparisons $p=NS$.

FIGURE 5.

Model predicted effects of saline inhalation on airway surface liquid (ASL) hydration in cystic fibrosis (CF). (A) Effect of aerosol deposition surface area (first 10 or 16 airway generations), fast or slow Na^+ absorption, and saline concentration. Model predicts volume relative to human bronchial epithelial cell cultures where dotted line is normal (non-CF) ASL volume. (B) Effect of oral (Pari LC Star) vs. nasal inhalation (tPad), and saline concentration, shown for airway generations 7, 8, and 9. Model predicts relative airway surface liquid height added. Gen or G=airway generation, HS=hypertonic saline.

Table 1

Age, gender, Pre Dose FEV₁, and central to peripheral (C/P) deposition ratio for subjects who completed both study days. Comparing Pre Dose FEV₁ and C/P ratio by study day, $p=0.76$ and 0.23 , by paired t-test.

Subject #	age	gender	HS visit			sham visit		
			FEV ₁ (L)	FEV ₁ (%p)	C/P	FEV ₁ (L)	FEV ₁ (%p)	C/P
1	29.5	M	3.72	90	1.7	3.57	89	0.9
2	58.4	F	2.21	85	0.8	2.29	88	0.9
3	31.5	M	3.66	80	1.4	3.89	85	1.6
4	34.3	M	2.05	51	0.9	2.05	51	0.9
5	22.7	F	3.18	99	1.1	3.26	102	0.9
6	31.1	F	2.58	84	1.7	2.44	79	2.1
7	37.1	M	3.13	67	1.0	3.25	71	0.9
8	36.9	M	2.46	62	1.2	2.53	64	1.0
9	25.2	M	3.02	66	3.4	3.00	67	3.5
10	23.1	M	2.74	68	1.9	2.66	66	1.5
11	25.8	M	3.41	102	1.3	2.78	68	1.1
12	25.9	F	1.80	59	1.1	1.99	65	1.0
average	31.8		2.83	76.1	1.5	2.81	74.6	1.3
st dev	9.7		0.63	16.3	0.7	0.60	14.2	0.8

Whole lung mucociliary clearance (MCC) measurements made after overnight HS and sham treatments from tPAD device. Measurements were begun at 31 ± 5 minutes after completion of the 8 hr overnight treatment. Comparisons at t=90min, 3hr, and 6hr, were p=0.75, 0.38, and 0.64 respectively, by paired t-test. Average differences HS-sham (95%CI) 90 min, 3 hr, 6hr: -1.8%(-12.7-9.0); -4.8%(-15.0-5.5); -1.7%(-8.8-5.3).

Table 2

Subject #	90 min		3hr		6hr	
	whole lung MCC (%) sham	whole lung MCC (%) HS	whole lung MCC (%) sham	whole lung MCC (%) HS	whole lung MCC (%) sham	whole lung MCC (%) HS
1	33.1	35.8	35.8	44.3	42.2	47.9
2	36.2	42.7	50.4	54.8	57.7	60.2
3	33.6	10.6	47.9	26.6	55.0	30.1
4	17.0	18.3	23.4	26.7	28.6	26.5
5	23.5	16.7	28.4	21.8	39.6	37.0
6	72.8	22.0	77.8	32.2	81.2	66.3
7	4.7	14.1	7.1	20.7	14.4	19.1
8	22.0	40.3	42.4	54.4	49.6	70.7
9	47.2	36.5	64.6	58.2	75.2	70.3
10	19.3	33.1	65.3	39.8	77.6	61.9
11	21.3	27.8	34.9	28.4	36.3	35.0
12	9.9	20.9	32.0	44.6	42.5	53.8
ave	28.4	26.6	42.5	37.7	50.0	48.2
stdev	18.2	10.9	19.9	13.4	20.4	18.2

Table 3

Whole lung DTPA absorptive clearance (ABS) measurements made after overnight HS and sham treatments from tPAD device. Measurements were begun at 3 ± 5 minutes after completion of the 8 hr overnight treatment. Comparisons at $t=90$ min, 3hr, and 6hr, $p=0.45$, 0.09 , and 0.37 respectively, by paired t-test. Average differences HS-sham (95%CI) 90 min, 3 hr, 6 hr: 3.7% ($-5.6-13.0$); 8.4% ($-0.5-17.3$); 4.1% ($-4.4-12.5$).

Subject #	90 min		3 hr		6hr	
	whole lung ABS (%) sham	whole lung ABS (%) HS	whole lung ABS (%) sham	whole lung ABS (%) HS	whole lung ABS (%) sham	whole lung ABS (%) HS
1	43.6	36.0	47.4	43.6	45.6	44.0
2	36.4	29.9	36.1	32.1	31.8	29.8
3	14.4	44.2	7.3	39.8	9.6	46.3
4	38.8	39.9	49.1	47.2	56.3	57.5
5	31.4	40.1	37.9	48.5	38.0	44.9
6	0.0	32.3	5.8	44.2	12.7	25.2
7	28.4	43.4	36.4	52.6	40.6	49.0
8	33.2	18.6	27.2	15.0	28.0	1.1
9	9.5	17.8	11.5	14.5	8.4	7.1
10	30.7	11.6	11.3	22.9	8.8	19.7
11	21.6	28.3	21.5	38.4	36.2	47.8
12	44.5	34.8	40.0	33.6	39.8	32.1
average	27.7	31.4	27.6	36.0	29.6	33.7
stddev	13.8	10.6	15.7	12.8	16.2	17.7