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Original article

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Acute and durable effect of inhaled hypertonic saline on mucociliary clearance in adult asthma

William D. Bennett [1,2], Allison Burbank [1,3], Martha Almond [1], Jihong Wu [1], Agathe Ceppe [2], Michelle Hernandez [1,3] Richard C. Boucher [2], David B. Peden [1,3]

1 Center for Environmental Medicine, Asthma and Lung Biology

2 Pulmonary and Critical Care Medicine, Department of Medicine,

3 Division of Allergy and Immunology, Department of Pediatrics

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Corresponding Author: William D. Bennett, PhD

104 Mason Farm Road, CB #7310

Center for Environmental Medicine, Asthma and Lung Biology

University of North Carolina at Chapel Hill

Chapel Hill, NC 27599

Phone (919) 966-6229

Fax (919) 966-9863

Email William_Bennett@med.unc.edu

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ABSTRACT

Background: Impaired mucus clearance and airway mucus plugging have been shown to occur in moderate to severe asthma, especially during acute exacerbations. In cystic fibrosis (CF), where airway mucus is dehydrated, it has been shown that inhaled hypertonic saline (HS) produces both acute and sustained enhancement of mucociliary clearance (MCC). The current study was designed to assess the acute and sustained effect of inhaled 7%HS on MCC in adult asthma.

Methods: Well-controlled, moderate-severe female asthmatics (n=8) were screened with a single test dose of albuterol (4 puffs by metered dose inhaler) followed by HS (7% NaCl, 4mL nebulized by Pari LC Star). Spirometry was measured at pre-treatment and 5- and 30-minutes post-treatment for safety. MCC was measured by gamma scintigraphy on three separate visits: at baseline, during inhalation of, and 4-h after a single dose of HS.

Results: MCC was acutely enhanced during HS treatment, mean clearance over 60 minutes of dynamic imaging Ave60Clr =8.9+/-7.9% (baseline) vs. 23.4+/-7.6% (acute HS) ($p<0.005$). This enhancement was not maintained however over a 4-h period where post HS treatment Ave60Clr =9.3+/-8.2%. In this small cohort we found no decrements in lung function up to 30-minutes post treatment (FEV1% pred =97.4+/-10.0 and 98.9+/-10.7 pre-treatment vs. 30-minutes post-treatment, respectively).

Conclusion: While MCC was rapidly enhanced during 7%HS treatment there was no effect on MCC at 4-hours post treatment. While these findings may not support aerosolized HS use for maintenance therapy they do suggest a benefit for treating acute exacerbations in moderate-severe asthmatics.

Keywords: asthma; mucociliary clearance; hypertonic saline; hydrator

INTRODUCTION

Mucociliary clearance (MCC) is a critical innate defense to remove mucus and associated toxins, bacteria, viruses, and inflammatory cells/cytokines from the lungs. In vitro studies have demonstrated that well-differentiated airway epithelial cultures lose their ability to transport mucus as they become progressively dehydrated, thus providing a key mechanistic link between mucus dehydration and defective MCC in-vivo (1). Hypertonic saline (HS) has been shown to enhance hydration of mucus and improve mucus rheology *in vitro* (2-4). In-vivo inhaled HS acutely enhances MCC in healthy volunteers as well as those with asthma and cystic fibrosis (CF) (3, 5-9). Moreover, in CF the enhancement is both acute and durable, lasting at least 4 hours with a single dose and 8 hours after repetitive dosing (3,10) and is associated with improved lung function over as little as a two-week treatment period (3). In healthy subjects, however, the stimulatory effect is acute and paradoxically slowed after 4 hours (7). Our recent clinical study in patients with chronic bronchitis also showed a general slowing of MCC over a 2-week treatment period (11), and a similar lack of sustained HS effects.

Airway mucus plugging and acute slowing of MCC during exacerbations is a key feature of asthma and contributes to the morbidity and mortality associated with the disease (12-14). Increased MUC5AC/MUC5B ratios and associated disulfide bonds in airway mucus (15) as well as ciliary dysfunction (16) are features of severe asthma that likely play a role in their reduced MCC. However, there is also evidence for increased dehydration of mucus obtained from asthmatics. Loughlin et al (17) found that induced sputum recovered from asthmatics under baseline (non-exacerbated) conditions had 2.2% solids compared to 1.6% in healthy volunteers, with % solids being related to neutrophilic content of sputum. While this level of dehydration in asthmatics is less than that observed in CF (18) they do overlap with %solids we recently reported in chronic bronchitis (1). Furthermore, a single treatment with inhaled dry powder mannitol in asthmatics, a hyperosmolar therapy, showed significant improvement in sputum rheology (19). These findings support the rationale and potential for the use of inhaled hypertonic saline to treat reduced MCC in asthma.

Because the clinical benefits from inhaled HS likely depend on the duration of this effect on MCC, assessment of MCC at later timepoints post-HS inhalation will help determine how this treatment may best be applied. In this current open label, pilot study we assessed both the acute (immediate) and durable (4 hours post treatment) efficacy of HS for improving MCC in well-controlled moderate to severe asthmatics. Finally, due to concerns of airway hyperresponsiveness in these patients we pre-treated patients with a bronchodilator (albuterol) and monitored lung function before and after HS treatment.

STUDY DESIGN/METHOD

Study subjects. Adult asthmatics aged 20-53 years with well-controlled moderate to severe asthma at enrollment were studied (defined by Step 3 therapy or greater or by degree of impairment secondary to asthma, per National Asthma Education and Prevention Program, NAEPP, Expert Panel Report 3 (20)). Participants were excluded if FEV1 <70% predicted without use of short acting bronchodilator [albuterol] in the previous 8 hours. All participants were on a combination LABA/Steroid medication (Advair, Symbicort or Breo) and self-reported adherence to their medication as prescribed during their entire study. All participants were stable, i.e. no signs of exacerbation, when studied.

Study design. Participants had a baseline MCC assessment by gamma scintigraphy imaging over a 2-hour period following inhalation of radiolabeled particles (Tc99m-sulfur colloid) as previously described in detail (7, 21) (Figure 1, Supplemental video). At the conclusion of the 2 hour baseline MCC assessment subjects were screened for bronchial hyper-reactivity associated with albuterol/HS treatment. Fifteen minutes after pretreatment with 4 puffs of albuterol (90 mcg each via metered dose inhaler (MDI) with spacer), subjects received a screening dose of HS inhalation by PARI LC Star nebulizer (4ml of 7% NaCl inhaled until sputter). Spirometry was measured at 5 and 30 minutes after completion of HS inhalation. Participants with a 10% fall in forced expiratory volume in 1 second (FEV1) that persisted for 30 minutes or more were excluded from further study.

At least one week after the screening/baseline MCC visit, we assessed the acute effects of HS on MCC (Figure 1). Immediately following the initial 4 min deposition scan of the MCC dynamic imaging, subjects received albuterol and 7%HS inhalation over a 25 min period (as described above for screening visit) while being scanned for MCC through the two-hour period (Fig 1). Cough frequency was monitored during the measure of MCC. After at least one-week, participants returned to assess the durability of albuterol/HS on MCC. Subjects again received albuterol pretreatment and HS inhalation as described above, but the radioaerosol inhalation and MCC measurement began 4 hours later. For each MCC measurement subjects returned the following day for a 30-min image to assess retention at 24hr (+/- 4hr) after initial deposition.

Baseline MCC measured in a control group of healthy non-asthmatic female adults (n=19) who participated in previous (7, 21) and current studies were included for comparison to baseline MCC in the asthmatic adults.

MCC Analysis. By computer analysis a rectangular whole and central region was circumscribed over the right lung defined by a Co57 transmission scan in each subject (7). The region was used to determine whole lung retention (Rt) (decay and background corrected) as a fraction of the initial counts over the 2-hour imaging period. To describe each retention vs. time data set (e.g., mean data shown in figure 2), the average % clearance [or 100 X (1 – Rt)] over the 60 and 120-min period of observation were computed (i.e., average of the 10-min clearance values from 10 to 60 or 120 min). These computed values are signified as Ave60Clr and Ave120Clr, respectively. This method for characterizing non-linear retention vs. time data over a given period (Figure 2) allows for all 10 min data points to be considered, in our case area under the curve expressed in terms of average clearance (22, 23) over that period. Regional deposition, a potential confounder of MCC measurements, was also determined by central-peripheral ratio (C/P) ratio for each measure of MCC. Increasing C/P is associated with an increase in average clearance (22, 23). The retention at 24 hours was also compared between study visits (figure 2) as an index of initial, regional deposition of radioaerosol between bronchial and alveolated airways (22).

MCC in the healthy control group was only compared through 60 min imaging (i.e. Ave60Clr) due to interventions post 60 minutes in some of these healthy control studies.

Statistics. The pre-specified primary study outcome was whole lung AveClr60 between baseline vs. acute vs. 4-hour post challenge visits. Secondary outcomes included changes in spirometry and other MCC outcomes (AveClr120, C/P, 24 hr retention). From previous studies we have seen that the distribution of MCC outcomes is normal (3, 7,11) nor did we expect strong outliers even under the conditions of low N.

Data were analyzed using a repeated measure ANOVA using visit as the primary fixed factor (baseline, acute HS, durability HS). Multiple comparisons between visits were then adjusted with Tukey. Effects of C/P and FEV1 were analyzed by adding them as covariates in the model. The relationship between specific outcomes were determined by Pearson's Correlations at each visit. Comparisons between asthmatic and healthy subjects were made with independent t-tests. P values < 0.05 were considered significant. All statistical analyses were conducted utilizing SAS v9.4 and JMP Pro 14 (SAS, Cary, NC) statistical softwares.

Study Approval. The study was approved by the University of North Carolina IRB, and subjects provided written informed consent. The study was registered at Clinical Trials.gov (NCT03556683).

RESULTS

Nine (8F/1M) asthmatics completed the study as designed. Due to the low number of males recruited to the study before interruption by the COVID-19 pandemic we narrowed our findings reported here to female subjects (n=8) including MCC comparison to healthy non-asthmatic females (n=19). No participants were excluded based on the HS screen. Mean (+/-SD) age was 29.6+/-12.1 and 27.7+/-6.6 for asthmatics and non-asthmatics respectively. On the screening study day, the FEV1 normalized as a percentage of the FEV1% predicted value was 97.4+/-10.0 pre HS treatment and 97.5+/-12.2 and 98.9+/-10.7 at 5 and 30 minutes post HS treatment, respectively (NS).

Figure 2 shows the significantly different mean retention in time data for the three MCC measurements in the female asthmatics (p=0.0017). The acute challenge with HS produced an immediate, rapid clearance of the radiolabeled particles compared to baseline (see supplemental video), Ave60Clr = 8.9+/-7.9% (baseline) vs. 23.4+/-7.6% (acute HS) ($p < 0.005$). Over the entire 120 min period of MCC measurement the average clearance was also different between the three MCC measures; greater for acute HS compared to baseline, Ave120Clr = 12.8+/-8.8% (baseline) vs. 31.1+/-8.6% (acute HS) ($p<0.002$). It was evident that only a small fraction of particles was still available for clearance between 60 min and 24 hours for the acute HS case. By contrast, there was no effect of HS on MCC measured 4 hours post challenge compared to baseline, Ave60Clr = 9.3+/-8.2% and Ave120Clr = 12.4+/-8.6% for 4 hours post challenge. The 24hr retention was not different between the baseline, acute HS, and 4 hours post HS study visits ($p = 0.14$); 0.51+/-0.06, 0.58+/-0.09, and 0.61+/-0.13 respectively.

Regional deposition (C/P) was not different between the 3 MCC measurements: C/P = 2.2+/-0.5 (baseline), 2.1+/-0.4 (acute HS), and 2.1+/-0.4 (4 hours post HS). Both Ave60Clr and Ave120Clr were correlated with C/P for the baseline MCC measurements ($R = - 0.84$, $p< 0.01$ and $R= -0.87$, $p < 0.01$ respectively). PreFEV1 was not a significant covariate for either Ave60 or Ave120. Spontaneous cough only occurred for the acute HS challenge in 6 of the 8 asthmatics during the MCC measurement and was minimal ($\leq$ 4 coughs for any subject, mean #coughs for all = 2.3).

Baseline MCC trended slower in the small group of female asthmatics compared to the non-asthmatic female cohort, Ave60Clr = 8.9+/-7.9 vs.13.9 +/-6.5% ($p= 0.09$) respectively, while neither C/P =2.2+/-0.2 nor 24hr retention =0.51+/-0.10 for healthy non-asthmatics was different from the asthmatics.

DISCUSSION

As expected the acute inhalation of HS in these female asthmatics enhanced MCC compared to baseline. The immediate and very rapid effect was somewhat unexpected especially without the accompanied coached coughing that is included in

HS inhalation/sputum induction protocols (24, 25). Despite this dramatic acute effect, MCC was unaffected 4 hours post treatment relative to baseline. This is in contrast to findings in CF, where we found enhanced MCC at 4 hours post HS inhalation, similar to that observed acutely relative to baseline (10). Unlike healthy volunteers, MCC (Ave60Clr and Ave120Clr) was unchanged between baseline and 4 hours post treatment suggesting that the resident mucus had not been depleted (compromised) by the acute HS treatment 4 hours earlier (7), at least in the larger bronchial airways. Our recent study on the effects of HS treatment in chronic bronchitis showed slowing of MCC relative to baseline after multiple treatments over a 2-week period (11).

Whether a longer-term effect in asthma may also occur is uncertain. It may also be that enhanced MCC could have been observed at earlier times post treatment (e.g. 2 hours). The dramatic, acute effect may be beneficial where acute mucus clearance is needed, e.g. acute exacerbations, where there may be severe slowing of MCC (13,14) and where in-patient treatment will allow monitoring of any HS-induced hyper-reactivity. This is analogous to the indications for use of established, quick relief medications for asthma (such as albuterol). While the absence of a durable HS effect in these asthmatics may not support its use for maintenance therapy, it may still be useful for asthmatics in whom periodic clearance of mucus may be beneficial. It will be important to consider the safety and duration of effect of HS when exploring potential uses for asthma.

We included MDI albuterol treatment prior to all HS treatment in the current study to mitigate potential airway hyperreactivity in these participants. It therefore should be emphasized that any treatment effects we observed on MCC were for the combination of MDI albuterol followed by nebulized HS. β-agonists delivered by MDI have been shown to acutely enhance MCC in asthma (26,27) but not to the extent observed in the present study. In fact, in one case, no stimulation of MCC was observed despite the fact that delivery of terbutaline by MDI produced significant bronchodilatation (28). These studies would suggest that a greater dose of beta-agonist is required for enhancement of MCC than is needed to induce bronchodilation. Our study design did not allow for distinguishing the relative contribution of HS vs. albuterol on MCC but it is clear that any

HS treatment will always include pretreatment with a short acting bronchodilator to mitigate any HS induced hyper-reactivity.

There was also some very infrequent, spontaneous cough (see supplemental data) associated with the acute treatment; average 2.3 coughs for all. In previous studies where we've incorporated 60 voluntary coughs during the 60-90 minute period of MCC measures in healthy adults (23) we found a 70% increase in clearance for MCC vs. MCC+cough, much less than what we observed here over the first 60 min (Ave60Clr), a 163% enhancement with only a few coughs. The individual data (supplement) showed that even those with no spontaneous coughing had a significant enhancement of MCC with albuterol/HS. While we cannot quantify the contribution of a few spontaneous coughs on clearance in the current study, it nevertheless can be argued that some spontanteous cough associated with the albuterol/HS treatment is advantageous if it aids in the clearance of mucus from the airways.

The single treatment of inhaled 7% HS in our study of adult females with moderate to severe asthma produced no evidence of airway hyper-reactivity, e.g. coughing or acute reduction in lung function. Retrospective analysis of induced sputum procedures in mild-moderate asthmatics (successive inhalation of 3, 4, and 5% HS) also showed no adverse effects associated with HS challenge (24). Nevertheless, the small number of participants in the current study does not allow for adequate power to exclude potential adverse effects from inhaled 7% HS. It also may be that a lower tonicity of saline (e.g. 3%) would prove to be as effective for acutely enhancing MCC while providing a greater margin for safety compared to 7% HS. Finally, it is not clear whether multiple HS treatments will be well tolerated but our experience with multiple induced sputum procedures in asthmatics has shown no HS-associated adverse events.

Finally, this pilot study was limited to female adults. While there is some suggestion that healthy males may exhibit slower baseline MCC than females (23) there is no data to suggest gender-based differences for MCC in asthmatics nor differences in HS responsiveness. Therefore, we think it unlikely that further addition of males to the study would change the fundamental findings we observed and report here in females.

Conclusion

Mucociliary clearance was dramatically enhanced during and immediately after acute treatment with inhaled 7% hypertonic saline delivered by Pari LC Star but had no prolonged effect at 4 hours post treatment. Due to the immediate and short-lived effect of HS on MCC in asthma, we hypothesize that this intervention may be most effective for periodic clearance of mucus or with viral or allergen-induced acute exacerbation where acute mucus slowing/plugging may be present. Future studies to assess the effect and safety of HS treatment on experimental challenges (14) in these patients may provide support for moving forward with such a treatment regimen.

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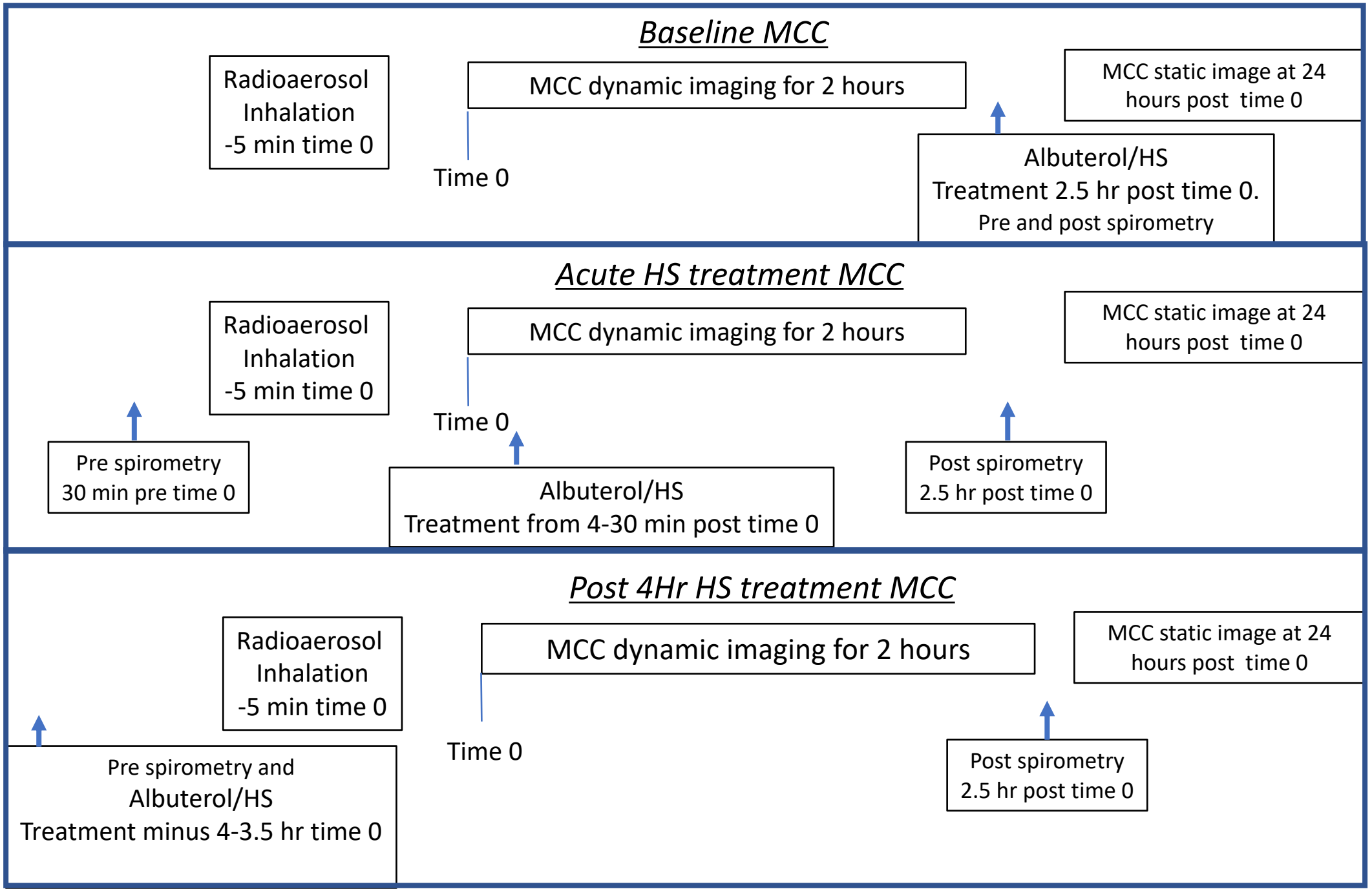
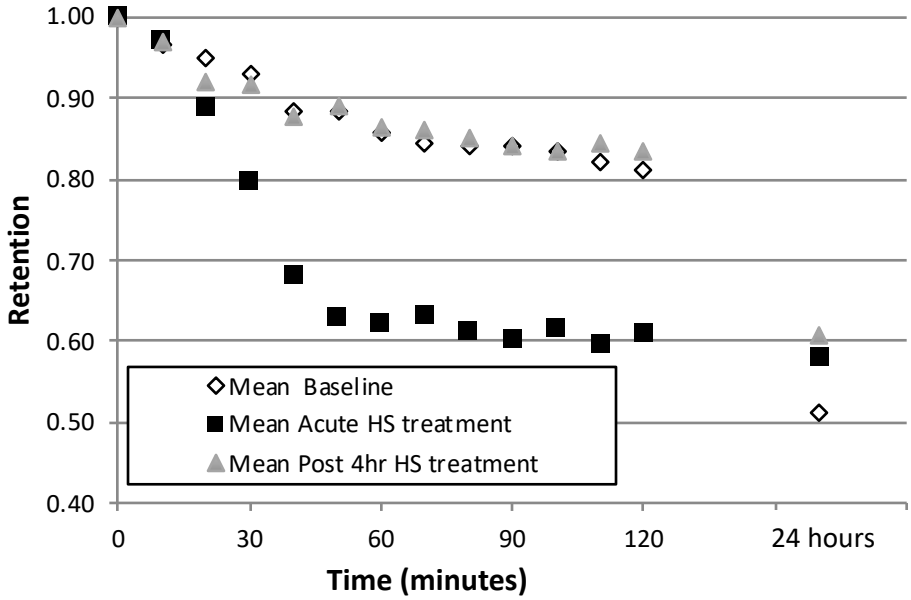
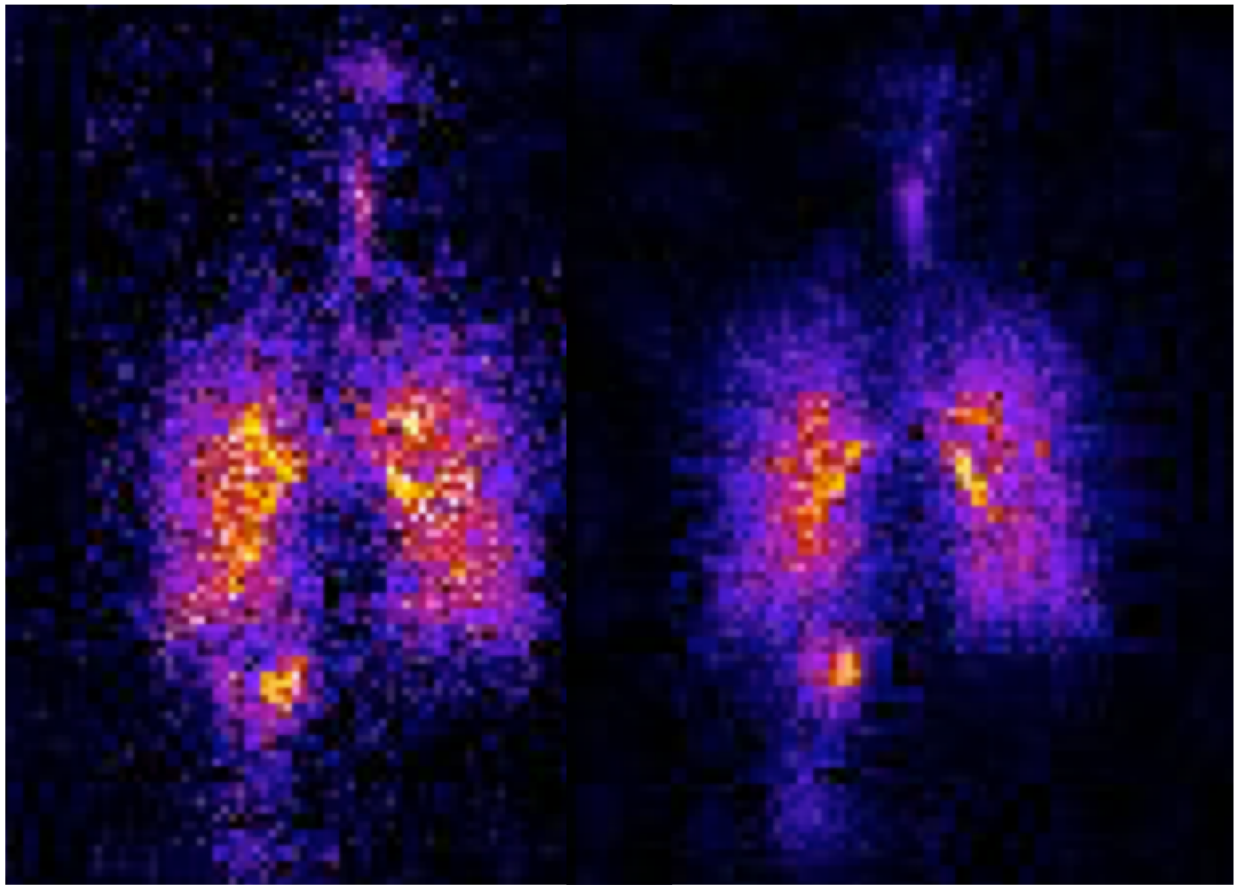

Baseline MCC
Radioaerosol Inhalation -5 min time 0
MCC dynamic imaging for 2 hours
Time 0
MCC static image at 24 hours post time 0
Albuterol/HS Treatment 2.5 hr post time 0.
Pre and post spirometry
Acute HS treatment MCC
Radioaerosol Inhalation -5 min time 0
MCC dynamic imaging for 2 hours
MCC static image at 24 hours post time 0
Time 0
Pre spirometry 30 min pre time 0
Albuterol/HS Treatment from 4-30 min post time 0
Post spirometry 2.5 hr post time 0
Post 4Hr HS treatment MCC
Radioaerosol Inhalation -5 min time 0
MCC dynamic imaging for 2 hours
MCC static image at 24 hours post time 0
Time 0
Pre spirometry and Albuterol/HS Treatment minus 4-3.5 hr time 0
Post spirometry 2.5 hr post time 0


1.00
0.90
0.80
0.70
0.60
0.50
0.40
Retention
Mean Baseline
Mean Acute HS treatment
Mean Post 4hr HS treatment
0
30
60
90
120
24 hours
Time (minutes)

Cine of 60 min Clearance in Asthmatic baseline (left)
and during acute treatment with inhaled HS (right)



Data Supplement

	Ave60Clr (%)				**Ave120Clr (%)**				**24hr retention**				**C/P**				**# of coughs**		
	Baseline	Acute	Durability		Baseline	Acute	Durability		Baseline	Acute	Durability		Baseline	Acute	Durability		Baseline	Acute	Durability
Subject																			
1	0.4	26.1	-0.8		5.3	35.4	1.6		0.60	0.62	0.74		1.8	1.7	2.3		0	0	0
3	18.4	16.8	17.5		20.7	22.5	19.8		0.42	0.66	0.53		2.7	2.6	2.1		0	0	0
4	11.7	22.0	6.8		17.1	27.4	10.7		0.46	0.49	0.50		2.6	1.9	2.1		0	4	0
5	-3.8	10.4	-3.4		-3.0	17.7	-2.4		0.53	0.61	0.77		1.6	1.6	1.3		0	2	0
6	14.8	23.9	9.4		17.0	30.8	15.2		0.55	0.70	0.64		2.3	2.4	2.2		0	4	0
7	13.6	27.3	11.1		19.4	34.1	15.7		0.55	0.52	0.56		2.2	2.0	1.9		0	4	0
8	12.7	36.4	19.4		20.1	45.1	21.3		0.52	0.57	0.73		2.8	2.6	2.8		0	1	0
9	3.1	24.7	14.7		6.0	36.1	17.5		0.46	0.45	0.41		2.1	2.0	2.2		0	3	0
Mean	8.9	23.4	9.3		12.8	31.1	12.4		0.51	0.58	0.61		2.2	2.1	2.1			2.3	
SD	7.9	7.6	8.2		8.8	8.6	8.6		0.06	0.09	0.13		0.5	0.4	0.4			1.8	