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Aerosol furosemide for dyspnea: Controlled delivery does not improve effectiveness

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Abstract

Aerosolized furosemide has been shown to relieve dyspnea; nevertheless, all published studies have shown great variability in response. This dyspnea relief is thought to result from the stimulation of slowly adapting pulmonary stretch receptors simulating larger tidal volume. We hypothesized that better control over aerosol administration would produce more consistent dyspnea relief; we used a clinical ventilator to control inspiratory flow and tidal volume. Twelve healthy volunteers inhaled furosemide (40mg) or placebo in a double blind, randomized, crossover study. Breathing Discomfort was induced by hypercapnia during constrained ventilation before and after treatment. Both treatments reduced breathing discomfort by 20% full scale. Effectiveness of aerosol furosemide treatment was weakly correlated with larger tidal volume. Response to inhaled furosemide was inversely correlated to furosemide blood level, suggesting that variation among subjects in the fate of deposited drug may determine effectiveness. We conclude that control of aerosol delivery conditions does not improve consistency of treatment effect; we cannot, however, rule out placebo effect.

Keywords

Dyspnea; Furosemide; Palliative care; Symptom management

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Conflicts of interest: none declared

1 Introduction

Dyspnea that persists despite maximal treatment of the underlying disease (refractory dyspnea) is a common cause of patient suffering (Kamal et al., 2011). At present, systemic opioids are the only evidence-based pharmacologic treatment available to alleviate refractory dyspnea (Bausewein et al., 2008; Currow et al., 2011; Dudgeon and Rosenthal, 1996; Ekstrom et al., 2015; Jennings et al., 2002). Opiates are perceived to have many disadvantages including constipation, confusion, nausea, respiratory depression and regulatory barriers (Currow et al., 2011; Rocker et al., 2012). Inhaled furosemide has shown promise in relieving refractory dyspnea with none of these side effects. A chloride channel blocker commonly used as a diuretic, furosemide also acts on vagal pulmonary receptors when administered as an aerosol (Sudo et al., 2000). Experiments conducted in rats have shown that slowly adapting pulmonary stretch receptors (which respond to inflation) are profoundly sensitized by furosemide while rapidly adapting stretch receptors (which respond to lung collapse) are desensitized. This generates vagal afferent traffic that presumably provides an illusory report of increased tidal volume to the brain. Increased tidal volume in humans relieves air hunger via vagal mechanoreceptors (Manning et al., 1992); thus it is proposed that aerosol furosemide acts through this pathway to effect relief by mimicking larger tidal volume (Moosavi et al., 2007). Air hunger is the most common form of clinical dyspnea (O'Donnell et al., 2013; Smith et al., 2009) and is associated with severe breathing discomfort; thus, it is reasoned that aerosol furosemide might provide a non-opiate treatment for many cases of refractory dyspnea.

Aerosolized furosemide has been tested as a treatment for dyspnea in controlled laboratory studies and small clinical trials (Jensen et al., 2008; Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000; Ong et al., 2004; Wilcock et al., 2008). Aerosolized furosemide administered at a dose of 20 to 40mg has proven effective in many individuals, but it has also been shown not to reduce dyspnea in many others. Large inter-individual variation in the perceptual response to inhaled furosemide is evident in all published studies.

The source of this wide variability in treatment effect is unknown, but several mechanisms can be postulated to explain lack of treatment effect in certain individuals. Inconsistent aerosol drug delivery is one of the most obvious possible mechanisms. Control of inspiratory flow or inspired volume during aerosol administration is poorly described, if at all, in published studies of furosemide inhalation. Inspiratory flow and tidal volume are key parameters in efficiency and location of particle deposition; if flow is high, particles will impact in the oropharynx and upper airways, not deeper in the lung where the slowly adapting stretch receptors are found (for more detailed description, see review in (Bennett et al., 2002; Brain and Valberg, 1979; Moren et al., 1994)). In addition, most published studies report administering drug via breathe-through nebulizers; aerosol generated during expiration is lost into the room under these conditions, so that the actual inhaled dose would vary depending on the ratio of inspiratory to expiratory time.

The variability of furosemide response could also stem from variable individual sensitivity to the relief of dyspnea by stimulation of slowly adapting pulmonary stretch receptors. The

potency of this neural pathway may vary among individuals due to differences in afferent input and central nervous system processing.

We tested the hypothesis that better control over aerosol administration would produce more consistent dyspnea relief. We also tested the hypothesis that furosemide works poorly in those individuals who exhibit an otherwise weak tidal volume relief.

In a crossover study, we used a laboratory model of dyspnea in which graded levels of hypercapnia were delivered to healthy subjects during constrained ventilation. Subjects experienced the same dyspnea challenge before and after treatment with aerosol furosemide and aerosol saline. Inspiratory flow and tidal volume were controlled during aerosol administration. We also compared the subjects' response to inhaled furosemide to the response to two "secondary" treatments designed to provide better understanding of mechanism: 1) We tested the response to larger tidal volumes to assess the potency of the pulmonary stretch receptor relief pathway. 2) We tested the response to intravenous furosemide to address the possibility that aerosol furosemide acts through the systemic effect of absorbed furosemide.

2 Methods

2.1 Subjects

This protocol was approved by the Committee on Clinical Investigations (Institutional Review Board) at Beth Israel Deaconess Medical Center. All subjects gave written informed consent. They were informed that we were studying shortness of breath, that they would be uncomfortable for periods during the study, and that they could interrupt procedures at any time. They were also informed that, while the drug was approved for use in other contexts, administration via inhalation was investigational (FDA IND 108667). On the first preliminary day subjects completed the Brief Symptom Inventory-18 to assess general psychological distress. Exclusion criteria are shown in Supplement section "Subjects: Selection and Characteristics". Twenty-three subjects signed consent and drug treatment data sets were obtained and analyzed for 12 subjects. Reasons for elimination of subjects from study or the analysis are in Supplement section "Subjects: Selection and Characteristics" (Table S-1). One data set was discarded before further analysis due to later discovery of a disqualifying event, thus data from 11 subjects are presented. Characteristics of the subjects are shown in Supplement section "Subjects: Selection and Characteristics" (Table S-2).

2.2 Aerosol delivery

To better control and optimize aerosol deposition, we used a standard clinical volume-control ventilator to control inspiratory flow and volume (Siemens Servo 900c, Siemens Elema AB, Solna, Sweden). Subjects were ventilated through a mouthpiece. The setup included three Aeroneb Pro-X nebulizers (Aeroneb Solo, Aerogen Ltd, Galway, Ireland) connected to 3 nebulizer heads mounted on a 3.5cm × 38cm ID acrylic manifold. Spacer tubes of similar diameter and 5cm or 10cm length could be added in order to provide a leading aerosol-free space proportional to the subjects predicted VC (0, 50 or 100 ml as

needed to scale the volume to the size of the subject); this was done to minimize delivery of aerosol to the alveoli, which are beyond the slowly adapting stretch receptors that are the presumed target of the drug. This manifold was connected to the inspiratory and expiratory lines of the ventilator and to a mouthpiece of similar internal diameter (Fig 1). Large diameter tubing and a large mouthpiece were used in the aerosol pathway to minimize gas velocity, thus minimizing particle impaction in oropharynx; the minimum cross sectional area of the external aerosol pathway was 5.7 cm².

The ventilator was set to provide tidal volume of 15% of predicted vital capacity at 15 breaths/min. In order to keep inspiratory flow between 0.3 and 0.5 liters/sec, we set TI/TTOT 0.33 for tidal volume less than 650ml and at 0.5 for tidal volume greater than 650ml. The inspired oxygen concentration was enhanced at 30%.

The ultrasonic screen nebulizers generated particles of respirable size (Mass Median Aerodynamic Diameter 3.4microns, ± 2.2 GSD). Ultrasonic nebulizers producing similar size particles were used in three previous studies of furosemide that showed positive effects (Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000).

The drug was nebulized in 7 minutes (mean, range from 5 min to 10 min). Because furosemide was nebulized at $\frac{1}{3}$ the rate of saline (but with the same particle size; personal communication, James Fink), we powered the three nebulizers simultaneously with furosemide and powered them successively with saline so that the density of inhaled mist and the total administration time would be similar.

2.3 Psychophysical measurements

2.3.1 Breathing discomfort scale—Subjects were asked to rate continuously their “breathing discomfort” described as “*how unpleasant or bad your breathing feels...*” using a vertical Breathing Discomfort Visual Analog Scale (BDVAS) labelled “no discomfort” at the bottom and “unbearable” at the top. Unbearable was further defined as “*you can’t stand it and you want us to stop it*”; a rating of unbearable triggered a sound signal and we informed subjects that we would immediately reduce the stimulus on activation of the signal. They were instructed to change the rating whenever they felt a change in discomfort. The scale was implemented electronically with a linear vertical LED visual readout that the subject adjusted by turning a knob. An analog signal was provided for continuous recording. BDVAS rating was the primary outcome measure for dyspnea challenge tests.

2.3.2 Multidimensional Dyspnea Profile—Immediately after each dyspnea challenge trial, subjects completed the Multidimensional Dyspnea Profile (MDP) focusing on the last 30 seconds of the trial (Banzett et al., 2015). MDP data were used to describe the nature of discomfort produced by the stimulus, and to determine whether that description changed with treatment.

2.4 Physiological measurements

During the experiment, tidal P_{CO2} and mouth pressure were sampled at the common line between mouthpiece and rehumidifier. Inspiratory and expiratory flows were measured by separate pneumotachometers (n°2 Fleisch with Omega PX163PC01D75 pressure transducer,

Omega, Stamford, CT). Tidal P_{CO_2} and P_{O_2} were monitored with an infrared analyzer; pulse rate, SpO_2 and non-invasive arterial blood pressure were monitored throughout each trial (all with Datex Cardiocap model CG-2GS, Instrumentarium Corp, Helsinki Finland). Data were digitized and recorded for later analysis (PowerLab/16s with Chart 5.1 software ADInstruments, Colorado Springs, CO and Macintosh G4 Powerbook; Apple Inc, Cupertino CA). ECG was monitored for safety. Airway pressure, flow, and gas instruments were calibrated daily.

On each day, blood furosemide level was assessed by a venous sample drawn 30 min following the end of aerosol administration. Samples were processed by two external laboratories because the hospital's contract supplier changed midway through the experiment series. The efficiency of aerosol absorption (the dose-adjusted ratio of furosemide blood level following an aerosol treatment to furosemide blood level following an intravenous dose) could be calculated in 8 subjects (blood data for two aerosol furosemide test days and one IV furosemide test day were missing due to lab or handling errors).

2.5 Response tests

2.5.1 Laboratory dyspnea challenge—During the dyspnea challenge, minute ventilation (V_E^o) was limited to 0.13 l/min/kg during hypercapnia using a system previously described (Banzett et al., 2011; Banzett et al., 2008; Moosavi et al., 2003). Breathing frequency was determined by instructing the subject to breathe in time with a metronomic sound; this technique fixed tidal volume because (V_E^o) was held constant. End-tidal P_{CO_2} (PET_{CO_2}) was altered by changing inspired P_{CO_2} and holding each PET_{CO_2} level for at least 3 minutes to achieve a steady state response (Banzett, 1996). We approximated step changes in PET_{CO_2} by initially overshooting the required level of PI_{CO_2} . Before each change, the limiting device was opened and subjects were told to take three breaths as large as desired. This served to 'reset' discomfort level (i.e., free breathing relieved dyspnea), and also promoted faster changes in PET_{CO_2} to facilitate achievement of the next step level. See Supplement section "Protocol" Fig 1 for detail.

2.5.2 Tests of the pulmonary stretch receptor relief pathway—The sensitivity to the "tidal volume relief" of dyspnea in each individual was assessed from two tests: In one test, the same dyspnea challenge was applied but subjects were allowed a minute ventilation up to 0.26 l/min/kg (twice the standard limit); respiratory frequency was held constant, set by a metronome. In the second test, subjects were free to breathe whatever tidal volume they desired; respiratory rate was again held constant. In both tests, inspired P_{CO_2} was raised in order to provide two to four stepwise PET_{CO_2} elevations at levels equivalent to those used in the standard dyspnea challenge test. The free-breathing test also allowed us to assess the effects of furosemide and placebo on respiratory drive.

2.6 Experimental protocol

At the beginning of each session, resting PET_{CO_2} was measured with a nasal sampling catheter while the subject was reading a non-emotive book in a quiet environment. Data were collected at the end of a 10–15 min reading period.

Preliminary study days—Subjects underwent three preliminary study days to familiarize them with the laboratory equipment, the rating procedure, the dyspnea challenge and the free-breathing CO₂ challenge. Dyspnea challenge included trials with random PET_{CO2} and some with staircase PET_{CO2} steps, including at least one stimulus step of adequate intensity to induce intolerable discomfort. Preliminary study days also served to assess the subjects' ability to rate reliably (we required a minimum correlation coefficient, R², of BDVAS rating vs. PET_{CO2} = 0.49 for inclusion in the study) and to provide opportunity to test the effect of larger tidal volume.

Treatment Test days—An intravenous catheter was placed in the forearm. After measuring resting PET_{CO2}, we performed two pre-treatment baseline trials of the dyspnea challenge response and a single free-breathing CO₂ response. Each dyspnea challenge trial comprised three or four 3 min staircase steps of increasing PET_{CO2} and lasted 10 to 15 minutes; an example is shown in Supplement Fig 1.

We then administered furosemide (4ml of 10mg/ml) or normal saline sham (4ml) over the course of 10 minutes by nebulization. On another day the subject received an intravenous dose of 15mg furosemide in 10 ml of saline administered over 5 minutes.

Beginning immediately after the drug administration, subjects completed three dyspnea challenge trials at the same PET_{CO2} steps as the pre-drug trials and completed a steady state free-breathing CO₂ test. These tests were administered over the course of 2 hours. Subjects were observed for adverse effects for at least 2 hours after drug administration, and were encouraged to call the lab or the covering physician if they noticed anything unusual in the following day.

2.7 Blinding and Randomization

The research pharmacy used a balanced randomization table to give approximately equal distribution of order of presentation of aerosol furosemide and aerosol saline. Subjects were informed that they would receive on a given day either nebulized furosemide (accurate), or nebulized albuterol (actually saline). On the intravenous treatment day, subjects were told that they would receive either furosemide or albuterol but they always received intravenous furosemide. This deception was to control for expectations by creating equal expectations for these conditions. For more details, see Supplement section “Blinding”. On experiment days, subjects consumed 500ml of orange juice upon arrival. We measured urine output and gave equal fluid replacement using a beverage containing potassium (665mg/l) sodium (175mg/l) and carbohydrate (57g/l).

2.8 Analysis

For analysis, 30 seconds of BDVAS ratings at the end of each 3 min step in PET_{CO2} were collected. This time period is expected to be steady-state, but to account for delay and rise time in perceptual response following changes in PET_{CO2} and tidal volume (Banzett, 1996; Evans et al., 2002), we matched BDVAS data to physiological variables (VT, PET_{CO2}, and fR) collected for the 60 sec period ending at the center of the rating period (details in Supplement Section “Data Reduction”, Fig 1).

As per our *a priori* analysis plan we determined a single number representing ‘treatment effect’, change in dyspnea at the PETCO₂ that caused breathing discomfort (BDVAS) equal to 60% of full scale (termed the ‘benchmark PETCO₂’). The process for determining treatment effect is detailed in Supplement Section “Determination of Treatment Effect” (Fig 2). We planned *a priori* to compare each subject’s furosemide response to the mean of all subjects’ responses to saline using an unpaired 2-tail T test, predicated on the supposition that placebo responses would be small and random. The *a priori* significance level was $p < 0.05$. Because this turned out not to be the case, we present other analyses as well; all lead to the same conclusions.

Exploratory descriptive correlation analyses were done to examine several potential explanatory factors. These analyses were linear regressions performed with Excel version 12.3.6, and were not tested for significance.

3 Results

3.1 Data Attrition

Nine of twelve subjects completed all of the experimental protocol on all 3 test days. One subject was excluded from analysis because of cannabis consumption, (not known until after the experiments because urine toxicology results were delayed). In two subjects, data on aerosol saline response are not available (one subject withdrew before performing the aerosol saline and IV furosemide experiments, one subject did not meet criteria for consistent dyspnea ratings on the saline experiment day, i.e., R^2 of BDVAS rating vs. PETCO₂ was less than 0.49 in pre-drug runs on that day; exclusion criteria are detailed in the Supplement).

3.2 Main analysis-effect on Breathing Discomfort

Both aerosol treatments relieved breathing discomfort in some subjects, and the effect for the group was significant in each case. The mean Treatment Effect following aerosol furosemide was –20% full scale ($p < 0.05$, 2-tail unpaired T Test). The response varied widely among individuals: 5/11 subjects (45%) showed a treatment effect of at least 20% full scale, a clinically meaningful reduction in Breathing Discomfort. The mean Treatment Effect following aerosol saline, however, was, nearly the same –20% full scale ($p < 0.05$, 2-tail unpaired T Test). The subjects who showed a meaningful response to aerosol furosemide also showed similar responses to aerosol saline (apart from subject AF3, who did not complete the saline study).

Both secondary treatments relieved breathing discomfort. The mean Treatment Effect following IV furosemide was –16% full scale ($p < 0.05$, 2-tail unpaired T Test), somewhat smaller than the effect of aerosol furosemide despite much higher blood levels of furosemide. The mean Treatment Effect of doubling tidal volume was –43% full scale ($p < 0.05$, 2-tail unpaired T Test). Mean Treatment Effect did not differ statistically between aerosol drug, aerosol saline, and IV drug (Fig 2). There was wide variation in individual response, but without worsening of Breathing Discomfort following aerosol (Fig 3).

Our *a priori* statistical test, aerosol furosemide treatment effect vs. mean aerosol saline treatment effect, showed a statistically insignificant difference between furosemide and saline ($p=0.99$). In *post hoc* analyses, paired analysis of those subjects completing both tests yielded p value of 0.77, and ANOVA yielded no significant F value.

The mean regression lines describing the group response indicate that both treatments shifted the response line rightwards by about 3 Torr, with a small increase in slope (Supplement Fig 3).

3.3 Potential explanatory factors for individual variation in furosemide response

3.3.1 Sham aerosol—Saline aerosol was used to control for a ‘non-specific treatment effect’ of the procedure itself, for instance a psychological ‘placebo effect’. The mean effect of saline was nearly the same as the mean effect of furosemide aerosol and there was a large overlap between responders to furosemide and responders to saline; however, 2 individuals responded to saline but not furosemide. This resulted in a weak correlation between treatment effects of aerosol furosemide and aerosol saline ($r^2=0.33$; Fig 4)

3.3.2 Pulmonary stretch receptor relief pathway—The treatment effect of free breathing and the treatment effect of increased tidal volume dyspnea challenge were used to assess the individual strength of the pulmonary stretch receptor pathway presumed to underlie aerosol furosemide’s action. The two tests were similar, and showed similar effect on breathing discomfort ($r^2=0.81$).

Most subjects experienced substantial relief with both tests (Fig 5). Two subjects (AF1 and AF17), however, showed very little dyspnea relief with either test (Supplement Fig4). Both of these subjects more than tripled tidal volume when allowed to breathe freely, and doubled tidal volume in the second test. The same two subjects also showed little relief with furosemide treatment. Conversely, all ‘responders’ to furosemide showed strong dyspnea relief with both tests. However, several subjects showed good relief with larger breaths, but little relief with furosemide; therefore, the individual treatment effect of both of these tests correlated weakly with the treatment effect of furosemide ($r^2=0.11$ and 0.26).

3.3.3 Systemic action of furosemide—A fraction of inhaled furosemide is absorbed into the blood. We included a study arm assessing the effect of intravenous furosemide on dyspnea to test the possibility that any treatment effect of aerosol furosemide was simply a consequence of systemic absorption in the lung. We chose a smaller dose of IV furosemide to account for incomplete aerosol absorption, but still obtained higher blood levels than with aerosol administration. Despite substantially higher blood levels, the average treatment effect of IV furosemide was smaller. Furthermore, individual treatment effect did not correlate to individual treatment effect of aerosol furosemide ($R^2=0.31$, Supplement Fig 5).

Furosemide deposited in the lung is variably absorbed into the blood. The plasma concentration of drug following inhalation ranged from less than the detectable level (0.08 mcg/ml) to 1.0 mcg/ml. The relationship between individual blood levels and individual treatment effect provides another opportunity to test the hypothesis that the treatment effect is due to systemic action. The magnitude of individual treatment effect was inversely

proportional to the individual blood level of furosemide following inhalation of aerosol furosemide ($r^2=0.56$; Supplement Fig 6).

To estimate aerosol absorption efficiency following aerosol we divided the blood level following 40mg aerosol administration by the blood level following 15mg iv furosemide in the same subject adjusted by the dose. In 8 of 11 subjects, blood furosemide values were available for both IV and aerosol days. Absorption efficiencies ranged from 0 to 30% of aerosolized dose. Individual absorption efficiency was highly inversely correlated to individual aerosol furosemide treatment effect ($r^2 = 0.90$; Fig 6).

3.3.4 Gender—Furosemide treatment effect in the 3 women (−23% Full scale) was not different from that in the 8 men (−23 % Full scale).

3.3.5 Psychological factors—The mean total BSI-18 score was in the normal range (7.3 ± 5.3). Responders to furosemide (AF3, 7, 9, 12 & 23) had slightly lower BSI-18 anxiety scores compared to non-responders to both interventions (AF1, 2, 4, 17), though all were in the normal range. See Supplement Table 1 for individual BSI scores. Consistent with this finding, ratings of breathing-related anxiety were lower for the responders in MDPs collected before drug treatment (mean $20\% \pm 7$ SE vs mean $50\% \pm 23$ SE full scale) despite nearly identical overall discomfort (mean 79% vs mean 77% full scale).

3.4 Sensory Quality and Emotional Response (Multidimensional Dyspnea Profile)

Due to the experimental design, MDP results are only available for the stimulus level at the end of each run, which was the highest stimulus for that run. The average overall breathing discomfort (A1) at the end of pre-drug runs was respectively 85% of scale (at mean $PET_{CO_2}=54.1$ Torr) for furosemide day and 80% of scale (at mean $PET_{CO_2}=52.5$ Torr) for saline day, and was reduced slightly by both treatments to 80% of scale (at mean $PET_{CO_2}=54.5$ Torr) following furosemide and to 78% of scale (at mean $PET_{CO_2}=52.2$ Torr) following saline. The dominant sensory quality was the air hunger group, confirming the stimulus design. The dominant emotional response was anxiety (Supplement Figure 9).

To look for more subtle changes that may have occurred in MDP responses we did a further analysis similar to that reported in an earlier study (Banzett et al., 2011). Since sensory quality (SQ) and emotional response (A2) are not necessarily linearly related to overall breathing discomfort (A1), it may not be appropriate to simply ‘normalize’ these components by dividing by overall discomfort. We therefore re-analyzed MDP results by finding matched A1 levels before and after treatment, and comparing the SQ and A2 items at matched A1. Matched pairs for aerosol saline and aerosol furosemide were available for 8 subjects. The analysis showed that there were no significant changes in the five SQ or the five A2 items with either treatment. Data are shown in Supplement Fig 10.

3.5 Hypercapnic ventilatory response

Minute ventilation during free breathing measured at the benchmark PET_{CO_2} was 1 to 4 times the minute ventilation allowed during dyspnea challenge. Minute ventilation during

unrestricted breathing did not significantly differ before and after furosemide administration (respectively $VE=21.1 \text{ L}\cdot\text{min}^{-1}$ vs $VE=18.8 \text{ L}\cdot\text{min}^{-1}$, $p=0.3$).

The average ventilatory response to hypercapnia did not differ among drug days; minute ventilation per kg body weight was consistent at 8 torr above resting between furosemide day ($V_E^o = 0.27 \text{ L}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) and saline day ($V_E^o = 0.25 \text{ L}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) and did not significantly vary ($p=0.3$). Hypercapnic ventilatory response was not correlated to furosemide treatment effect ($r^2=0.05$).

Perceptual sensitivity to hypercapnia during unrestricted breathing did not significantly vary across days. The mean BDVAS at 8 torr above resting PET_{CO_2} was 14%FS on furosemide day and 21 %FS on saline day ($p=0.2$).

3.6 Physiological data

Minute ventilation at benchmark PET_{CO_2} remained constant following treatment administration showing successful implementation of minute ventilation control (Table 1). As expected, minute ventilation was at $0.13 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in every subject. Paired T tests showed that ventilation in each individual was not significantly different between treatment days (overall mean saline: $VE=10.1 \pm 2.8 \text{ L/min}$, furosemide: $VE=10.2 \pm 2.9 \text{ L/min}$). Airway pressure at benchmark PET_{CO_2} , a reflection of inspiratory effort, did not significantly change after furosemide inhalation ($p=0.12$), or after saline administration ($p=0.12$) (Table 1).

3.7 Side effects

There were no significant or unexpected adverse events. All subjects experienced the expected increase in urine output after aerosol and IV furosemide as compared to aerosol saline. Cumulative urine output 60 minutes after 40 mg aerosol furosemide administration was $1069\text{ml} (\pm 435\text{SD})$, after aerosol saline $500\text{ml}(\pm 264\text{SD})$, and after 15mg IV furosemide was $1556\text{ml} (\pm 435\text{SD})$. Subject AF17 seems to have absorbed the greatest fraction of drug: he had identical blood levels and nearly identical urine output following 40mg aerosol furosemide and 15 mg iv furosemide. As would be expected, urine output following aerosol furosemide was positively correlated to furosemide blood level ($r^2 = 0.75$; Supplement Fig 8).

4 Discussion

4.1 Overview

Inhaled furosemide relieved breathing discomfort associated with experimental dyspnea challenge in healthy subjects, but the treatment effect was highly variable among subjects. Nearly all subjects experienced some relief of dyspnea following furosemide inhalation and none of them reported worsening of breathing discomfort. The effect of aerosol saline was somewhat greater than in previous studies of evoked dyspnea (Jensen et al., 2008; Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000; Ong et al., 2004; Wilcock et al., 2008), but substantial aerosol saline effect has been reported in several studies of dyspnea in

patients at rest (Panahi et al., 2008; Stone et al., 2002). Our results suggest that the effect may be related to a larger placebo effect.

Our data tested several hypotheses that might have explained variability in response to aerosol furosemide:

1. Controlling the factors that affect aerosol deposition did not improve the consistency of treatment response among subjects.
2. The variance in innate responsiveness of individuals to tidal volume relief only partially explained the variance in response to aerosol furosemide. The 2 subjects who showed little relief with large tidal volume also showed little relief with furosemide treatment and all 5 subjects who had a substantial response to furosemide also had a substantial response to larger breaths. However, there were 3 subjects with substantial tidal volume relief who had little relief from furosemide.
3. Systemic absorption of furosemide cannot explain the treatment effect of aerosol furosemide: higher blood levels following IV dose produced a smaller average response: blood levels following aerosol drug were inversely related to treatment effect.
4. Subjects who experienced a meaningful treatment response to aerosol saline showed similar response to aerosol saline.

Our most unexpected finding was a significant improvement of breathing discomfort in response to aerosol saline. Treatment with saline reduced breathing discomfort by 20% of full scale on average, and 6 of 11 eleven subjects (55%) showed a clinically significant effect (at least 20% reduction). An average sham treatment effect of this magnitude has not been seen in prior laboratory studies of aerosol furosemide using the aerosol saline sham arm (Moosavi et al., 2007; Nishino et al., 2000). Only one laboratory study reported individual results (see Fig 2/Moosavi et al). This study found that some subjects had a large reduction in dyspnea following saline, but it also found a much smaller net effect of saline, and a large variability of response to both saline and furosemide. We used the same dyspnea stimulus as Moosavi and colleagues (Moosavi et al., 2007). Mean treatment effect of furosemide was nearly identical to the one in the Moosavi et al. study (20% in this study, 18% in the Moosavi et al. study), however the mean treatment effect of saline differed (20% in this study, 9% in the Moosavi et al. study). The reason for the difference in mean saline effect was that Moosavi et al. saw a seemingly random effect of saline aerosol, with both positive and negative responses averaging to near zero, while we never saw worsening of dyspnea following saline. In the present study, air hunger was achieved by limiting tidal volume during mild hypercapnia. Tidal volume was kept constant over the experiment in all subjects and was the same after furosemide administration and after saline administration (table 1). We can find nothing in the physiological data relevant to the dyspnea stimulus that explains the observed responses or the variability in response to furosemide or saline.

4.2 Possible psychological “placebo effect”

Placebo effect frequently plays a role in response to treatment. A review of the placebo effect in pain studies reports that the mean effect of placebo on pain is a reduction of 20% of full scale in VAS pain ratings, and that 27 to 56% of subjects respond to placebo analgesic; consistent with the effect seen in the present study (Price et al., 2008). Expectation and verbal suggestion are important factors in placebo response (Price et al., 2008; Tracey, 2010). Although our subjects were healthy, and knew the dyspnea they were experiencing could be stopped at a moment's notice, they may have been influenced by what they were told when recruited and informed prior to consent. The subjects knew our intention was to test treatments for dyspnea. Although we told subjects that we did not know if the treatments were effective, the subjects may well have deduced that we would probably be testing drugs likely to be effective. In this study, there is a further complication: we deceived the subjects by telling them they would receive two active treatments, namely either furosemide or albuterol. This was done to balance expectations because subjects would have been able to identify aerosol furosemide from taste associated with the drug and the subsequent diuresis (Moosavi et al., 2007). Although this deception balanced expectation, it also probably created an expectation that both treatments would work, thus enhancing placebo effect (Pollo et al., 2001).

If expectation and suggestion are the key factors, we would expect that the same subjects who responded to furosemide would also respond to saline. The fact that there was no subject who responded to furosemide who did not also respond to saline favors the idea that this is a placebo effect. To our knowledge, strong placebo effects on air hunger evoked by a controlled stimulus have not been previously reported – in fact it is surprising that psychological factors can diminish air hunger in light of the observation that this primal sensation does not seem to be altered by intensive training for competitive breath hold diving (Binks et al., 2007).

4.3 Possible alternative explanations for the observed responses

Although a psychological placebo effect seems a ready explanation for our findings, it is possible that furosemide (dissolved in saline) and saline act via other mechanisms; thus we will consider the other possible sources of variability.

4.3.1 Possible explanations for the variability of response to furosemide

4.3.1.1 Methodological issues: Subjects were told to remain passive as much as possible when P_{CO_2} increased. Although no subject was able to completely relax during high stimulus, they behaved similarly among treatment days as shown by the peak airway pressure (Table 1).

4.3.1.2 Subject characteristics: In our study population, we did not observe any particular link between subjects' characteristics in terms of gender, respiratory drive and perceptual sensitivity to hypercapnia. We did see a tendency toward lower trait anxiety in responders (BSI-18; Supplement Table 1). Furthermore, the Multidimensional Dyspnea Profiles of responders revealed two differences: they reported less breathing-related anxiety and they

reported less air hunger (Supplement Fig 10). It is not clear to us how these differences might increase response to furosemide and saline.

Aerosol deposition may differ according to gender (Kim and Hu, 1998). Nevertheless, gender was not balanced in this study with 3 women and 8 men, and the small number does not allow us to totally rule out this factor. Furosemide is not supposed to act on ventilatory drive and CO₂ chemosensitivity (Minowa et al., 2002). Minute ventilation recorded during our free-breathing test confirms this. One might hypothesize that subjects with higher ventilatory drive or higher perceptual sensitivity to CO₂ may behave differently in response to furosemide inhalation. The finding that hypercapnic ventilatory response did not correlate with furosemide treatment effect argues against this hypothesis.

Aerosol furosemide modulates sensory endings by increasing the activity of pulmonary stretch receptors and inhibiting vagal irritant receptors; illusory increase in tidal volume due to increase in stretch receptor activity is the most likely mechanism explaining alleviation of the sensation of air hunger (Manning et al., 1992; Nishino et al., 2000; Sudo et al., 2000). We hypothesized that individual perceptual responsiveness to increased stretch receptor activity could explain the large inter-individual variation in the perceptual response to inhaled furosemide observed in all published studies (Jensen et al., 2008; Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000; Ong et al., 2004; Wilcock et al., 2008). Our observations suggest that a robust stretch receptor relief pathway may be a necessary but not sufficient condition for aerosol furosemide effectiveness – other factors such as poor aerosol deposition and or rapid washout may prevent an effect in some subjects.

4.3.1.3 Drug deposition site: In the present study, response to inhaled furosemide was inversely correlated to furosemide blood level ratio. This result may provide a clue regarding mechanism of inter-subject variation. There are number of factors that influence absorption efficiency – how much aerosol actually deposits (collection efficiency), the location in the airway tree where aerosol deposits, permeability of airway wall and capillaries to the aerosolized substance, and local blood flow at site of deposition (Bennett and Ilowite, 1989). We controlled the main external factors that determine collection efficiency and location, adjusting our delivery to body size; nonetheless, individual anatomic variation may have caused deposition at different levels. If, despite our precautions, aerosol in some subjects deposited in deep alveolar regions, it would be quickly absorbed into the blood. At the same time, the alveolar regions are not the site of the pulmonary stretch receptors that are the presumed target of the treatment. Alternatively, higher bronchial blood flow and/or higher bronchial permeability may have allowed faster clearance of furosemide from the airway walls in some individuals. This would indeed result in the observed inverse correlation.

4.3.2 Possible explanations for the effectiveness of saline aerosol

4.3.2.1 Possible physiological effect of mechanical ventilation: Prior studies of furosemide did not use a ventilator to deliver aerosol. In our study mean tidal volume during drug delivery was set at 744 ml (10.3 ml.kg⁻¹), consequently subjects were slightly hyperventilated during aerosol delivery as shown by a mild decrease of PET_{CO2}, but PET_{CO2} was subsequently raised by delivering inspired CO₂ during testing. Increasing tidal

volume is also known to relieve air hunger via vagal mechanoreceptors (Manning et al., 1992) but this effect is not long-lasting and disappears in 30 to 60 seconds (Evans et al., 2002). The increase in tidal volume during aerosol delivery therefore cannot explain the observed dyspnea relief with aerosol saline or furosemide.

4.3.2.2 Possible physiological effect of saline: Deposition of saline in the airways was common to both the aerosol treatments, as the diluent for furosemide was normal saline. Several studies report that aerosol isotonic saline leads to reduced breathlessness in COPD patients (Khan and O'Driscoll, 2004; Poole et al., 1998). Nebulized salbutamol, but not saline, leads to an improvement in lung function but both treatments lead to a comparable improvement in breathlessness at rest (Poole et al., 1998). Nebulized isotonic saline effect has also been assessed in COPD exacerbation using an active, and a sham nebulizer (particle size in a range of 2.5 to 2.8 microns) in a randomised single-blind study (Khan and O'Driscoll, 2004). Patients reported a 23% improvement in dyspnea following active saline nebulization without effect of sham aerosol. The authors suggested that aerosol saline relieves dyspnea in COPD patients by airway-moistening and sputum-inducing effect. It also may be suggested that aerosol saline modifies the bronchial ionic environment.

4.4 Effectiveness of intravenous furosemide on dyspnea

Intravenous furosemide significantly reduced breathing discomfort. Its effect was smaller than that seen with aerosol furosemide and was not correlated with the effect of aerosol furosemide across subjects. Intravenous furosemide has been shown to relieve dyspnea in acute or chronic heart failure (Banerjee et al., 2012; Felker et al., 2011). Our healthy subjects were unlikely to have pulmonary vascular congestion; however, there is a discrepancy between the diuretic effect and the alteration of dyspnea (Hammarlund et al., 1985). Furthermore, it has been shown that dyspnea relief is not parallel to diuresis in prior studies (Llorens et al., 2014) suggesting an alternative mechanism of action. A placebo effect induced by administration of intravenous furosemide cannot be ruled out. Indeed, intravenous furosemide effect was correlated to aerosol saline effect ($r^2=0.59$ – see Supplement Fig 7).

4.5 Conclusions and clinical significance

Aerosol furosemide and aerosol saline relieved laboratory dyspnea but our results show substantial inter-subject variability, consistent with findings in previous studies (Jensen et al., 2008; Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000; Ong et al., 2004; Wilcock et al., 2008), suggesting that inhaled furosemide will not be effective for all patients experiencing dyspnea. Variability may be attributed to the variability in location of aerosol deposition, but we have shown that control of aerosol delivery conditions beyond the delivery methods used in clinical practice does not improve consistency of treatment effect. Although placebo effect seems a ready explanation for these treatment effects, there is also the possibility of physiological action. Further studies are needed to determine whether increasing the dose of furosemide will produce effective relief in most subjects.

The effectiveness of both these aerosol treatments in many subjects, combined with low side effect profiles, suggests that these may be useful treatments in some patients with refractory

dyspnea. Taking our findings together with published evidence, aerosolized furosemide seems more likely to be effective than aerosolized saline for relieving dyspnea, although additional research is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We tested hypotheses that might explain failure of aerosol furosemide to alleviate experimental dyspnea.
- Control of aerosol delivery did not increase the proportion of subjects who responded.
- Response variation was partially explained by variation of response to large breaths.
- Response variation was inversely correlated with efficiency of furosemide uptake into the blood.

Fig 1. Aerosol delivery system

Three nebulizer heads are mounted on a clear acrylic manifold, the inspiratory line of the mechanical ventilator is connected to the right extremity of the manifold, the expiratory line is connected close to the mouthpiece (upward arrow). A spacer tube of similar diameter and 5cm or 10cm length can be added between the expiratory line and the nebulizer heads in order to provide a leading aerosol-free space.

Fig 2. Average response for each intervention

Each bar represents the mean treatment effect for all participating subjects. (namely, the change in breathing discomfort at the benchmark PET_{CO_2}). Each bar is represented with a standard deviation according to the intervention: inhaled furosemide (black, n=11), inhaled saline (white, n=9), larger tidal volume (hatched white, n= 10), intravenous furosemide (hatched black, n=10).

Fig 3. Individual subject treatment effect in response to aerosol furosemide (black bars) and to aerosol saline (white bars)
 Bar labels indicate individual subject codes, in order of response to furosemide. The response to aerosol saline is not available in two subjects, as indicated by asterisks (* subject AF3 dropped out before completing the saline study; ** data from Subject AF4 were inadequate on the saline study day). The maximal possible decrease would be 60%.

Fig 4. Linear regression between individual response (treatment effect) to aerosol furosemide and individual response to aerosol saline
Each circle indicates individual subject response, as labelled.

Fig 5. Individual subject treatment effect in response free breathing (panel A) and to higher tidal volume (panel B). For comparison, responses to aerosol furosemide are repeated from Figure 3 Bar labels indicate individual subject codes. Subjects are ordered according to the aerosol furosemide treatment effect. In the free breathing challenge, subjects were free to breathe the tidal volume they desired. In the higher tidal volume session, subjects were allowed to raise their minute ventilation up to 0.26 L/kg/min, while respiratory frequency was held constant. The maximal possible decrease would be 60%.

Fig 6. Linear regression between individual response (mean treatment effect) to aerosol furosemide and furosemide blood level ratio (indicating the aerosol absorption efficiency and calculated by dividing the aerosol furosemide blood level to intravenous furosemide blood level related to dose (40mg/15mg))

Each circle indicates individual response.

Table 1
Minute ventilation and peak airway pressure at the ‘benchmark PETCO₂’ before and after intervention

Physiological data are averaged respectively on pre-treatment runs and post-treatment runs and are expressed as mean with standard deviation. Minute ventilation is an extensive variable. The standard deviation shown is due to the variation in body weight; each subject was ventilated at 0.13liters/min/kg. The paired statistical test takes this variation into account. Airway pressure is an intensive variable, thus does not vary with body size. The standard deviations shown for peak inspiratory airway pressure reflect differences in subjects’ respiratory behaviors.

		Pre-treatment	Post-treatment	p
VE (L.min ⁻¹)	furosemide	10.2 ± 2.9	10.1 ± 2.7	0.45
	saline	10.1 ± 2.8	10.0 ± 2.7	0.47
Peak airway pressure (cmH ₂ O)	furosemide	-12.6 ± 6.7	-9.8 ± 3.9	0.13
	saline	-12.1 ± 3.7	-10.1 ± 3.6	0.13