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Summary

Acid fog is a relatively frequent phenomenon in California, but the health effects of exposure to such fog are unknown. Because people with asthma may be especially sensitive to the inhalation of air pollutants, we examined the bronchoconstrictor effects of various acid aerosols and fogs on subjects with mild to moderate asthma in three separate studies.

Most of the toxicological data base on acid aerosols involves sulfate compound particles, primarily submicrometer sulfuric acid (H_2SO_4). In previous experiments, we found that titratable acidity appears to be more important than specific chemical composition in predicting the bronchoconstrictor potency of acid aerosols. However, given that nitric acid (HNO_3) is a major constituent of California acid fog, it is necessary to study the effects of HNO_3, as well as those of H_2SO_4, in human subjects. By having subjects with asthma inhale fog-like aerosols of H_2SO_4, HNO_3, a 1:1 mixture of H_2SO_4 and HNO_3, or saline, we were able to study the bronchoconstrictor potency of these aerosols (Project 1). Although all 4 of these dense aerosols caused mild bronchoconstriction when inhaled during moderqate exercise, there were no significant differences between the bronchoconstrictor effects of the acid aerosols and that of neutral saline aerosol.

Naturally occurring fogs are usually hypoosmolar with respect to body fluids. Because both hypoosmolarity and acidity can cause bronchoconstriction, we studied whether there was a positive interaction between these stimuli in subjects with asthma (Project 2). We administered aerosols of hypoosmolar H_2SO_4, HNO_3, a 1:1 mixture of H_2SO_4 and HNO_3 , or saline. We also administered an aerosol of isoosmolar H_2SO_4. For each aerosol challenge a dose-response curve was generated using degree of bronchoconstriction as the response. For most subjects studied, all 3 hypoosmolar acid aerosols caused a leftward shift in the dose-response curve from that generated for hypoosmolar saline (i.e., the acid aerosols were more potent at inducing bronchoconstriction than saline aerosol). There were no statistically significant differences in bronchoconstrictor potency among the three acid aerosols studied.

Isoosmolar H_2SO_4 did not cause bronchoconstriction in any subjects, even when delivered in a concentration in excess of 40 $\mu g/m^3$. The results of this study demonstrate that acidity can potentiate the bronchoconstriction caused by inhalation of a hypoosmolar aerosol in subjects with asthma. Thus, the interaction of acidity and osmolarity needs to be considered in the design and interpretation of studies of the respiratory effects of acid fog.

In contrast to the "acid haze" conditions (small particle size and low liquid water content (LWC)) that frequently occur during summer months in the eastern United States and Canada, the "acid fog" conditions that occur along the California coast are characterized by larger particle size and higher LWC. Most previous controlled human exposure studies of the respiratory health effects of H_2SO_4 have employed haze-like submicronic aerosols of low LWC. In order to better assess the bronchoconstrictor potential of acid fogs, we administered fogs of varying acidity and LWC to subjects with asthma in an exposure chamber (Project 3). This chamber was outfitted with a fog generation and monitoring system that was custom-built by a subcontractor, Atmospheric Technology, during the performance period of this contract. The components of the system are described briefly under Project 3 in the body of this report and in great detail in Appendices 1 and 2. The 4 fogs studied were low LWC (0.5 g/m^3) H_2SO_4, high LWC (1.8 g/m^3) H_2SO_4, low LWC saline, and high LWC saline. The exposure period lasted 1 hour, with alternate periods of rest and exercise. The concentration of sulfate in the exposure chamber for the low LWC and high LWC content acid fogs were 960 and 1400 $\mu g/m^3$, respectively. None of the 4 fogs induced statistically significant bronchoconstriction. The lack of a dose-response effect with regard to LWC suggests that the density of a fog, at least in the range of what has been measured in the environment, is not an important factor in terms of its bronchoconstrictor potency. While other investigators have reported small decrements in lung function in subjects with asthma after inhalation of submicronic aerosols containing H_2SO_4, the negative results we report after inhalation of large-particle acid fogs are similar to those of a previous report. The H_2SO_4 concentrations administered in this study are at least an order of magnitude higher than those that are likely to occur in the environment. Thus, we conclude that individuals with asthma are not likely to develop clinically significant bronchoconstriction when

exposed to fogs containing concentrations of H_2SO_4 in the ambient range. However, we did not study acid pollutants other than H_2SO_4, and it is possible that HNO_3, the principal acid constituent of southern California fog, may have a greater bronchoconstrictor effect. Furthermore, combined or sequential exposures to acid fogs and oxidant pollutants may interact positively to cause clinically significant respiratory tract toxicity. Such toxicity may be manifested by effects other than bronchoconstriction, such as inflammatory cellular response and mediator release, increased epithelial permeability, synthesis of stress proteins, altered secretion of mucus glycoproteins, initiation of fibrosis, etc.

Conclusions

The projects completed under this contract permit the following conclusions:

1. Inhalation of dense (38 g/m^3) aerosols through a mouthpiece during moderate exercise for a brief period (10 minutes) can cause cough and mild bronchoconstriction in subjects with asthma (Project 1). There were no significant differences between the bronchoconstrictor effects of the 3 acid aerosols studied (H_2SO_4, HNO_3, and a 1:1 mixture of H_2SO_4 and HNO_3) and that of neutral saline.

2. In relatively large (5 to 6 microns) particle hypoosmolar aerosols of extremely high LWC (up to 87 g/m^3) inhaled through a mouthpiece, the most important bronchoconstrictor effect of acidity is potentiation of the bronchoconstrictor effect of hypoosmolarity (Project 2).

3. Clinically significant bronchoconstriction did not occur in subjects with mild-moderate asthma exposed to H_2SO_4-containing fogs for 1 hour in a chamber during intermittent exercise (Project 3). The H_2SO_4 concentrations administered in this study are at least an order of magnitude higher than those that are likely to occur in the environment.

4. The lack of a dose-response effect with regard to LWC in the exposure chamber study (Project 3) suggests tha the density of a fog, at least in the range of what has been measured in the environment, is not an important factor in terms of its bronchoconstrictor potency.

Recommendations

1. More information with regard to the bronchoconstrictor effects of HNO_3, especially in the vapor phase, is needed.

2. Since animal toxicological data suggest the enhancement of the toxic effects of oxidant pollutants by acid aerosols, experiments involving exposure of human subjects to acid fogs in sequence with ozone should be conducted.

3. Effects of acid aerosols on end-points other than bronchoconstriction, such as *in vivo* inflammatory cellular response, mediator release, and epithelial permeability (assesssed by means of bronchoalveolar and proximal airway lavage), as well as *in vitro* secretion of mucus glycoproteins, synthesis of stress proteins, and synthesis/secretion of cytokines, should be studied.

Disclaimer

The statements and conclusions in this report are those of the contractor and not necessarily those of the California Air Resources Board. The mention of commercial products, their source, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products.

Body of Report

General Introduction

Complex mixtures of acid pollutants occur commonly in California, especially along the coast where the pH of ambient fog has been measured to be as low as 1.7 (1). Present scientific evidence is insufficient to allow regulatory agencies to accurately predict the potential adverse effects of acid aerosols, such as acid fog, on human respiratory health.

The experiments performed as part of this contract were designed to determine whether specific chemical composition, a potential interaction between hypoosmolarity and acidity, and exposure of freely breathing subjects during exercise are important factors in mediating any adverse effects of acid fog on the respiratory tract. One of the best-described health effects of acid aerosols and acid precursors (e.g., sulfur dioxide) is bronchoconstriction in subjects with asthma (2-5). Thus, the studies performed under this contract were designed to determine the relative potencies of sulfuric and nitric acid fogs, the nature of the interaction between hypoosmolarity and acidity, and the effects of simulated fog conditions in an exposure chamber as stimuli to bronchoconstriction in subjects with asthma.

Project I

Relative Potencies of Sulfuric Acid, Nitric Acid, and a Combination of the Two in Causing Bronchoconstriction in Subjects with Asthma.

Introduction

Sulfuric (H_2SO_4) and nitric (NHO_3) acids are the major contributors to acidity in fog (1,6). However, the relative contribution of each acid varies widely, depending in large part on the primary source of pollutants in the location where the fog occurs. The design of rational pollutant control strategies aimed at acid fog requires information about the relative potencies of these two acids and their combination in causing adverse respiratory health effects.

Most of the toxicological data base on acid aerosols involves sulfate compound particles, primarily submicrometer H_2SO_4. There are few data for nonsulfuric constituents of acid fogs, such as HNO_3. It has been suggested that the toxic effects of inhaled acid sulfates may be due to hydrogen iron (H+) rather than to sulfate. In previous experiments, we found that titratable acidity appears to be more important than specific chemical composition in predicting the bronchoconstrictor potency of aerosols of several acid solutions (7). However, given that HNO_3 is a major constituent of California acid fog, it is necessary to expose human subjects to aerosols containing HNO_3, as well as to those containing H_2SO_4.

We hypothesized that the degree of bronchoconstriction caused by inhalation of an aerosol of HNO_3 at a given pH would be similar to that caused by aerosols of both H_2SO_4 and a 1:1 mixture of HNO_3 and H_2SO_4 at that same pH. We chose a pH of 2 since that is near the lower limit of the acidity that has been measured in California fogs (1). Because in our previous experiments we found that inhalation of high concentrations of acid aerosols was required to cause bronchoconstriction during resting exposures (7,8), we exposed subjects during moderate exercise in this study.

Methods

The subjects were 7 non-smoking volunteers who were informed of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Research of the University of California, San Francisco. All subjects had asthma as defined by a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction previously documented by a physician. No subjects took oral or inhaled corticosteriods during the study period. All subjects denied having an upper respiratory tract infection within 6 weeks prior to the study. Subject characteristics are listed in Table 1. Predicted values for the spirometric parameters described are those of Knudson and co-workers (9).

On the initial study day, baseline spirometry (No. 822, Ohio Medical Products, Madison, WI) was performed and a screening dose-response curve to inhaled methacholine (0.063, 0.125, 0.25, 0.5, 1.0 and 2.0 μg/ml) was generated. Only subjects who developed ≥ 100% increase in specific airway resistance (SRaw) continued in the study. Such subjects then exercised for 3 minutes at a workload of 100 watts on a cycle ergometer (No. 18070, Gould Godart, Bilthoven, the Netherlands) while breathing humidified air. Expiratory airflow during the exercise was measured by having the subjects exhale through a heated pneumotachograph (No. 3, Fleisch, Lausanne, Switzerland) and registering the signal on photosensitive paper (No. 1858 Visicorder, Honeywell, Denver, Co). Minute ventilation was recorded by integrating the signal from the pneumotachograph with a respiratory integrator (No. FV 156, Validyne, Northridge, CA) and was corrected to body temperature and pressure saturated.

The subjects inhaled aerosol through a mouthpiece connected to a glass T-piece (with a > 2L outflow reservoir) that was directly attached to the downstream end of the second y-type connection without a respiratory valve. For the exercise challenge without aerosol, filtered, fully humidified air was inhaled (75 L/min). The subjects wore noseclips during the challenges. The temperature of the inhaled stream was measured continuously at the mouthpiece.

The liquid water content of the aerosol at the mouthpiece was measured by drawing the airstream across a Teflon filter (Gelman Sciences, Ann Arbor, MI). The filter holder was capped and the entire apparatus was weighed before and immediately after each sample was obtained. Because under the conditions of these experiments, the airstream was fully saturated with water and the sampling system and airstream were at room temperature, these measurements of filter weight change, divided by the known air sample volume, yielded effective liquid water content of the delivered aerosol. The particle size of the aerosol was measured using a low-flow, 7-stage cascade impactor (In-Tox Products, Albuquerque, NM).

To determine whether the mean changes in SRaw after the various inhalational exposures were significantly different from the mean baseline values, the paired t-test was employed. To assess the differences in mean changes in SRaw after each of the 4 aerosol challenges and after the exercise challenge, a 2-way analysis of variance was employed. To assess the differences in temperature of the inspired air and baseline SRaw values among the various challenges, we also employed 2-way analysis of variance. A p value of < 0.05 was considered statistically significant.

Results

Inhalation of all 3 acid aerosols at pH2 (HNO_3, H_2SO_4, and a 1:1 mixture of the two) during exercise caused significant increases in SRaw above baseline values in most subjects (Figure 1). However, inhalation of neutral saline aerosol during exercise caused similar increases in SRaw in most subjects (Figure 1). Only 1 of 7 subjects developed greater increases in SRaw after inhalation of all 3 acid aerosols than that after inhalation of neutral saline aerosol.

Most subjects developed small increases in SRaw after 10 minutes of exercise while breathing humidified, filtered air (mean increase 87% above baseline). In 4 of 7 subjects, the increases in SRaw after exercise without inhalation of fog aerosol were less than those after all 4 aerosol challenges.

Most subjects developed cough after inhalation of the acid aerosols. There were no significant differences in cough frequency among the 3 acid aerosols. Throat irritation, tracheal irritation, dyspnea, and chest congestion were experienced occasionally after inhalation of the acid aerosols. One subject who experienced the greatest percent increase in SRaw (302%) after an acid aerosol challenge also experienced wheezing after that challenge. Only 1 subject developed any symptoms (cough) after inhalation of neutral saline aerosol.

The particle size (mass median aerodynamic diameter (GSD)) of the aerosol generated from the combined nebulizer output was 5.2 (1.6) at the mouthpiece. The liquid water content was 38.4 g/m^3 at the mouthpiece.

No significant differences were found among the mean baseline SRaw values prior to the 4 aerosol challenges and the exercise challenge. There were also no significant differences among the mean temperatures of the inspired air during the various challenges.

Discussion

The results of this study suggest that inhalation of dense aerosols through a mouthpiece during moderate exercise for a brief period (10 minutes) can cause cough and mild bronchoconstriction in subjects with asthma. This finding was not entirely unexpected by us and may be due to an effect of airway cooling by these dense aerosols. Although the aerosols were at room temperature at the mouthpiece, the specific cooling capacity of the inhaled droplets may have caused a significant reduction in the temperature of the lumen of the larger airways. Since the solution from which the aerosols were generated were isoosmolar, it is unlikely that their bronchoconstrictor effect was due to an alteration in airway osmolarity.

Our failure to find significant differences between the bronchoconstrictor effects of the acid aerosols at pH 2 (HNO_3, H_2SO_4, and a 1:1 mixture of the two) and that of neutral saline aerosol may have been due to the complex nature of our exposure conditions in which 3 bronchoconstrictor stimuli were present simultaneously: exercise, acidity, and low temperature. On the basis of previous Air Resources Board-funded work in our laboratory, we anticipated that each acid aerosol would cause a similar degree of bronchoconstriction since the solution from which they were generated all had the same pH and titratable acidity (7). Since none of the acid aerosols tested caused significantly more brochoconstriction than did isoosmolar saline, this study did not allow us to determine their relative brochoconstrictor potencies.

On the basis of the concentration of H_2SO_4 in the solution used to generate the aerosol containing only H_2SO_4 and the liquid water content measured at the mouthpiece, we estimate that our subjects inhaled air containing approximately 38 $\mu g/m^3$ of H_2SO_4 during exposure to this aerosol. This concentration is approximately 1000 times greater than that found in polluted outdoor air (10). Therefore, the results of this study suggest that the acidity present in naturally occuring fogs is not, by itself, likely to produce bronchoconstriction in individuals with asthma during short-term exposures, even when coupled with moderate excercise. These results do not preclude potentially important interactions between

acidity and other bronchoconstrictor stimuli present in natural fogs or significant effects on end-points other than bronchoconstriction.

Project II

Acidity Potentiates Bronchoconstriction Induced by Hypoosomolar Aerosols

Introduction

The recent finding that California coastal fog can have a pH as low as 1.7 (1) has focused attention on the possible adverse health effects of breathing acidic fog, especially on potentially sensitive segments of the population, such as patients with asthma. On the basis of the limited measurements of ionic strengths in liquid fog water reported to date (1,6), we calculate that most acid fogs have an osmolarity of less than 30 mOsm (based on data from 1,2; appendix). Inhalation of hypoosmolar aerosols is well-established as a potent stimulus to bronchoconstriction (11-14). Thus, we thought it would be important to characterize the nature of the interaction, if any, between hypoosmolarity and acidity in causing bronchoconstriction in subjects with asthma. Because of the limited bronchoconstrictor effects of unbuffered acidic aerosols demonstrated in a previous study in our laboratory (7), we hypothesized that acidity would be more likely to potentiate the bronchoconstriction induced by hypoosmolarity than to have a significant independent effect. To test this hypothesis, we studied in subjects with asthma the bronchoconstrictor effects of aerosols that varied with regard to both their osmolarity and their acidity. The major ions present in acid fog are hydrogen, sulfate, nitrate, and ammonium (1,6), suggesting that the low pH is in large part due to the presence of sulfuric and nitric acids in polluted air. We chose, therefore, to study the effects of aerosols of sulfuric acid (H_2SO_4), nitric acid (HNO_3) and a 1:1 mixture of the two.

Methods

The subjects were 17 non-smoking volunteers who were informed of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Research of the University of California, San Francisco. All subjects had asthma as defined by a history of recurrent episodes of wheezing, chest tightness and reversible airway obstruction previously documented by a physician. Twelve of the 17 subjects recruited for the study completed the full protocol. Methacholine inhalation challenge results were available for 10 of these 12 subjects (Table 2). Methacholine responsiveness was tested by measuring the subject's specific airway resistance (SRaw) before and after inhalation of 10 tidal breaths of phosphate-buffered saline and doubling concentrations of methacholine (0.063, 0.125, 0.5, 1.0, 2.0 and 4.0 mg/ml) delivered by a Devilbiss nebulizer (Devilbiss Co., No. 646, Somerset, PA) with a dose-metering device calibrated to deliver 0.01 ml per breath. The concentration of methacholine which provoked a 100% increase in SRaw from the post-saline SRaw value was calculated by log-linear interpolation. No subject took theophylline or ß-adrenergic agonists within 24 hours or consumed caffeine within 4 hours before any experiment. No subject took oral corticosteroids during the study period. All subjects denied having an upper respiratory tract infection within 6 weeks prior to the study. Subject characteristics are listed in Table 2. Predicted values for the spirometric parameters described are those of Knudson and coworkers (9).

On the initial study day, baseline spirometry (Ohio Medical Products, No. 822, Madison, WI) was performed and a screening dose-response curve to inhaled hypoosmolar (30 mOsm) saline aerosol (pH 5.5, the pH of H_2O in equilibrium with atmospheric CO_2) was generated. Only subjects who developed bronchoconstriction after inhaling this aerosol were continued in the study. Four of 17 subjects initially screened were excluded on this basis. One additional subject was excluded because she developed significant bronchoconstriction after the first dose. On 5 subsequent, randomly separated days, a dose-response curve was generated for inhalation of one of the following: hypoosmolar (30 mOsm) saline aerosol (pH 5.5); hypoosmolar (30 mOsm) H_2SO_4 aerosol (pH 2); hypoosmolar (30 mOsm) HNO_3 aerosol (pH 2); a hypoosmolar (30 mOsm)

particle size of the aerosol delivered to the mouthpiece at the selected settings using a phase/Doppler particle analyzer (Aerometrics, Mountain View, CA).

Responsiveness to the screening hypoosmolar saline aerosol was tested by measuring the SRaw of each subject every 30 seconds for 2 minutes before and for 2 minutes beginning 1 minute after he or she inhaled doubling outputs of aerosol. Each aerosol output was inhaled during tidal breathing for 3 minutes. The mean value of 5 consecutive measurements of SRaw was calculated during each 2 minute measurement period. Each challenge was continued until SRaw increased by 100% or 10 L x $cmH_2O/L/s$, whichever was greater. Four subjects who did not develop such an increase in SRaw by the fifth and final dose (7.6 g/min) were excluded from further study. One additional subject who developed a >100% increase in SRaw after the first dose was excluded because we felt it would be difficult to quantitatively evaluate potentiation of her response.

In an identical fashion, output-response curves were generated for the 5 randomly-ordered aerosols. Each solution was prepared and its pH was measured (Beckman pH Meter No. 43, Irvine, CA) immediately before nebulization. The osmolarity of each solution was measured with a vapor-pressure osmometer (Wescor No. 5700B, Logan, UT).

To analyze the bronchoconstrictor effects of each aerosol for each subject, we plotted SRaw against the nebulizer output (in g/min). Because the experiment was conducted with roughly doubling increases in nebulizer output, the data were plotted using a log base 2 abscissa. For each aerosol output-response curve, the nebulizer output required to increase SRaw by 100% above baseline was calculated by log-linear interpolation, and these values were called the provocative output (PO_{100}). PO_{100}s could not be calculated from the isoosmolar H_2SO_4 output-response curves. To determine whether there were significant differences among the subjects' airway responses to inhalation of the 4 hypoosmolar aerosols, we compared PO_{100}s using a 2-way analysis of variance with a Newman-Keuls multiple range test. In one subject (Subject 8), SRaw did not increase by 100% during the randomized exposure to hypoosmolar saline. We therefore considered the highest

output given (7.6 g/min) as the PO_{100} for the purpose of statistical analysis. To determine whether there were significant differences amont the subjects' cough responses to inhalation of the 4 hypoosmolar aerosols, we compared cough frequencies using a 2-way analysis of variance. The mean values of baseline SRaw before administration of each aerosol were compared using a 2-way analysis of variance. To determine whether there was any correlation between baseline SRaw and PO_{100} for any of the 4 hypoosmolar aerosols, we performed linear regression analyses. To determine whether the slopes of the regression lines were significantly different from each other, we performed analysis of covariance. The mean temperatures of the inhaled aerosols during each 3 minute exposure period for each of the 5 solutions were compared by a 1-way analysis of variance. A p value of < 0.05 was considered statistically significant.

Results

The mean provocative nebulizer output required to increase SRaw by 100% above baseline was significantly lower for each of the hypoosmolar acid aerosols at pH 2 (0.95 + 0.11 g/min (log_2 mean + SEM) for H_2SO_4, 1.05 + 0.20 g/min for HNO_3, and 0.90 + 0.14 g/min for a 1:1 mixture of the two) than for the hypoosmolar saline aerosol at pH 5.5 (1.65 + 0.43 g/min) (all p values < 0.025) (Figure 2). There were no significant differences in mean PO_{100} among the 3 hypoosmolar acid aerosols. Seven of 12 subjects (#2,3,4,7,8,10, and 11) demonstrated a shift to the left in the output response curve generated during inhalation of doubling outputs of each of the hypoosmolar acid aerosols at pH 2 as compared to that generated during inhalation of doubling outputs of hypoosmolar saline at pH 5.5 (Figure 3). Isoosmolar H_2SO_4 aerosol at the same pH (pH 2) as the hypoosmolar acid aerosols did not increase SRaw by 100% above baseline in any subjects, even at the highest nebulizer output (7.6 g/min). There were no significant differences in cough frequency among the 4 hypoosmolar aerosols. Isoosmolar H_2SO_4 aerosol rarely induced cough.

There was no correlation between the baseline SRaw 's of the subjects and their subsequent PO_{100}'s for any of the 4 hypoosmolar aerosols. Each of the slopes of the 4 regression lines was not significantly different than zero. Analysis of covariance showed that none of the slopes was significantly different from the others.

The relationship between nebulizer output and gravimetrically determined aerosol concentration at the mouthpiece (expressed as g/m^3) is shown in Table 3. Both values increased in parallel from the lowest to the highest output, demonstrating that increases in nebulizer output accurately predicted increases in available aerosol at the mouthpiece. Based on the concentration of H_2SO_4 in the solution used to generate aerosols at pH 2 (0.5 g/L) and on the gravimetrically measured aerosol concentration, we calculated the concentration of H_2SO_4 in the airstream at the highest output setting to be 43.5 mg/m^3. This value is quite similar to the value of 47.3 mg/m^3 calculated on the basis of the colorimetric measurement of sulfate extracted from filter samples obtained at the same output setting.

Although the particle size of the inhaled aerosol tended to increase as the nebulizer output was increased, the mass median aerodynamic diameter (MMAD) remained in the range 5.2-6.3 microns (Table 3). The temperature of the inhaled aerosol also tended to increase as the nebulizer output was increased (Table 3), but there were no significant differences in mean temperatures at any given nebulizer output among the 5 aerosols studied.

Discussion

The results of this study suggest that acidity can significantly potentiate the bronchoconstriction caused by inhalation of a hypoosmolar aerosol in subjects with asthma. Since each of the 3 hypoosmolar, acidic solutions studied (H_2SO_4, HNO_3 or a 1:1 mixture of the two) had an equivalent bronchoconstriction-potentiating effect, the specific chemical composition of the solution did not appear to be an important factor. As we have reported previously (7), large particle aerosols (MMAD 5.3 - 6.2 microns) of unbuffered isotonic H_2SO_4 caused little bronchoconstriction, even at H_2SO_4 concentrations in excess of 40 mg/m^3.

This study was not designed to simulate natural exposure to acid fogs, but rather to examine the potential interaction between hypoosmolarity and acidity in causing bronchoconstriction. The conditions of exposure we studied (particles of relatively uniform diameter delivered through a mouthpiece) are quite different from those encountered in the environment. Furthermore, the liquid water contents of the aerosols we studied (ranging from 5.9 to 87.1 g/m^3, Table 3) were many times higher than the liquid water content that has been measured during even "worst case" natural fog conditions. Natural fogs generally have a liquid water content less than 2 g/m^3 (16). In addition, the H_2SO_4 concentrations we studied were many times higher than those encountered in natural fog. Thus, it is not possible to extrapolate directly from the results of this study to predict the effects of naturally occurring fog.

The lack of bronchoconstrictor potency of isoosmolar H_2SO_4 aerosols we report here confirms and extends the results of a previous study in which we reported very little increase in SRaw after inhalation of an unbuffered H_2SO_4 aerosol of similar size and pH (pH 2) at a concentration in excess of 10 mg/m^3 (7). In that study we found that aerosols of buffered solutions of H_2SO_4 at pH 2 did cause bronchoconstriction. The presence of buffers (such as weak organic acids) may be important in natural acid fogs: at a given pH, buffered acid aerosols would have greater titratable acidity but at the same time greater osmolarity. The effect of buffering the acid aerosols on the magnitude of induced bronchoconstriction was not examined in the present study.

Other investigators have found that H_2SO_4 in concentrations as low as 100 to 450 $\mu g/m^3$ has caused bronchoconstriction when delivered as a submicronic aerosol (4,5). Utell and coworkers (5) demonstrated minimal mean increases (19% and 21%, respectively) in SRaw in adults with asthma after resting exposure to 450 $\mu g/m^3$ and 1 mg/m^3 H_2SO_4 for 16 min, over 5 times longer than the exposure duration used in our protocol. Koenig and coworkers (4) showed no increase in total respiratory resistance (Rt) after resting exposure, and a small (48%) mean increase in Rt after exposure during exercise to 100 $\mu g/m^3$ H_2SO_4 in adolescents with asthma, rather than in adults at rest. The osmolarities of the aerosols used in both of these previous studies were not measured.

In 7 of the 12 subjects responsive to hypoosmolar aerosol that we studied (#2,3,4,7,8,10, and 11), each of the acid solutions studied caused an increase in the bronchoconstrictor potency of the hypoosmolar aerosol (Figure 3). In the other 5 subjects, no such pattern was apparent. These results suggest the possibility that some subjects with asthma are sensitive to the effect of acidity whereas others are not. One weakness in the present study, however, is that we made no effort to measure or control for the presence of oral ammonia in our subjects. The generation of ammonia by oral bacteria has been previously shown to be an important determinant of the response to inhaled acids (17,18), diminishing the response presumably by neutralizing the acidity. It is thus possible that differences in oral ammonia may have contributed to the differences we observed among subjects. Furthermore, failure to take measures to eliminate oral ammonia may have resulted in an overall underestimation of the potency of acid aerosols in the present study. However, the relatively large particles used in our study would be less effectively neutralized by oral ammonia than would smaller particles.

In conclusion, the results of the present study suggest that in relatively large (5-6 microns) particle, unbuffered, hypoosmolar aerosols, the most important bronchoconstrictor effect of acidity is potentiation of the bronchoconstrictor effect of hypoosmolarity. Extrapolation of this finding to naturally occurring fogs will require further studies of simulated fogs under more realistic exposure conditions. In designing

these studies, both osmolarity and acidity will need to be considered as critical variables.

Appendix

The highest concentrations of ions in acid (pH 2.25) fogwater reported by Waldman and coworkers were collected in Pasadena on 1/17/82. The measured concentrations (in µeq/L) were as follows: H^+, 5,625; Na^+, 2,180 ; K^+, 500; NH_4^+, 7,870; Ca^{+2}, 2,050; Mg^{+2}, 1,190; F^-, 637; Cl^- 676; NO_3^-, 12,000; SO_4^{-2}, 5,060. The contribution of each ion to the total osmolarity (in mOsm) is approximately as follows: H^+, 5.6; Na^+, 2.2; K^+, 0.5; NH_4^+, 7.9; Ca^{+2}, 1.0; Mg^+, 0.6; F^-,0.6; Cl^-, 0.7; NO_3^-, 12.0; SO_4^{-2}, 2.5. The total osmolarity of this fogwater is thus 33 mOsm. The osmolarities of 4 other acid fogs with relatively high concentrations of ions as reported by Waldman and coworkers (1,6) were similarly calculated and were all less than 30 mOsm.

Project III

Lack of Bronchoconstrictor Response to Sulfuric Acid-Containing Fogs in Freely Breathing Subjects with Asthma

Introduction

Characterization of the risk of adverse effects from the inhalation of acidic air pollutants is required so that appropriate regulatory decisions can be made about how best to protect the public health. Controlled human exposure studies provide an important component of the data base used to characterize the potential toxicity of air pollutants. Studies in which normal, healthy subjects were exposed to aerosols of sulfuric acid (H_2SO_4) have consistently failed to demonstrate any significant detrimental effects on lung function (19). However, the sensitivity of individuals with asthma to the inhalation of acid aerosols remains an issue of some controversy.

Several groups of investigators have reported small decrements in lung function in subjects with asthma who were exposed to submicronic aerosols of H_2SO_4 with relatively low liquid water contents (4,5,20). The range of H_2SO_4 concentrations administered in these studies is 100 to 1000 $\mu g/m^3$. However, data from our laboratory indicated that when subjects with asthma inhale aerosols of larger particle size (5-6 microns) and higher liquid water content (i.e., "acid fogs"), much greater concentrations (5-10 $\mu g/m^3$) of H_2SO_4 are required to cause significant bronchoconstriction (7,8). We administered acid fogs for brief periods by mouthpiece in these earlier studies to subjects who were breathing tidally while at rest. In order to effectively increase the dose of H_2SO_4 administered in fogs without increasing the concentration of H_2SO_4 in the inhaled atmosphere much above 1000 $\mu g/m^3$, we performed the study reported here in an exposure chamber using freely breathing subjects who were intermittently exercised over the course of 1 hour. Because neutral fogwater itself is a potential bronchoconstrictor stimulus due to hypoosmolarity, we designed an experimental protocol that varied liquid water content as well as acidity.

Methods

The subjects were 10 non-smoking volunteers who were informed of the risks of the experimental protocol and who signed consent forms approved by the Committee on Human Research of the University of California, San Francisco. All subjects had asthma as defined by a history of recurrent episodes of wheezing, chest tightness, and reversible airway obstruction previously documented by a physician. No subject took theophylline or B-adrenergic agonists within 24 hours or consumed caffeine within 4 hours before any experiment. No subject took oral corticosteroids during the study period. All subjects denied having an upper respiratory tract infection within 6 weeks prior to the study. Subject characteristics are listed in Table 4. Predicted values for the spirometric parameters described are those of Knudson and co-workers (9).

On the initial study day, baseline spirometry (No. 822, Ohio Medical Products, Madison, WI) was performed and a screening dose-response curve to inhaled methacholine (0.063, 0.125, 0.25, 0.5, 1.0, and 2.0 μg/ml) was generated. Only subjects who developed > 100% increase in specific airway resistance (SRaw) continued in the study. On 4 subsequent, randomly separated days, subjects inhaled one of 4 fogs: low liquid water content (0.5 g/m^3) saline at pH 5.5; low liquid water content H_2SO_4 at pH 2; high liquid water content (1.8 g/m^3) saline at pH 5.5; and high liquid water content H_2SO_4 at pH 2. The fog challenges were randomly ordered, occurred at the same time on separate days, and were performed in a single-blind fashion. The subjects were exposed to the fogs in an 8' x 8' x 8' stainless steel and glass inhalation challenge chamber (Vista Scientific, Ivyland, PA) The exposure period lasted 1 hour, with alternate 15-minute periods of rest and exercise, in that order. Exercise was performed on a constant-load cycle ergometer (No. 18070, Gould Godart, Bilthoven, the Netherlands) at a workload of 100 watts. Subjects were not exposed to fog on days when their baseline SRaw's were < 50% or > 150% of their usual baseline. In order to reduce neutralization of inhaled aerosol by oral ammonia, the subjects brushed their teeth and gargled with antiseptic mouthwash prior to each challenge. To assess airway responses of the subjects to the inhaled fogs, airway resistance (Raw) and thoracic gas volume (Vtg) were measured in a constant-volume body plethymograph (No. 09103, Warren E. Collins, Braintree, MA) and expressed as the product of Raw and Vtg, SRaw. Five measurements of SRaw, one every 30 seconds, were made before each challenge,

after the initial 15-minute resting exposure, after the initial 15-minute exercise exposure, and after the completion of the 1-hour exposure. The subjects left the inhalation challenge chamber during the 1-hour exposure period only for the time required to measure their SRaw's (approximately 3 minutes) at 15 minutes and 30 minutes after the onset of exposure. Throat and respiratory symptoms were assessed by a post-exposure questionnaire with an 11-point rating scale for each of 9 symptoms.

Fogs were generated by a custom-built system (Atmospheric Technology, Calabasas, CA) using hydraulic atomizers located on several manifolds mounted inside a sealed chamber. Manual release allowed the selection of one or more manifolds containing combinations of atomizers in order to control liquid water content. Two series of screens were located downstream of the atomizers to remove larger droplets in order to control the droplet size distribution. The fog droplets produced by the droplet generator were circulated through the inhalation challenge chamber using a centrifugal blower. Ducts were mounted along the ceiling of the chamber to evenly distribute the fog. The exhaust air from the chamber passed through ducts mounted along the perimeter of the chamber floor and then was directed through a mesh filter (to remove larger droplets and the majority of liquid matter) followed by a HEPA filter (to remove the remaining small droplets). The air that had been thus filtered was returned to the droplet generator for recycling.

A portion of the chamber air was replaced to eliminate the buildup of exhaled gases produced by the subjects. Approximately 10% of the flow was exhausted from the chamber outlet and replaced with air drawn through the chamber's primary air purification system. The makeup air was added at the inlet to the mesh filter, which acted as a humidifier, since it contained a large surface area covered with moisture from entrained droplets. Thus, the air returning to the droplet generator should have been near saturation, even though a fraction of unsaturated air had been added to the system.

The fog droplets in the chamber were monitored in terms of both physical and chemical characteristics. A phase/Doppler particle analyzer (Aerometrics, Mountain View, CA) linked to a microcomputer (Model AT, International Business Machines, Armonk, NY) was used to measure the fog droplet size distribution and liquid water content within the chamber on a continuous basis. Because the particle analyzer was noted to routinely underestimate the liquid water content

of fog during pre-delivery testing by Atmospheric Technology, a gravimetric method of measuring this parameter was also employed. Fog was drawn across 47 mm glass fiber filters (Gelman Sciences, Ann Arbor, MI) with an effective retention of 0.3 microns at a flow rate of 14 L/min for 4 minutes for the high liquid water content fogs and 8 minutes for the low liquid water content fogs. The filter holder was capped, and the entire apparatus was weighed before and immediately after each sample was obtained Because under the conditions of these experiments the chamber air was fully saturated with water and the sampling apparatus and chamber air were at room temperature, the measurements of filter weight change, divided by the known air sample volume, yielded liquid water content. At least 3, and usually 4 gravimetric measurements of liquid water content were made during each 1-hour exposure period.

Chemical characteristics of the fog droplets in the chamber also were measured by multiple methods. A modified California Institute of Technology string fogwater collector was used to obtain samples of fog for continuous measurement of pH (pHI 40 Beckman, Irvine, CA) and semi-continous measurement of sulfate concentration by ion chromatography (4000i, Dionex, Sunnyvale, CA) using a Dionex AS4A HPIC column, a Dionex AMMS-1 suppressor column, and an eluant containing 0.0056 M sodium bicarbonate and 0.0048m sodium carbonate. The sulfate concentrations of the gravimetric filter samples were also measured by washing the filter with 10 ml of deionized water and injecting 2-3 ml aliquots of this filter wash into the ion chromatographic system described above. The sulfate concentration of the sample divided by the known air sample volume yielded the sulfate concentration of the chamber atmosphere.

Fogs were generated from deionized water to which sodium chloride or dilute H_2SO_4 was added to achieve an osmolarity of 30 mOsm as measured by a vapor pressure osmometer (No. 5700B, Wescor, Logan UT). The pH of each solution was measured immediately before and after fog generation (pHI 40, Beckman, Irvine, CA).

To determine whether there were significant differences among the subjects' airway response to inhalation of the 4 fogs, we compared the mean changes in SRaw from pre-exposure baseline values after inhalation of each fog using a 2-way analysis of variance. To analyze the symptoms experienced after

each fog by each subject, we grouped the 9 symptom scores into 3 categories: lower respiratory symptoms (chest pain, chest tightness, wheezing, shortness of breath, cough, and sputum production); b) throat irritation; and c) non-respiratory symptoms (back pain and headache). To determine whether there were significant differences among the subjects' reported symptoms following inhalation of the 4 fogs, we compared the symptom category scores by means of a 2-way analysis of variance. To assess whether there were differences among the mean baseline SRaw values prior to exposure to the 4 fogs, we also employed a 2-way analysis of variance. A p value of < 0.05 was considered statistically significant.

Results

The SRaw of most subjects actually decreased slightly from their pre-exposure baseline values following inhalation of 3 of the 4 aerosols. Only after inhalation of the low liquid water content H_2SO_4 fog was there a slight increase in mean SRaw (1.7%). The mean changes in SRaw (in L x cm H_2O L/s) ± SE from pre-exposure baseline values were as follows: -0.66 ± 0.91 for low liquid water content saline fog; +0.16 ± 0.83 for low liquid water content H_2SO_4 fog; -0.22 ± 0.64 for high liquid water content saline fog; and -0.97 ± 0.91 for high liquid water content H_2SO_4 fog (Figure 4). There were no significant differences in mean change in SRaw among the 4 fogs. There were no significant differences in pre-exposure baseline SRaw among the 4 fogs.

Only 1 subject (subject #5) developed an increase in SRaw after inhalation of each fog. His increases in SRaw from pre-exposure baseline values for the two acid fogs (80% for low liquid water content H_2SO_4 and 92% for high liquid water content H_2SO_4) were greater than for the neutral saline fogs. No other subject developed greater increases in SRaw after inhalation of the acid fogs than after inhalation of neutral saline fogs.

Only 1 subject experienced as much as "moderate" (symptom score 4 on a 0-10 scale) throat irritation after inhaling the low liquid water content saline fog. Seven other subjects experienced "moderate" (symptom scores 4-6) respiratory symptoms (chest pain, chest tightness, wheezing, cough, sputum production, shortness of breath) after inhaling various fogs. The mean scores for throat irritation and respiratory symptoms were not significantly different among the 4 fogs (Table 5).

The mean exposure characteristics for the 4 different fog conditions studied are summarized in Table 6. The measured liquid water contents of the inhaled fogs were close to the target levels. The mean particle sizes of the 4 fogs were not significantly different (range 6.2-6.6 microns). The mean temperatures in the chamber also were not significantly different among the 4 fog exposures.

The mean atmospheric sulfate concentrations during the acid fog exposures were 960 $\mu g/m^3$ for the low liquid water content H_2SO_4 fog and 1400 $\mu g/m^3$ for the high liquid water content H_2SO_4, respectively. The mean atmospheric sulfate concentration during the high liquid water concentration during the high liquid water content acid fog exposure was close to the target level. Since the liquid water content of the low liquid water content acid fog was approximately 3 times less than that of the high liquid water content acid fog, we had expected that the atmospheric sulfate concentration during the less dense acid fog exposure would have been proportionately lower as well. The fact that the atmospheric sulfate concentration of the low liquid water content acid fog was approximately 2/3 of that of the high liquid water content acid fog suggests that considerable concentration of sulfate, presumably through evaporation, must have occurred with the measurement of sulfate during the less dense acid fog exposure.

Discussion

The concentrations of H_2SO_4 administered in this experiment are at least an order of magnitude higher than those that are likely to occur in the North American environment (10). Thus, the results of this study suggest that individuals with mild to moderate asthma are not likely to develop clinically significant bronchoconstriction when exposed to fogs containing concentrations of H_2SO_4 in the ambient range.

In contrast to the "acid haze" conditions (small particle size and low liquid water content) that frequently occur during summer months in the eastern United States and Canada, the "acid fog" conditions that occur along the southern California coast are characterized by larger particle size and higher liquid water content. Most previous controlled human exposure studies of the respiratory health effects of H_2SO_4 have employed submicronic aerosols with low liquid water contents that are more relevant to Eastern acid haze conditions than to California acid fog.

On the basis of reports of small but statistically significant functional decrements in subjects with asthma after their exposure to haze-like aerosols (4,5,20), it has been suggested that such individuals are especially sensitive to acid aerosols. Given the percentage of the general population with asthma (5-10%), it follows that bronchoconstriction induced by acidic air pollutants may be a major public health problem. However, there are data from several investigators which demonstrate little bronchoconstrictor potency for haze-like acid aerosols (21,22). In any case, studies of the effects of submicronic acid aerosols with low liquid water contents may have little relevance to acid fog exposure.

Previous experiments from our laboratory, involving protocols in which fog-like acid aerosols were administered for brief periods by a mouthpiece, demonstrated bronchoconstrictor effects in adult subjects with mild to moderate asthma only at very high H_2SO_4 concentrations (7,8). A recent study by Avol and co-workers in which both normal and asthmatic subjects were exposed to light fogs (10 micron median droplet diameter, 0.1 g/m^3 liquid water content) in an exposure chamber also failed to produce substantial decrements in lung function.

Naturally occurring acid fogs are hypoosmolar ($\leq$ 30 mOsm) relative to body fluids such as that lining the airways (~ 300 mOsm) (8). Inhalation of a hypoosmolar aerosol is a well-documented stimulus to bronchoconstriction in individuals with asthma (11-14). Thus, exposure to even neutral fogs could conceivably induce bronchoconstriction in such individuals. In an earlier experiment, we demonstrated a positive interaction between acidity and hypoosmolarity with regard to the bronchoconstrictor potency of inhaled fog-like aerosols in subjects with mild to moderate asthma (8). However, this positive interaction was noted at levels of both H_2SO_4 and liquid water content that far exceed those likely to occur in the environment. The lack of a dose-response effect with regard to liquid water content in the present study suggests that the density of a fog, at least in the range of what has been measured in the environment, is not an important factor in terms of its bronchoconstrictor potency.

The negative results reported here compel us to raise several points regarding the applicability of these results to the assessment of risk form environmental exposure to acid fogs. The study population was small, young, and with relatively low medication requirements. Our subjects may not be representative of all persons with asthma. We did not study acid pollutants other than H_2SO_4, and it is possible that nitric acid, the principal acid constituent of southern California fog, may have a greater bronchoconstrictor effect. Finally, the possibility that acid pollutants may enhance the respiratory tract toxicity of oxidant gaseous pollutants needs to be examined in controlled human exposure studies before an adequate assessment of the health risks associated with acid aerosols can be made.

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Table 1

PROJECT I

SUBJECT CHARACTERISTICS

Subject	Sex	Age (yrs)	Ht (cm)	FEV_1 (L)	FEV_1 (% pred)	FVC (L)	FVC (% pred)	Baseline SRaw * (L x cm H_2O/L/s)	Methacholine Responsiveness † (mg/ml)	Medications
1	F	24	175	3.37	94	4.53	104	5.3	0.14	B-agonist inhaler
2	M	30	173	2.80	71	3.99	81	4.5	0.10	B-agonist inhaler
3	M	35	178	3.83	93	5.34	105	3.4	0.50	B-agonist inhaler
4	F	27	163	2.79	92	3.53	97	4.1	0.40	B-agonist inhaler
5	M	31	185	4.36	94	4.53	104	8.1	0.16	B-agonist inhaler theophylline
6	M	32	185	3.89	85	6.83	121	5.0	0.50	B-agonist inhaler
7	F	28	165	2.52	79	3.38	88	12.1	<0.06	B-agonist inhaler theophylline

* mean of pre-exposure baseline values from 4 separate days
† concentration of methacholine required to produce a 100% increase in SRaw above baseline calculated by linear log interpolation

Table 2

PROJECT 2

SUBJECT CHARACTERISTICS

Subject	Sex	Age (yrs)	Height (cm)	FEV1 (L)	FEV1 (% pred)	FVC (L)	FVC (% pred)	SRaw* $(L \times \frac{CmH2O}{L/s})$	Methacholine** Responsiveness (mg/ml)	Medications
1	M	32	185	4.36	94	5.49	96	4.3	0.55	ß-agonist inhaler theophylline
2	M	24	185	5.62	117	6.28	111	2.7	0.53	ß-agonist inhaler
3	M	35	184	4.65	107	6.72	124	4.4	0.76	ß-agonist inhaler
4	M	27	178	3.84	105	5.52	122	5.5	0.15	ß-agonist inhaler beclomethasone
5	F	27	163	2.79	92	3.53	97	4.7	0.44	ß-agonist inhaler
6	M	33	183	4.25	96	5.55	101	3.0	0.21	ß-agonist inhaler theophylline
7	F	41	155	2.20	87	3.02	99	5.5	nd	ß-agonist inhaler
8	F	31	165	2.91	97	4.07	112	4.8	1.64	ß-agonist inhaler beclomethasone
9	F	25	175	3.35	94	4.66	107	4.3	0.14	ß-agonist inhaler
10	F	30	173	2.51	77	4.12	104	9.7	0.24	ß-agonist inhaler
11	F	28	168	1.84	60	2.87	77	9.6	<0.06†	ß-agonist inhaler theophylline
12	M	30	168	4.07	110	5.37	117	4.3	nd	ß-agonist inhaler theophylline, beclomethasone

* Mean of pre-exposure baseline values from 6 separate days

** Concentration of methacholine required to produce a 100% increase in SRaw above baseline calculated by linear log interpolation.

† Subject responded to first dose of methacholine (0.063 mg/ml) with a > 100% increase in SRaw

nd Not done

Table 3

PROJECT 2

EXPOSURE CHARACTERISTICS

Nebulizer setting	Nebulizer output (g/min)	Gravimetric aerosol concentration (g/m^3)	MMAD ± GSD (microns)	Temperature (°C)
1	0.5	5.9	5.3 ± 1.5	22.7
2	0.9	–	–	22.7
3	2.0	25.4	5.3 ± 1.5	23.1
4	3.8	–	–	23.5
5	7.6	87.1	6.1 ± 1.5	24.9

Table

PROJECT III

SUBJECT CHARACTERISTICS

Subject	Sex	Age (yrs)	Ht (cm)	FEV_1 (L)	FEV_1 (% pred)	FVC (L)	FVC (% pred)	Baseline SRaw * (L x cm H_2O/L/s)	Methacholine Responsiveness † (mg/ml)	Medications
1	M	23	178	2.70	61	4.83	87	11.1	0.42	B-agonist inhaler theophylline
2	M	34	178	3.65	89	4.82	91	4.4	0.26	B-agonist inhaler
3	F	29	168	2.12	66	2.67	66	9.8	0.33	B-agonist inhaler theophylline
4	F	28	157	2.26	78	3.29	95	7.4	0.16	B-agonist inhaler beclomethasone
5	M	34	178	1.90	45	4.00	74	7.2	0.70	B-agonist inhaler
6	M	28	166	4.11	113	5.62	126	7.3	0.50	B-agonist inhaler
7	M	28	183	2.61	57	5.55	99	24.7	0.58	B-agonist inhaler beclomethasone
8	M	36	168	3.09	84	4.32	93	11.4	0.15	B-agonist inhaler
9	M	23	180	4.30	95	5.88	103	4.5	0.40	B-agonist inhaler
10	M	24	175	3.04	70	4.46	83	5.8	0.59	none

* mean of pre-exposure baseline values from 4 separate days

† concentration of methacholine required to produce a 100% increase in SRaw above baseline calculated by linear log interpolation

TABLE 5

MEAN SYMPTOM SCORES, PROJECT III

		Low LWC NaCl	High LWC NaCl	Low LWC H_2SO_4	High LWC H_2SO_4
Symptom Category	Throat	0.8 (0.5)	1.0 (0.4)	1.0 (0.4)	1.2 (0.4)
	Respiratory	6.1 (1.3)	7.1 (1.9)	5.9 (1.2)	6.5 (1.3)
	Non-Respiratory	0.9 (0.4)	0.6 (0.4)	0.7 (0.4)	1.3 (0.6)

Mean scores (SEM) for 3 symptom categories, throat (maximum score 10), respiratory (maximum score 60), and non-respiratory (maximum score 20), after inhalation of 4 fogs.

Table 6

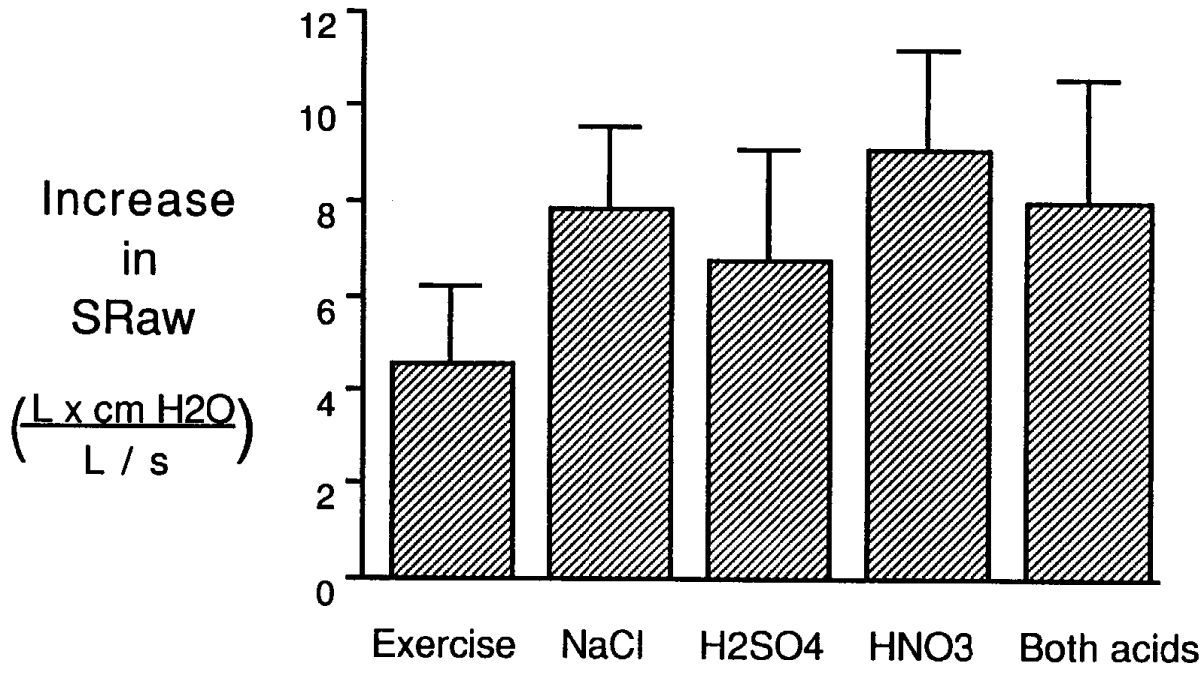
Project III

Mean Exposure Characteristics*

	LOW LWC NaCl	HIGH LWC NaCl	LOW LWC H_2SO_4	HIGH LWC H_2SO_4
LWC (g/m^3)	0.48 ± 0.1	1.87 ± 0.1	0.50 ± 0.1	1.82 ± 0.2
VMD (μm)	6.2 ± 0.4	6.45 ± 0.4	6.44 ± 0.5	6.59 ± 0.1
pH	5.16 ± 0.3	5.31 ± 0.4	2.18 ± 0.2	2.07 ± 0.2
SO_4^{-2} ($\mu g/m^3$)	- -	- -	960 ± 0.2	1400 ± 0.3
temperature (°C)	26.9 ± 1.1	27.8 ± 0.9	27.7 ± 1.1	27.6 ± 0.8

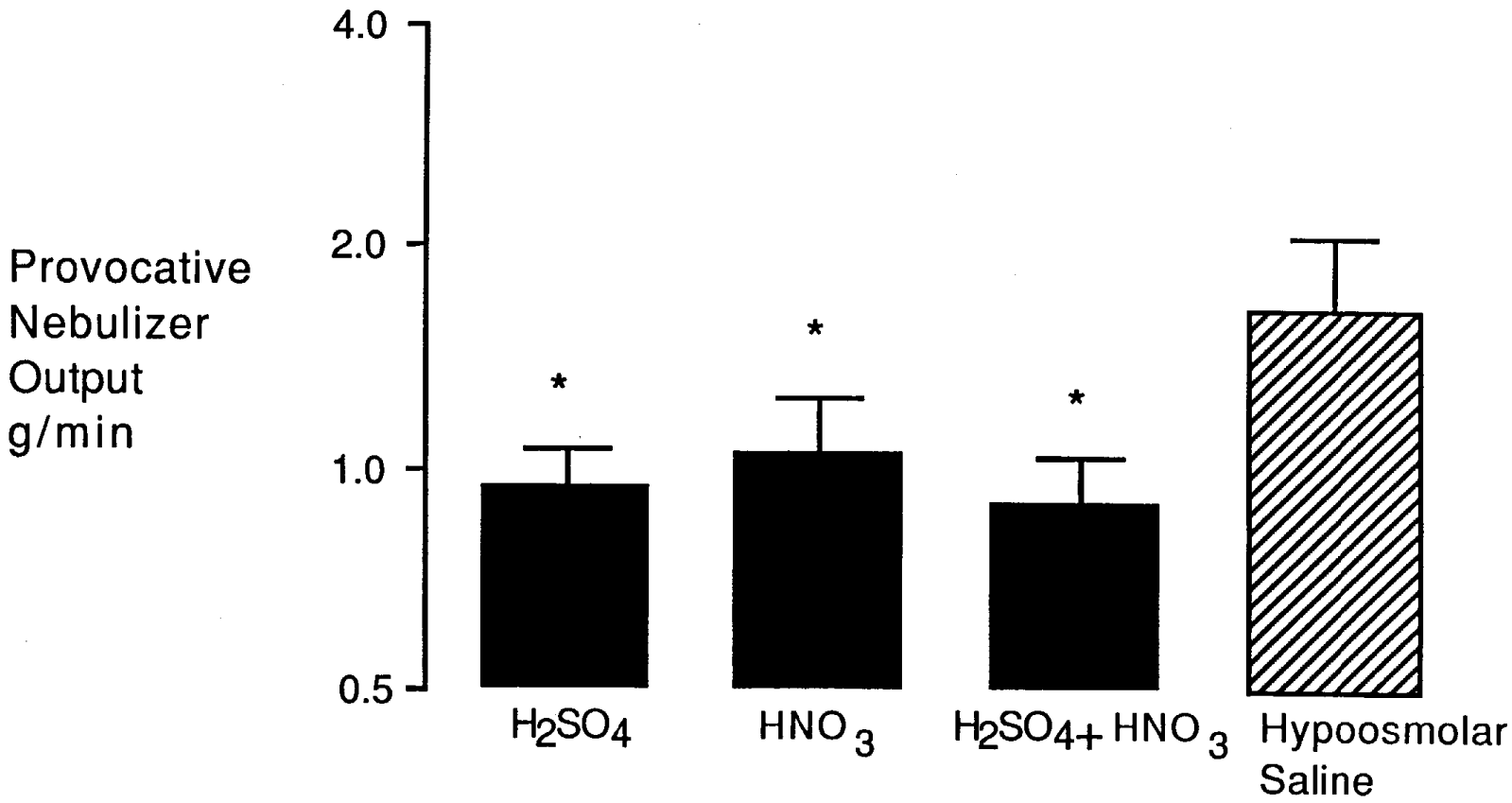
* all data mean ± SD

Figure 1



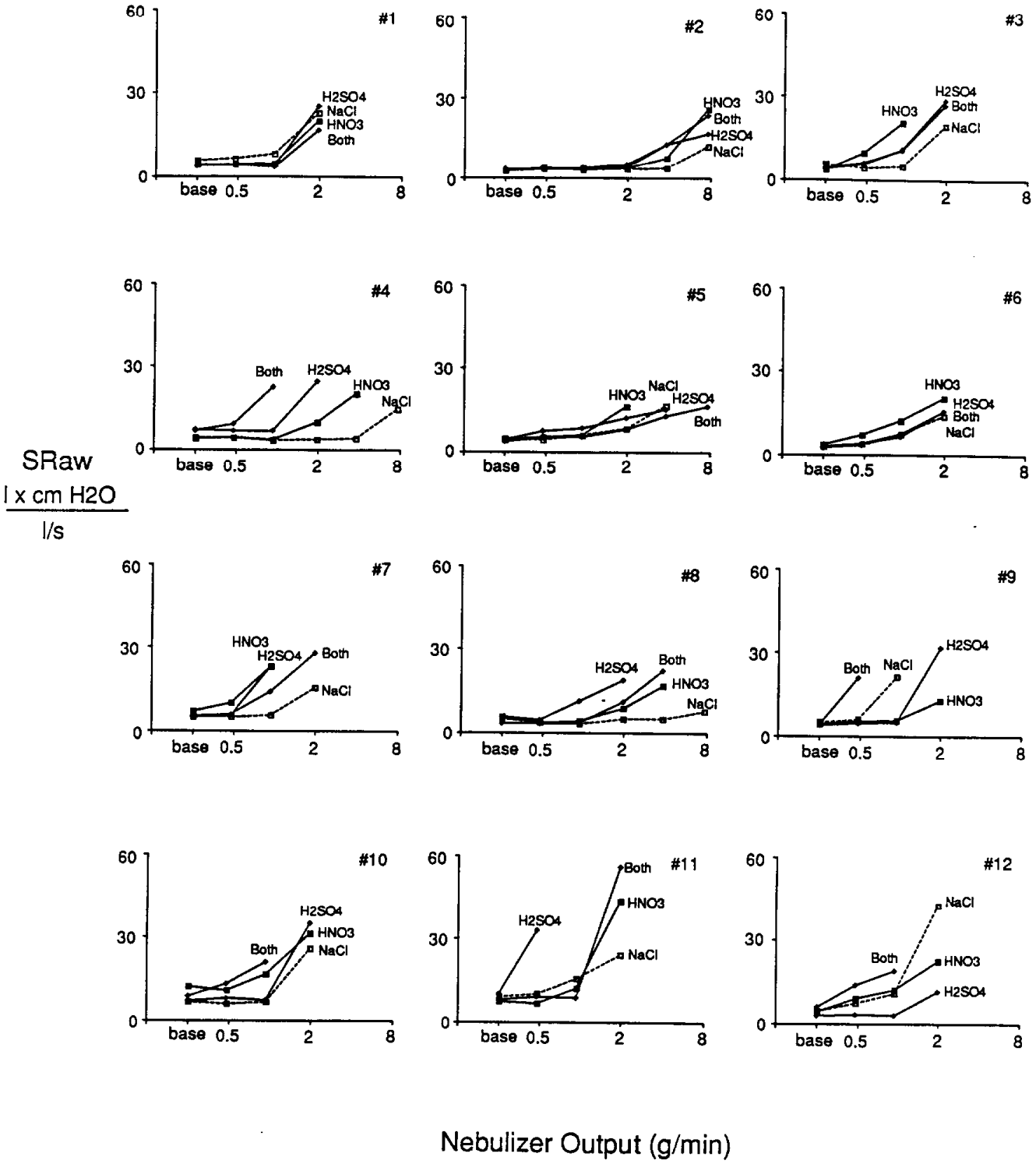
Mean values for the increase in specific airway resistance (SRaw) after the inhalation of 4 fogs and after exercise alone.

Figure 2



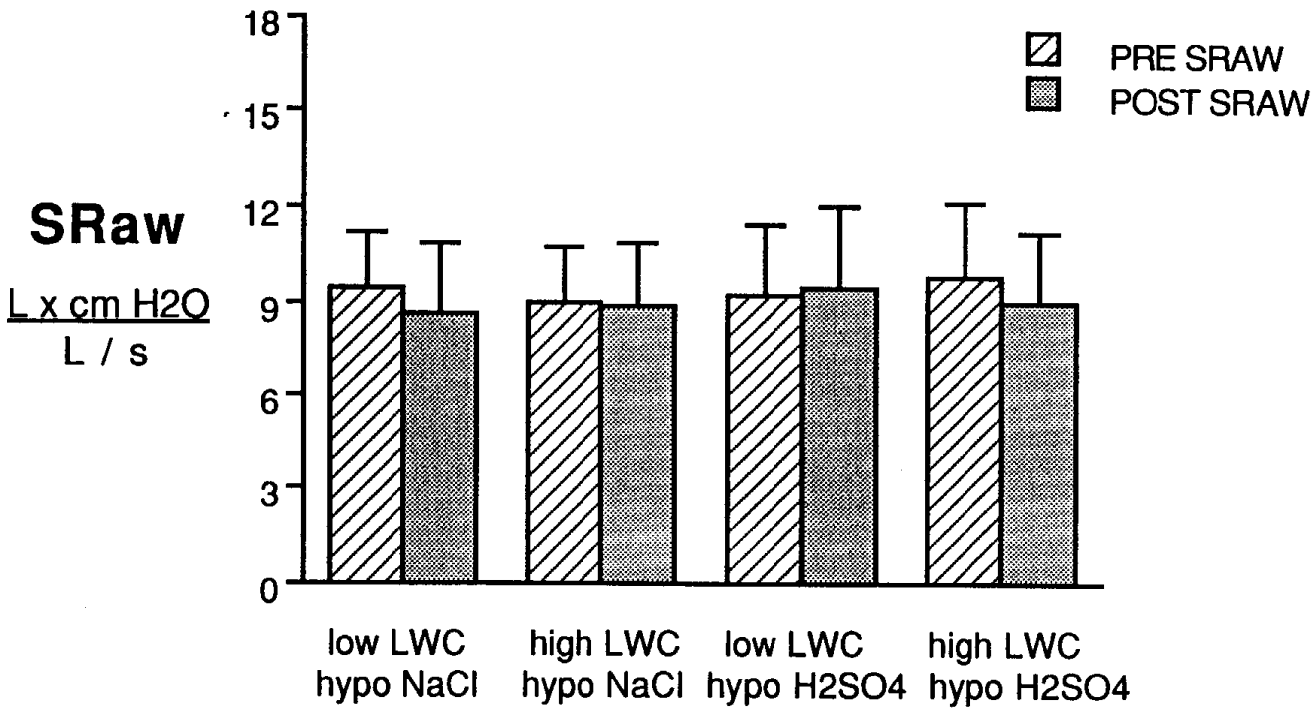
Mean + SEM values for the provocative nebulizer output required to increase specific airway resistance (SRaw) by 100% above baseline for aerosols of hypoosmolar NaCl (pH 5.5) and 3 hypoosmolar acids (H_2SO_4, HNO_3, and a 1:1 mixture of H_2SO_4 and HNO_3, all pH 2) in 12 subjects with asthma. Asterisk (*) indicates significantly lower mean PO_{100} as compared to hypoosmolar saline control ($p < 0.025$).

Figure 3



Specific airway resistance (SRaw) before and after inhalation of aerosols of hypoosmolar NaCl (pH 5.5) and 3 hypoosmolar acids (H_2SO_4, HNO_3, and a 1:1 mixture of H_2SO_4 and HNO_3 [both], all at pH 2) at as much as 5 doubling nebulizer outputs. Individual dose-response curves are shown for each of 12 subjects with asthma.

Figure 4



Mean SRaw pre- and post-exposure to 4 different fogs.

Appendix 1

DEVELOPMENT OF A FOG GENERATION AND MONITORING SYSTEM FOR HUMAN EXPOSURE STUDIES

FINAL REPORT

for

University of California
San Francisco, California 94110

by

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November 23, 1988

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1. INTRODUCTION

Atmospheric Technology (ATEC) and ERT have designed, installed, and tested an acid fog generation and monitoring system under contract from the University of California San Francisco. The system is capable of generating and characterizing synthetic acid fog within a 12 m^3 human exposure chamber over a range of droplet sizes, mass concentrations, and chemical compositions. The overall design of this system is based on a preliminary design concept developed under Phase I of the State of California Air Resources Board (ARB) Contract A4-079-33.

The general specifications for the fog generation and monitoring system are reviewed in the next section, followed by an overview of the integrated system. Section 3.0 presents the results of evaluations performed on several key components which were required before the final system could be constructed. Section 4.0 discusses all of the components on an individual basis, including selection rationale, operating characteristics, and performance limitations. The performance results of the installed system operating under various conditions are presented in Section 5.0, followed by a summary of key findings and recommendations.

2. GENERAL SPECIFICATIONS

The Fog Generation and Monitoring System has been designed to produce acidic fogs for human exposure studies over a wide range of conditions. In general, the system is capable of:

(1) producing and monitoring fog droplets ranging in size from 0.5 to 50 microns (with emphasis on droplet below 10 microns in diameter) at concentrations exceeding one gram per cubic meter;

(2) generating stable and uniform fogs within the exposure chamber for periods of several hours;

(3) varying the initial size and chemical composition of the fog droplets;

(4) determining the fog size distribution, liquid water content, and chemical composition on a semi-continuous basis;

(5) accommodating aerosol generation and monitoring equipment for future multi-component studies;

(6) providing computerized data acquisition and storage to minimize operator intervention during experiments.

2.1. System Overview

The fog generation and monitoring system, shown schematically in Figure 2.1, consists of three subsystems: (1) a generation subsystem which produces droplets from a bulk solution, (2) a delivery subsystem which circulates the fog through the exposure chamber, and (3) a monitoring subsystem which determines the size distribution, liquid water content, and chemical composition of the droplets.

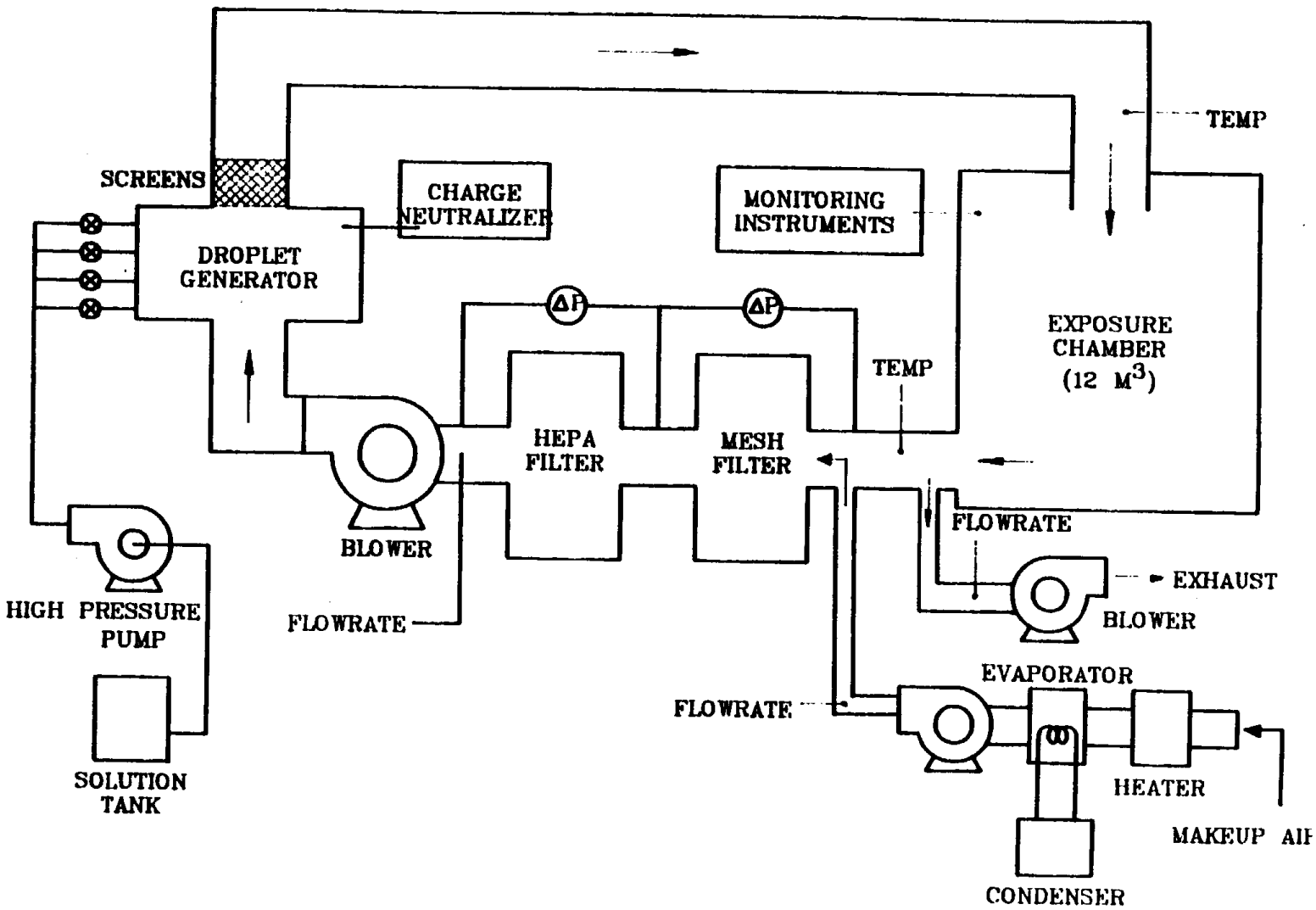


Figure 2.1 Fog Generation and Monitoring System Schematic

2.1.1. Fog Generation Subsystem

Fog droplets are produced using hydraulic atomizers located on several manifolds mounted inside a sealed chamber. Bulk solution is stored in a tank and pumped to the atomizers. Manual valves allow the selection of one or more manifolds containing combinations of atomizers. Two series of screens are located down stream of the atomizers to remove larger droplets in order to control the droplet size distribution.

2.1.2. Fog Delivery Subsystem

The fog droplets produced by the droplet generator are circulated through the exposure chamber using a centrifugal blower connected with flexible ducts. Distribution ducts are mounted along the ceiling of the exposure chamber to evenly distribute the fog. The exhaust air from the chamber passes through ducts mounted along the perimeter of the chamber floor and then flows to a mesh filter which removes the larger droplets and the majority of liquid water. The output from the mesh filter is directed through a HEPA filter to remove the remaining small droplets. The remaining filtered air at high humidity is returned to the droplet generator, where fog droplets are generated and cycled back to the chamber.

A portion of the chamber air is replaced to eliminate the buildup of contaminating gases produced by human subjects. Approximately 10% of the flow is exhausted from the chamber outlet and replaced with air drawn through the existing chamber air purification system. The makeup air is added at the inlet to the mesh filter, which acts as a humidifier, since it contains a large surface area covered with moisture from entrained droplets. Thus, the air returning to the droplet generator is near saturation, even though a fraction of unsaturated air has been added to the system.

2.1.3. Fog Monitoring Subsystem

The fog monitoring system consists of automated instrumentation capable of physically and chemically analyzing fog droplets within the exposure chamber on a semicontinuous basis. A droplet sizing instrument, capable of detecting droplets as small as 0.3 microns in diameter, is located inside the exposure chamber and samples at predetermined time intervals, depending on the fog concentration.

A fogwater collector continuously samples the chamber air and extracts droplets for chemical analysis. Fogwater samples are analyzed for sulfate, nitrate, ammonium, and pH on a semi-continuous basis. A series cyclone sampler and total filter are used to obtain additional information on liquid water content and chemical composition.

Data from the sizing and analytical chemistry instruments is processed and stored using two microcomputers. Figure 2.2 provides a schematic representation of the data transfer and control signals used in this process. In addition, the computers provide status information and historical data for the experiment in progress.

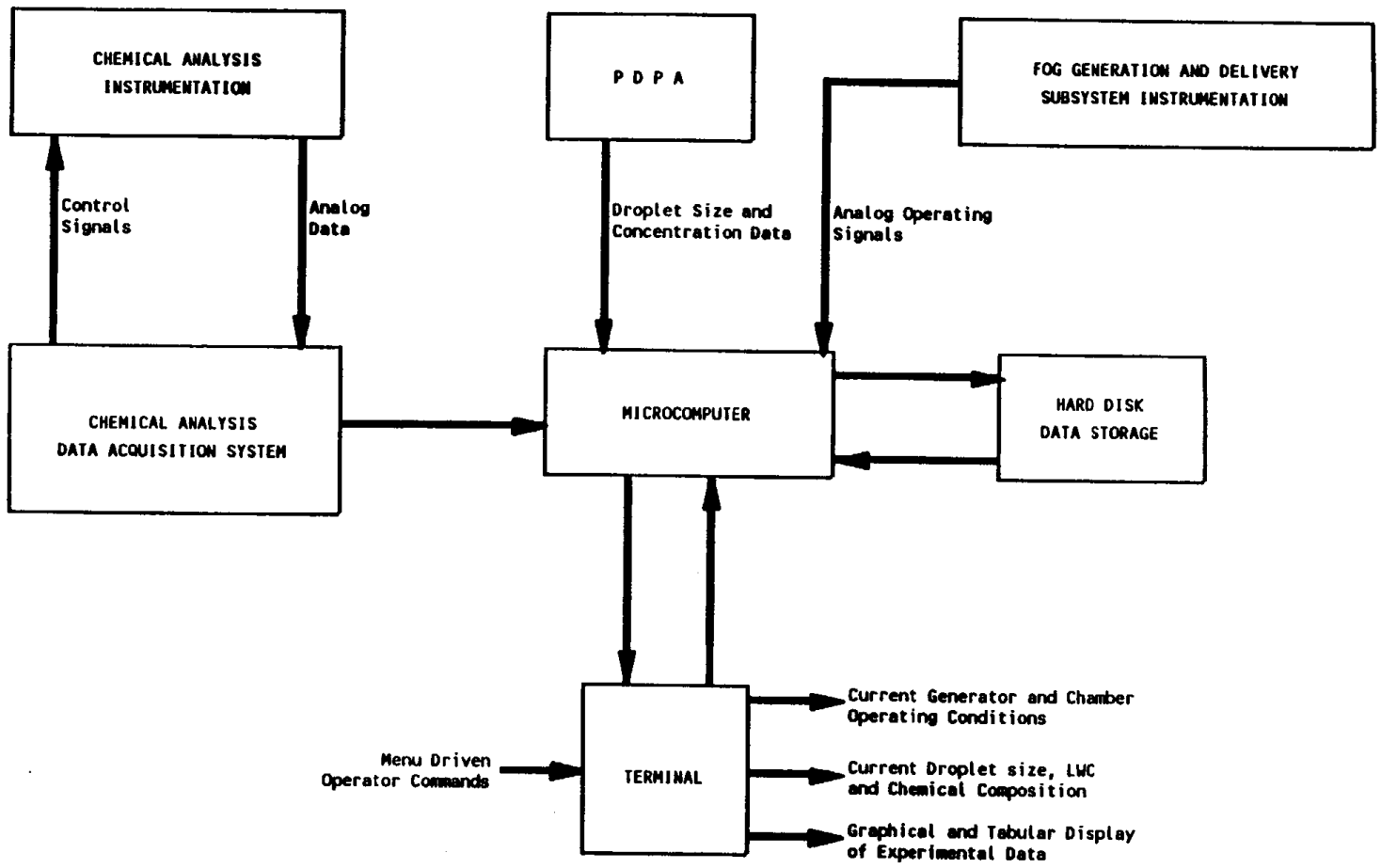


Figure 2.2. Fog Generation and Monitoring Data Acquisition System Schematic

3. COMPONENT EVALUATION

An evaluation of several key system components was performed prior to constructing the final Fog Generation and Monitoring System. The evaluation criteria used to select the final design were based on the overall Design Specification presented in Section 2.0

3.1. Fog Nozzle Evaluation

Fog nozzle evaluations were conducted with a bench scale fog chamber using an Aerometrics Phase Doppler Particle Analyzer (PDPA) and a total filter to determine the fog droplet size distribution and liquid water content. The Bete PT series, Spraying Systems TG 0.3, and Delavan 30610-6 and 30615-15 nozzles were evaluated under a wide range of operating conditions to select a nozzle which would produce the smallest droplet size with the highest liquid water content. The Bete and Spraying Systems nozzles are a high pressure pneumatic type, while the Delavan nozzles are an air atomizing design. Measurements made with the PDPA showed that both the air atomizing and pneumatic nozzles produced a large number of small droplets in the 0.5 to 5 micron size range. However, the liquid water content was found to be very sensitive to the number of larger droplets that were present. The Bete PT8 nozzle appeared to provide the largest proportion of small droplets with a reasonable liquid water content.

All of the nozzles tested showed only a slight change in droplet size with variations in operating conditions. Table 3.1 illustrates the output characteristics of several Bete PT nozzles operating at different liquid pressures. In the initial design concept, the droplet size was to be changed by varying nozzle operating conditions. However, these test results suggested that this approach could not provide the wide range in droplet sizes that would be necessary for human fog exposure studies.

In order to vary the droplet size, aluminum 18 x 18 mesh (0.011 inch wire diameter) impaction screens were tested to determine if the screens mounted down stream of the fog nozzle would remove the larger droplets and decrease the volume mean diameter. One Bete PT8 nozzles was positioned in

Table 3.1. Number Mean and Volume Mean Diameters for Bete PT Nozzles Operating at Pressures from 65 to 1000 psig.

Nozzle	Operating Pressure (psig)					
	65		500		1000	
	Number Mean Diameter (um)	Volume Mean Diameter (um)	Number Mean Diameter (um)	Volume Mean Diameter (um)	Number Mean Diameter (um)	Volume Mean Diameter (um)
PT 5	17.6	32.3	8.7	24.6	7.3	23.7
PT 8	15.5	31.8	9.0	23.0	8.3	20.2
PT 12	16.5	27.1	16.1	29.6	10.0	24.6
PT 15	15.2	27.3				

a 4 inch diameter plastic tube mounted in a horizontal position. Various numbers of screens were placed in a vertical orientation at the outlet of the tube. A small blower was used to move the fog through the screens at a velocity that could be regulated between 0 and 1.5 m/sec. The output from the screens was ducted to the Aerometrics PDPA droplet analyzer to measure the droplet size distribution and liquid water content. A glass fiber filter was used to sample the fog in order to measure the liquid water content. To evaluate the effects of the screens, the nozzle operating pressure and the blower flowrate were held constant, while the number of screens was changed. The results of these tests are present in Table 3.2, which show that the volume mean diameter could be varied form 9.7 to 3.4 microns depending on the number of screens that were used.

3.2. Fogwater Collector Evaluation

Several fogwater collector designs were evaluated for their ability to obtain representative fogwater samples from the exposure chamber for subsequent chemical analyses. The designs included impactors, cyclones, and string collectors.

Fogwater collectors were evaluated for their ability to achieve:

1) 50% collection efficiency for 2.5 um diameter droplets;
2) adequate sample volume for analyses at 5 minute intervals over a range of 0.2 to 2.0 g/m^3 liquid water content (LWC); and
3) flowrates up to 2.0 m^3/min at pressure drops up to 50" of water.

The evaluation of the fogwater collector assumed that the smallest droplet size distribution sampled would have a mass median diameter of 4 um and a geometric standard deviation of 1.5 to 2.0.

A secondary objective of the evaluation process was to recommend a collection method for selectively collecting droplets with diameters smaller than 2.5 um.

Table 3.2. Variations in Droplet Number Mean Diameter, Volume Mean Diameter, and Liquid Water Content using 18x18 Mesh Screens at a 0.9 m/sec Fog Velocity.

No. of Screens	Number Mean Diameter (um)	Volume Mean Diameter (um)	Liquid Water Content (gm/m^3)
0	2.8	9.7	1.15
1	2.5	8.4	--
2	2.5	7.3	0.80
3	2.4	7.0	0.69
4	2.2	5.9	0.50
5	2.2	5.5	0.45
6	2.3	4.3	0.24
7	2.0	4.2	0.25
8	2.1	4.0	0.20
9	2.0	3.7	0.23
10	2.0	3.5	0.17
15	1.9	3.4	0.17

3.2.1. Evaluation of Existing Fog Water Collectors

A preliminary survey of existing fog water collectors was conducted during the design phase. The findings of the survey are summarized in Table 3.3. Impactor-type collectors were chosen for evaluation because they provide relatively sharp cut points and because the impactor theory used to evaluate design changes is simple and reliable. The three impactors considered for modification to meet chamber design requirements were the DRI rectangular jet impactor (Katz and Miller, 1984), the Caltech active string collector (Jacob et al., 1985), and the May glass bulb collector (May, 1961). Figures 3.1, 3.2 and 3.3 illustrate the three very different designs for the May, DRI, and Caltech collectors, respectively. Appendix B contains evaluations of the May and DRI impactors including results of pressure drop measurements and discussions with researchers at Rancho Los Amigos Hospital using the DRI impactor in an exposure chamber.

The May collector is simple in design, but unfortunately, there is no easy way to scale up this collector to provide the high sample flowrates needed to collect adequate amounts of fogwater for chemical analysis when the LWC is low.

The DRI collector has the advantage of nearly complete removal of large droplets from the sample stream. This is an important feature for collecting a fine size fraction of fog droplets downstream of the collector. However, the relatively large pressure drop might destroy this potential by causing small droplets to evaporate in the low pressure sampling regime. Further, the collector has not been tested in modified designs. The complexity of the DRI collector would make design changes impractical after initial construction, thus reducing the flexibility of the sampler.

The Caltech collector was chosen as the fogwater collector for use in the UCSF chamber on the basis of simplicity, flexibility, and proven performance in a variety of different designs. The principle design parameters controlling the cutpoint are string diameter and air velocity (which is controlled by duct dimensions for a given flowrate). Additional

Table 3.3. Fogwater Collector Comparison

	Flow Air m^3/min	Flow Liquid ml/min	Pressure Drop In. H_2O	Cut Point	Pros	Cons
DRI Impactor	1.2	0.080	50.0	5.0	Sharp Cut Point Used in Chambers Theory Well Treated	High Pressure Drop Complicated Expensive
Modified DRI Impactor	1.2	0.110	50.0 400.0	2.5	Predictable Cut Point Sharp Cut Point	High Pressure Drop Possible Particle Breakup Untested at New Cut Point Expensive
String Collector	10.0	0.840	0.4	3.8	Simple No Moving Parts	Cut Point Untested Must Be Scaled Down
Axial Flow Cyclone	4.2	0.400	14.0	<5.0	No Moving Parts Small	Needs Scale Up or Scale Down Developers in UK
Tangential Cyclone	10.0	0.700	0.15	5.0	Simple Low Pressure Drop Cheap No Moving Parts	Cut Point Uncertain Cut Point Unsharp Large Wetted Surface Untested for Fog
May Impactor	0.05	0.005	--	4.1	Simple No Moving Parts	Very Low Volume Not Easily Scalable
Mesh	10.00	0.700	0.2	5.0	Very Simple Very Cheap	Cut Point Uncertain Cut Point Unsharp Cut Point not Designable

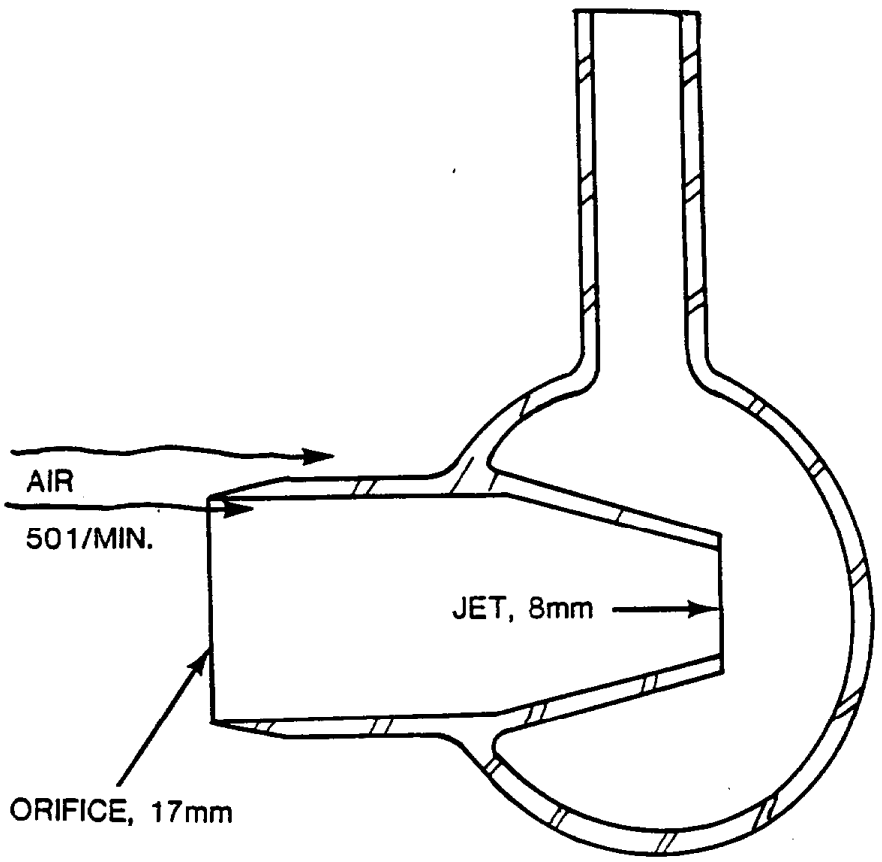
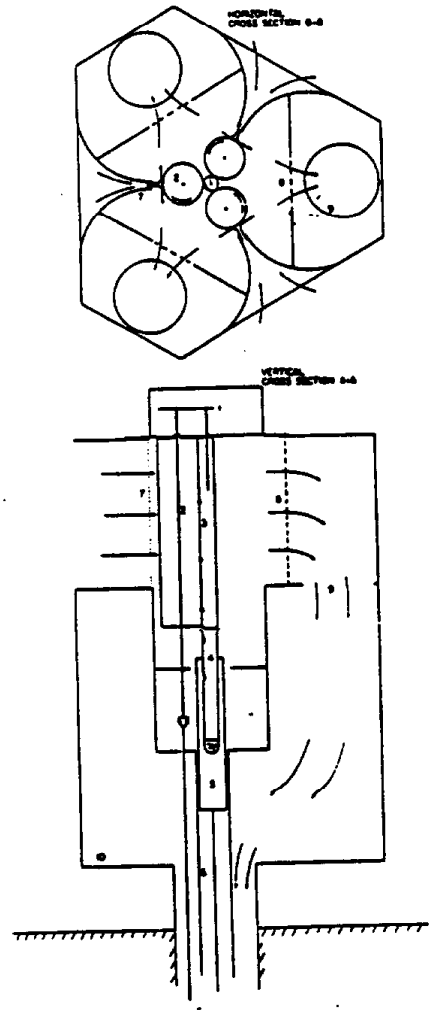


Figure 3.1. May Collector



Horizontal and vertical cross section of linear-jet impactor for collecting cloud water. (1) gears for control of Teflon roller rotation; (2) one of three Teflon rollers (2.5 cm diameter) serving as droplet impaction surface; (3) small central Teflon roller guiding collected water into (4) sample water receptacle; (5) holder to guide water receptacle: (6) sample entry/exit tube; (7) slot shaped nozzle to form cloud air jet, width W = 0.4 cm, length L = 8.3 cm; (8) diffusor to distribute air flow evenly over length of nozzle; (9) suction ports; (10) plenum; (11) shaft connecting one Teflon roller with motor outside of housing.

Figure 3.2. DRI Collector

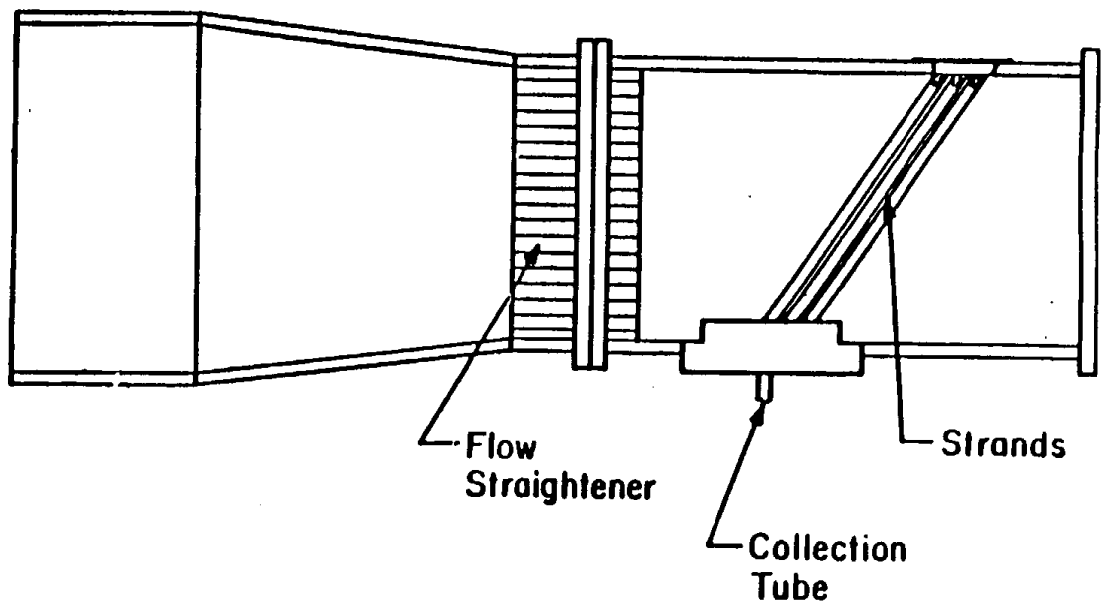


Figure 3.3. Caltech Active String Collector

parameters that determine sample collection capacity, and also influence cutpoint, are string spacing, the number of banks of strings, and total flowrate. A major advantage of this collector is that researchers at Caltech have experimented with the above parameters and are familiar with the practical working limits of the design. Appendix A provides a discussion of design considerations for the Caltech collector.

3.2.2. Testing of the Modified Caltech String Collector

A working design for a small fogwater collector used by Caltech in the field as a fogwater detector was modified to fit the needs of chamber sampling. To reduce the 50% cutpoint, the string diameter was reduced and the air velocity increased. To improve collected sample volume for low density fogs, the string spacing was decreased and the number of string banks was increased.

The MCSC was tested for practical utility during and after construction. Qualitative findings include:

- String diameters that are too narrow result in broken strings.
- Air velocities that are too high require large blowers and may result in droplet recirculation.
- String spacings that are too close result in droplets bridging several strings and failing to run into the collector.
- Too many banks of strings result in the last banks being nearly dry, so that the sample does not run to the base of the collector.

Based on analysis of impaction theory for the string collector and on its practical limitations, the design goals for 50% cutpoint and sample volume were achieved.

The MCSC was tested to determine:

1) the pressure drop through the collector at various air volume sampling rates;

2) the adsorption characteristics of the collector strings for sulfate, nitrate, and ammonium;
3) the variation in string diameter after successive wetting and drying cycles; and
4) the actual 50% cutpoint under normal operating conditions.

Test results are described in the following paragraphs.

3.2.2.1. Pressure Drops and Sampling Flows.

The pressure drop across the flow straightener was measured with a Magnahelic gauge under dry conditions. Air velocity was measured concurrently with a TSI hot-wire velocity probe. The probe was inserted into the middle of the flow channel downstream of the strings through a small hole drilled into the plexiglass frame of the MCSC. The results of these tests showed that velocity varied linearly with pressure drop according to the following equation.

$$V = 32.4 \times P + 1.29$$

where: V is air velocity in m/sec,
P is the pressure drop in inches of water.

The index of determination for this linear relationship based on eight data points is 0.994.

Therefore, to achieve the design cutpoint of 2.5 microns diameter, the velocity should be maintained at 6 m/sec by adjusting the blower controller to maintain a pressure drop of 0.15 inches of water across the fogwater collector.

Air sampling rate can be derived from the velocity by multiplying the velocity by the cross-sectional area of the MCSC inlet. At the design velocity, the sampling rate of the MCSC is 2.0 m^3/min.

The above values are derived from measurements made under dry conditions. Velocity measurements under wet conditions were not possible with the TSI probe. The water layer that forms on the collector strings should increase the pressure drop and decrease the flow for a given blower setting. The degree to which this factor will change the cutpoint and other operating parameters was not determined, although they are not expected to be significant.

3.2.2.2. Chemical Adsorption/Desorption Characteristics of Nylon Strings

Samples of the nylon string used in the MCSC (Stren 4 lb. test monofilament fishing line) were extracted overnight in minimum volumes of acidified (pH 2) distilled water. The extraction solution was analyzed for sulfate, nitrate, and ammonium by IC. Concentrations of all species in the extract were below the detection limits for the IC.

Samples of the nylon string were soaked in minimum volumes of weak (5 ueq/l) sulfate, nitrate, and ammonium solutions. The solution concentrations did not show detectable changes after the overnight soaking.

3.2.2.3. String Diameter Variations

The nominal diameter of the nylon string used in the MCSC was 0.011 inches (280 microns). Samples of string were soaked for varying lengths of time in distilled water, and neutral (pH 7) and acidic (pH 2) solutions of sodium sulfate, sodium nitrate, ammonium chloride, and sodium chloride at 10 meq/l concentration. The first and second one hour soaks were in neutral solutions, while the third soak was done at pH 2. The strings were soaked, dried, their diameters measured under a microscope, and the process was repeated. The results of these tests are shown in Table 3.4.

The test results show that the string diameter is irreversibly increased by 5% after repeated wetting and drying cycles. Neither acidity nor the chemical composition of the soaking solutions had a significant effect on this result.

Table 3.4. String Diameter Variations

Solution	% Change from Untreated String		
	1st 1hr. soak	2nd 1hr. soak	3rd 1hr. soak
Distilled water	+2.5*	+2.5	-·-
Sodium sulfate	+5.0	+5.0	+5.0
Sodium nitrate	+2.5	+5.0	+5.0
Ammonium chloride	+5.0	+5.0	+5.0
Sodium chloride	+2.5	+5.0	+5.0

*The first distilled water soak was for 17 hours to thoroughly wet the nylon string.

3.2.2.4. Measurements of the 50% Cutpoint Diameter of the MCSC

Measurements of the collection efficiency of the MCSC were made using the PDPA to sample the fogwater size distribution before and after it had passed through the MCSC. The sampling conditions were those recommended for normal operations. Several droplet distributions were sampled for one minute at locations upstream and downstream of the MCSC. Subsequently, these distributions were subtracted from one another to determine the percent collection efficiency as a function of droplet diameter. Figure 3.4 shows a representative collection efficiency curve for these tests.

The experimentally determined 50% collection efficiency for the MCSC was found to occur at a droplet diameter of 2 microns, in very good agreement with theoretical predictions shown in Figure 3.5.

3.2.3. Fog-water Collector String Evaluation

The nylon stings currently employed in the fog-water collector were found to be subject to attack by high concentrations of acid. Cole-Parmer rates the resistance of nylon to dilute concentrations (concentrations less than 10%) of nitric and sulfuric acid as fair (satisfactory up to 72 degrees F). These concentrations are far in excess of those intended to be employed in the exposure chamber. During testing, the acid fog test solution was inadvertently allowed to dry out and thus concentrate on the strings, with the result that the strings were weakened and broke under tension. During routine operation, this situation can be avoided by rinsing the strings with distilled water after collecting acid fogs.

Alternative string materials were considered for two reasons: 1) to find materials more resistant to acid; and 2) to reduce the aerodynamic diameter of the aerosol 50% cutpoint. Teflon and stainless steel were considered as alternative materials. Teflon is very resistant to acids, but the available Teflon strings in the diameters used in the fog-water collector have very low tensile strength. Stainless steel is rated superior to nylon for resistance to weak nitric acids. However, for weak sulfuric acid, the

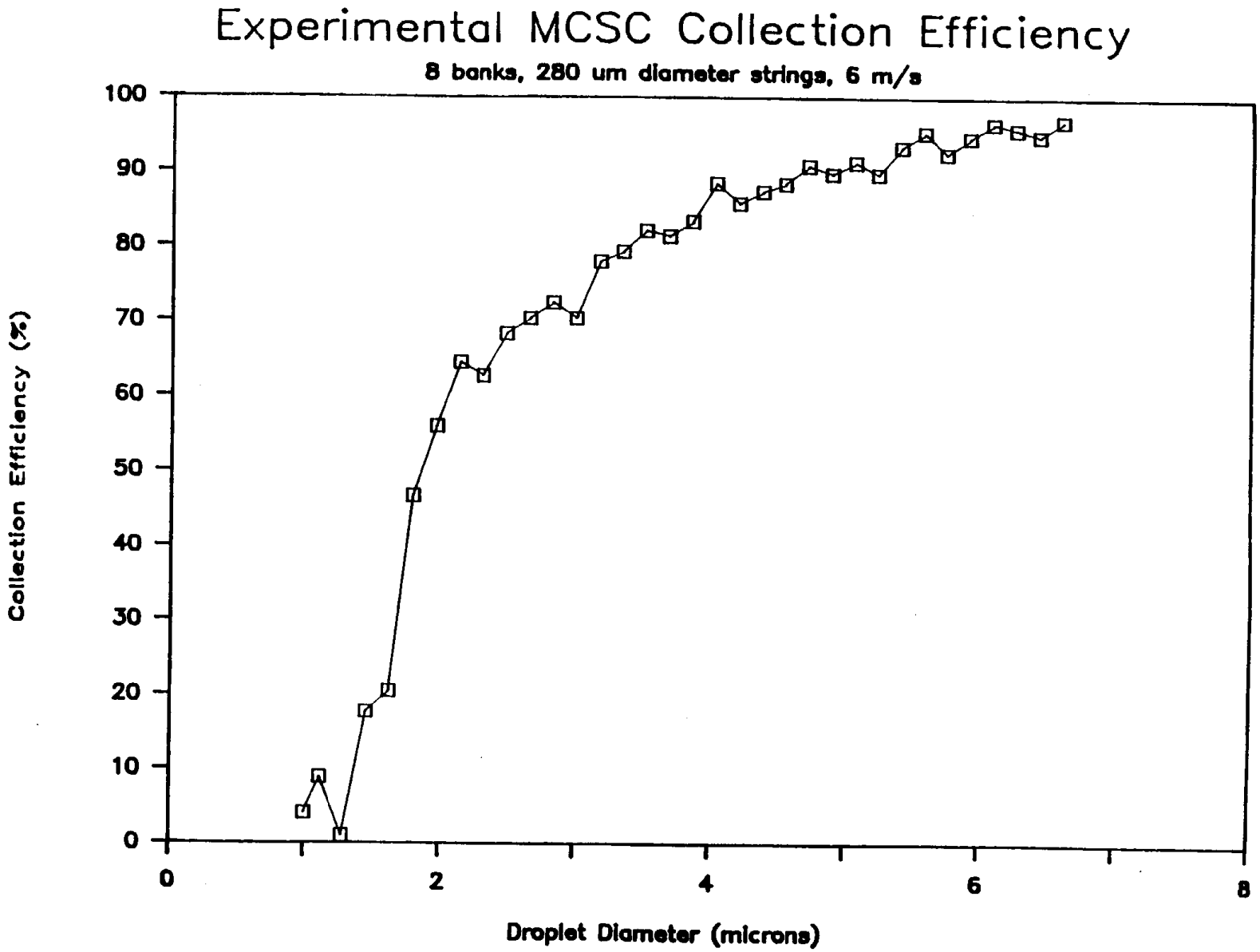


Figure 3.4. Experimental MCSC Collection Efficiency

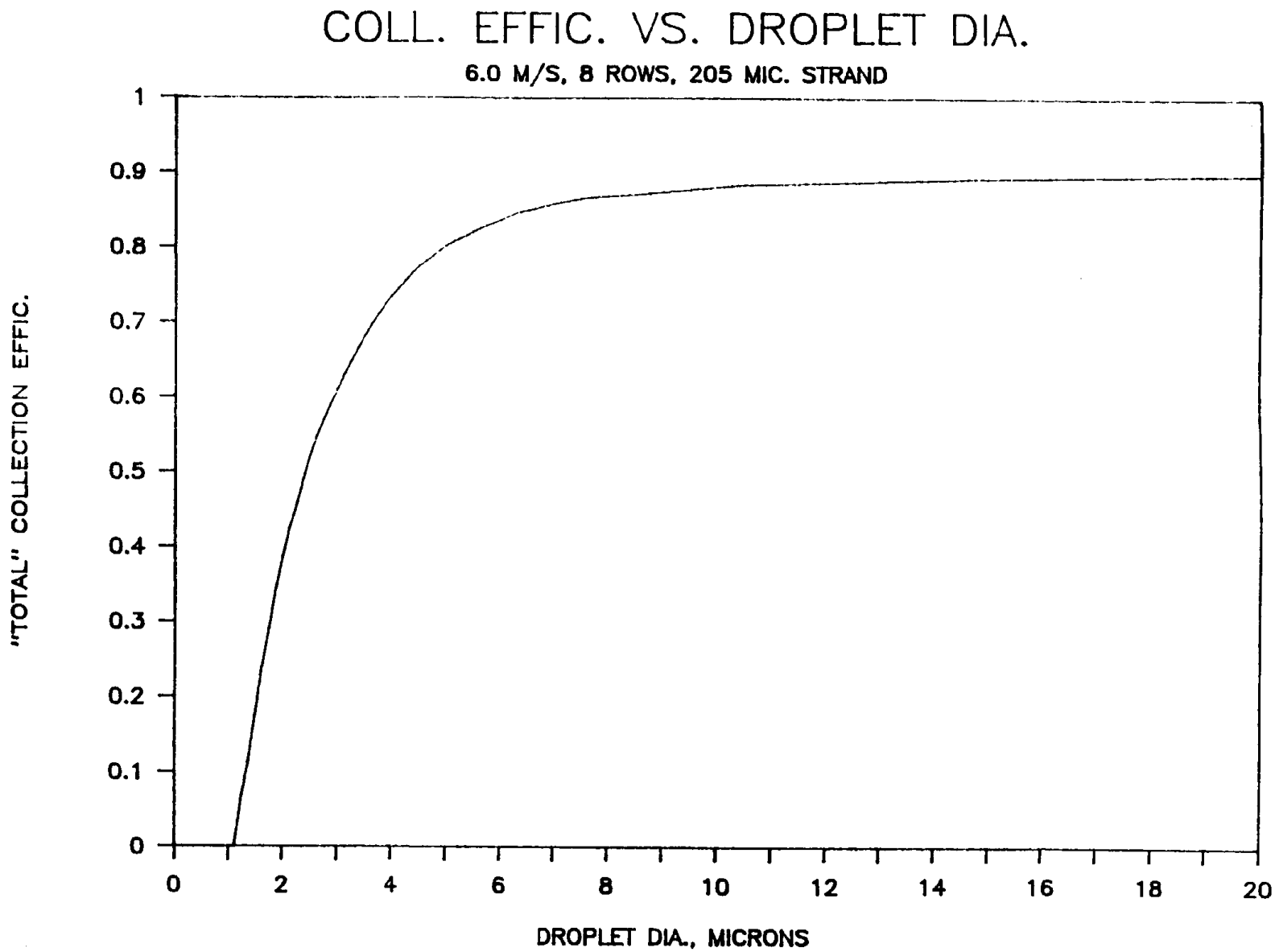


Figure 3.5. Theoretical MCSC Collection Efficiency

rating depends on the type of stainless steel. Type 304 is rated inferior to nylon, type 440 equal to nylon, and type 316 superior to nylon, but still not excellent.

Stainless steel wire was rejected because all alloys are rated very poor when exposed to the concentrated solutions, which will result when the fog-water collector is allowed to dry out without a distilled water rinse. Also, stainless steel has such high tensile strength that winding the steel string on the collector frame is extremely difficult. The process warps the frames, leading to loose wires on parts of the frame (Daube, 1987).

The collection efficiencies of three wire diameters were calculated using theoretical models employed by Caltech. Table 3.5 shows the collection efficiencies for string diameters of 0.009, 0.011, and 0.020 inches. The 0.009 inch diameter is that of the smallest readily available steel wire; 0.011 is the diameter of the currently employed nylon string; and 0.020 is the diameter of the smallest Teflon string that has sufficient tensile strength for practical use.

Table 3.6 shows that the improvements in size cutpoints offered by the 0.009" wire are minimal. Further, the loss in collection efficiency when using the 0.020" string is significant. The reduction in efficiency for 0.020" string results from having to drop the number of strings per bank in half due to spacing considerations.

In summary, the poor resistance of stainless steel to the concentrated acids resulting when the collector is allowed to dry, combined with the frame winding difficulties and the minimal improvement in cut size lead us to reject stainless steel wire as an optional material for the MCSC. The significant reduction in collection efficiency for 2.5 micron diameter particles and the fragility of Teflon lead us to reject Teflon string. As a result, we recommend continuing with the nylon string.

During testing, the nylon held up fine if rinsed with distilled water after use. A distilled water rinse should be incorporated into routine procedures. Finally, if the string is subjected to concentrated acid, and

breaks as a result, the nylon string employed is inexpensive, readily available at any fishing tackle store, and easy to wind around the string frames -- all important factors in the reliability of the overall system.

3.2.4. Considerations for a Two Stage Sampler

The feasibility of designing and constructing a two stage fogwater collector with a 50% cutpoint at 2.5 um diameter was evaluated during the course of this study. There are several considerations unique to sampling this size fraction that must be considered.

1) The volume of fog droplets below 2.5 um diameter is a small fraction (typically << 10%) of the total volume distribution of the fogwater generated for chamber studies.
2) These small droplets are extremely subject to evaporative loss with subsequent concentration of the chemical constituents in the droplets. Evaporative loss will be exacerbated in a two stage series collector due to the pressure drop across the first stage.
3) The first stage collector must be highly efficient at removing large droplets. Even a small number of large droplets collected on the second stage could have a significant impact on measured chemistry of the second size fraction.

Once the MCSC was selected for chamber applications, development of two stage capabilities was focused on this collector. A total filter was the preferred second stage in order to collect a maximum sample volume. The MCSC operating in take-off mode has a very small pressure drop of 0.15 inches of water. The low pressure drop will minimize evaporation of droplets that pass through the string collector and are collected on the total filter. Because a small fraction (about 5%) of the air volume that passes through the MCSC does not interact with the string collector, a method to remove large droplets before they reach the total filter will be necessary.

A suggested configuration that will likely address the points raised in the preceding paragraph is a total filter located downstream of the flow

straightener. The inlet of the second stage filter would be through the plexiglass after wall of the MCSC, oriented perpendicular to the flow. The inlet would be designed as a virtual impactor with a sharp cutpoint at or below 2.5 um, effectively excluding large droplets from reaching the filter. Because of the small amount of fogwater associated with smaller droplets, it is likely that only one or two filter samples could be collected during a one hour sampling period.