

Water vapour and temperature dynamics in the upper airways of normal and CF subjects

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ABSTRACT: Water vapour partial pressure (P_{H_2O}) and temperature (T) were measured together, continuously, at the airway opening (either lips or nares) and at the oropharynx of human subjects with normal lungs or with cystic fibrosis (CF). No apparent differences in P_{H_2O} or T were found between normal and CF groups breathing ambient air ($22 \pm 2^\circ\text{C}$). During inspiration the relative humidity at the pharynx for nose breathing (95%) was higher than for mouth breathing (75%). For hot air breathing ($48 \pm 2^\circ\text{C}$), the P_{H_2O} and relative humidity of inspired gas at the pharynx was lower for the CF group than for the normal group. Also, the CF group had a higher airway surface temperature at the airway openings on inspiration. These data suggest that when the rate of evaporation is sufficiently high, the rate-limiting step may be water transport through the mucosal tissue and/or secretions. At least for the upper airways, this rate limitation is more evident for CF patients than for normal subjects. *Eur Respir J. 1988, 1, 407-414.*

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The underlying hypothesis of this study is that respiratory heat and water exchange (or humidification) differs between subjects with normal lungs and those with cystic fibrosis. One rationale for this hypothesis is that the physico-chemical properties of mucus of subjects with cystic fibrosis differs from normal mucus [1, 2]. Such a difference could affect, or be affected by, the water transport at the airway surfaces. This can be shown theoretically by incorporating possible surface phenomena in a mathematical model of airway heat and water transport [3].

In addition to mucosal surface effects caused by disease, the primary factors influencing humidification are the inhaled gas conditions (temperature and water partial pressure) and the pathway travelled by the inspired gas. These factors can exacerbate or ameliorate the problems of inadequate humidification caused by disease. Bypassing the nose, for example, puts a much greater burden for humidification on the distal airways, whilst exercise-induced asthma is inhibited with higher humidity in the inspired air [4].

Even though the fundamental process of humidification in human airways is well understood, direct measurements [5] have been sparse. Most continuous humidity measurements from humans have been restricted to the airway opening [6, 7], whilst temperature measurements have been obtained in the upper, larger conducting airways [8-10].

Recently, we have developed a system for the simultaneous measurement of temperature and water vapour in the respiratory tract [11]. In the present study we used this system to observe gas conditions at the lips or nares and the oropharynx for normal subjects and patients with cystic fibrosis breathing ambient or hot air.

Methods

Subjects

Two groups were studied. The first consisted of seven, non-smoking, healthy adults (age 22-41 yrs, five male, two female) with no history of chronic pulmonary disease and no acute respiratory symptoms at the time of the experiment or during the week preceding it. A total of eight experimental procedures were performed on these subjects. The second group consisted of six patients (age 19-25 yrs, five male, one female) with cystic fibrosis, but in a stable condition.

Instrumentation

The measurement system used in the experiments has been described in detail elsewhere [11]. It utilizes a specially designed catheter probe, which permits the simultaneous and continuous measurement of temperature and partial pressures of H_2O , CO_2 and other components of respired air and local temperature of

the wall in the upper airways. The probe is constructed from a stainless-steel catheter (0.8 mm O.D.) which is constricted at its tip. The catheter is connected to the inlet of a mass spectrometer (Perkin-Elmer, 1100 MGA). The low pressure within the catheter, caused by the constricted tip, prevents condensation on internal surfaces of the catheter at temperatures above 0°C. Eliminating condensation and evaporation in the catheter and mass spectrometer in this way improves the step-response time of the mass spectrometer for water vapour. Also, a lead-compensating filter was applied to the water vapour signal to improve the dynamic response. Consequently, the 90% step-response time for water vapour is approximately 250 msec. The step-response for dry gas is less than 100 msec.

Local gas and airway wall temperatures were measured by micro-bead thermistors mounted on a protective cage at the tip of the probe. The step-response of the thermistor for gas temperature is less than 120 msec in still air; that of the wall temperature thermistor is less than 100 msec in water. Temperature and water vapour steady-state calibrations were established relative to a dew-point hygrometer (General Eastern, Model 1100 AP).

The rate of change of lung volume was evaluated continuously by differentiating a signal corresponding to change of lung volume. This signal was obtained in some subjects by variable inductance transducers (Respirace) and in others by mercury strain gauges (Parks Elec. Lab., Model 270) placed on the rib cage and abdomen. Both of these techniques, calibrated by having the subject breathe either into a spirometer or through a pneumotachometer, were of comparable accuracy.

The instrument response times for all continuously measured variables were sufficiently fast to permit resolution of intra-breath events [11]. Furthermore, the wave-shapes observed during most breathing manoeuvres had substantial periods of relatively constant values, so that transients at the beginning and end of the phases of a breath could be easily discriminated and analysed appropriately.

Experiments

Water vapour partial pressure was measured simultaneously with gas and wall temperatures during three breathing patterns (quiet, tidal volume; fast, shallow panting; slow, large volume). For most subjects, the fast inspiration lasted 0.4–0.6 s; the quiet inspiration 1.2–1.5 s; the slow inspiration 2–5 s. The estimated average flows, as an approximation to minute ventilation, were in the range of 10–30 $l \cdot \text{min}^{-1}$. The measurements were repeated at three locations (in the pharynx, in the mouth at the lips, and in the nose at the nares) for the same patterns. Respired gas moved either through the nose with the mouth closed or through the mouth with the nose blocked. The studies were repeated for two sets of inhaled gas temperatures: ambient ($22 \pm 2^\circ\text{C}$) and hot

($48 \pm 2^\circ\text{C}$). The inhaled water vapour pressure varied in the range of 0.4–1.0 kPa.

Under ambient conditions the subject breathed from the atmosphere in the room. The probe was inserted through the mouth to the pharynx. The thermistor at the tip of its protective cage was placed against the mucosal surface at the back of the throat to measure wall temperature. Most subjects could suppress their gag reflex for a sufficient time to permit measurements at this location. Then, either the nose was blocked, using nose-clips, and mouth breathing ensued, or the mouth was closed and nose breathing occurred. The subject was instructed to adjust the rate and depth of breathing to produce one of the desired patterns, *i.e.*, quiet, fast or slow. The probe was then withdrawn from the mouth and placed at the airway opening, either at the lips or nares, with the tip of the cage touching the most proximal accessible mucosal surface. The same breathing patterns were repeated.

Before and during the positioning of the probe at the airway opening or in the pharynx, the subject breathed ambient air. As soon as the probe was in position, the subject started to breathe the conditioned air at a given rate, *viz.*, normal, slow or fast. At any one of these rates, an apparent steady state was reached after a few breaths as indicated by the water vapour and temperature signals. In the steady state, data were taken for 15 to 30 s. Then the subject breathed at another fixed rate until a new steady state was achieved. Again, data were taken for 15 to 30 s. This process was repeated for the third time at another breathing rate.

For the subjects to inhale gas in a non-ambient condition, they were fitted with a modified disposable oxygen mask having a plastic hood. A sufficient flow of gas was supplied to the mask to ensure a continuous washout of all expired gas. Hot air was produced using a common hairdryer. Gas temperature in the mask was monitored with an electric telethermometer (Omega Eng., Model 5800).

The following variables were recorded on a strip-chart recorder (Brush, 660): mucosal wall temperature (T_w), gas temperature (T), water vapour partial pressure ($P_{\text{H}_2\text{O}}$), rate of change of lung volume (\dot{V}_L) and partial pressure of carbon dioxide (P_{CO_2}). As an indication of body core temperature, the subject's sublingual temperature was taken with a mercury thermometer at the beginning and end of the experiment. Using the values of local gas temperature and water vapour partial pressure at peak flows in a breath, we calculated the local relative humidity.

Results

Characterization of the data

Typical dynamic recordings of the variables measured simultaneously in the nares (fig. 1A) and in the pharynx (fig. 1B) are shown for a normal subject who inhaled ambient air during either quiet, fast or slow breathing. For a given breathing manoeuvre, the wall and gas temperatures and H_2O

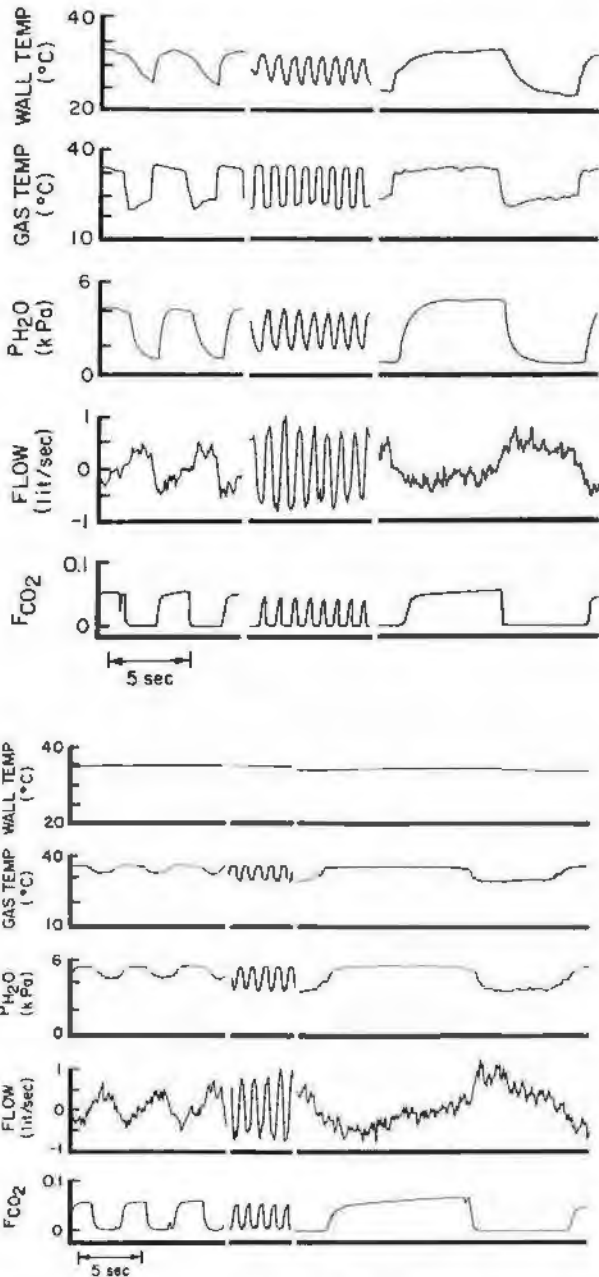


Fig. 1. Data from a normal subject breathing ambient air through the nose: A. Measurements at the airway opening (nares); B. Measurements at the pharynx.

partial pressure vary substantially more at the airway opening than at the pharynx. After accounting for time delays among signals, corresponding landmarks during a breath can easily be identified for each variable. The steady-state wave-shapes are established within two to five breaths after a change in breathing pattern. The T and PH₂O signals had distinctive reproducible characteristics on inspiration and expiration. The wave-shapes are similar regardless of the inspired air condition, pathway travelled or measurement location. Given the reproducibility of the data for each breathing pattern, we chose to quantify the

wave-shapes by their values during the expiratory plateau and the extreme values during inspiration. The peak flow (or rate of lung volume change) for each phase of the breath was used as a relative measure of air flow for comparison of variables among breathing patterns.

The characteristic values of the variables were plotted with respect to flow during inspiration and expiration. Inspiratory and expiratory values of T and PH₂O at the airway openings and pharynx are shown in figures 2A and 2B for ambient air breathing by a typical normal subject. The values of T and PH₂O tended to vary with inspiratory flow in the pharynx, but this variation was within 1°C and 1 kPa over the range of experimental flows and is more evident for inspiration of ambient air than hot air. For the flow range studied, an average taken over all flow conditions is adequate. Thus, we averaged the peak values, using three to five breaths, of each variable measured at a particular location for inspiration or expiration through either nose or mouth.

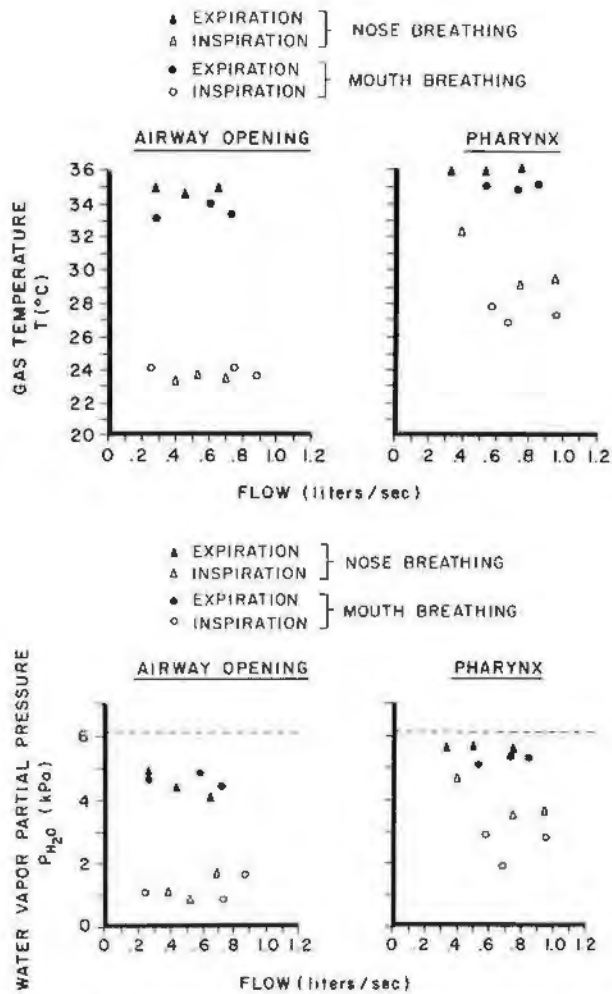


Fig. 2. Inspiratory and expiratory T and PH₂O versus peak flow at the airway opening and pharynx of a normal subject during nose and mouth breathing of ambient air: A. Gas temperature; B. Water vapour partial pressure (equilibrium water vapour pressure at 37°C shown by the dashed line).

Under ambient conditions, the changes in T and P_{H_2O} between inspiration and expiration are in the same direction because the processes of heat and water exchange are analogous, *i.e.*, the energy and water balance equations and boundary conditions are similar for T and P_{H_2O} [3]. This provides a check for consistency of the independent measurements from the transducers. Results for hot air breathing are shown in figures 3A and 3B. The results differ from those during ambient air breathing in that the changes in T and P_{H_2O} on inspiration of hot air do not correspond. With the hot inspired air, the transfer processes of heat and water are in opposite directions.

Complete data sets were obtained from three normal subjects and from four CF patients. Incomplete data sets were caused by: (a) the inability of some subjects to tolerate the probe in the oropharynx; (b) saturation of the thermistor from a coating of mucus; (c) plugging of the tip of the probe.

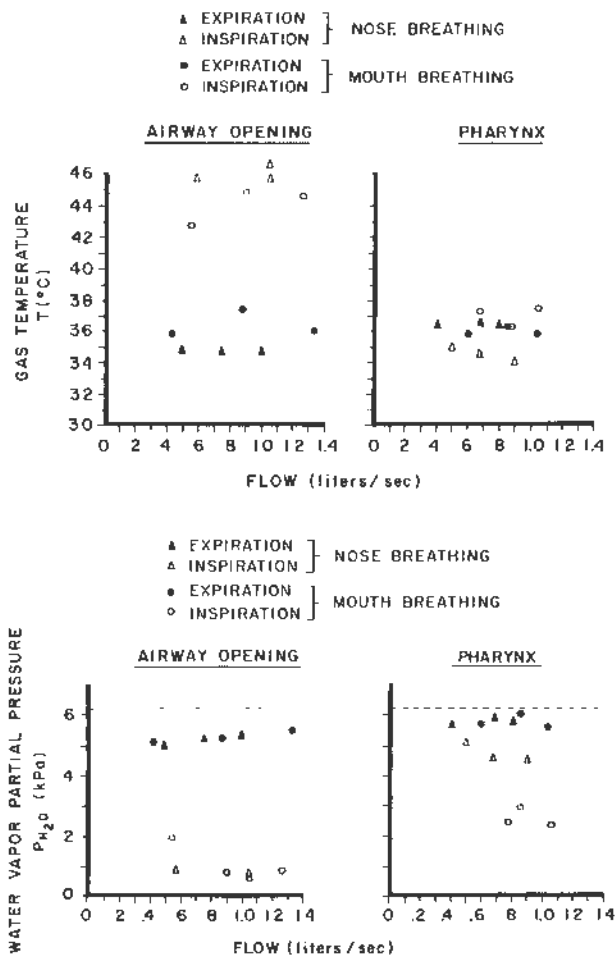


Fig. 3. Inspiratory and expiratory T and P_{H_2O} versus peak flow at the airway and pharynx of a normal subject during nose and mouth breathing of hot air: A. Gas temperature; B. Water vapour partial pressure (equilibrium water vapour pressure at 37°C shown by the dashed line).

Inspiring ambient air

Flow-averaged gas and mucosal temperatures, water vapour partial pressure, and relative humidity were obtained. When breathing ambient air (figs 4A, 4B, 4C), there were no outstanding differences between the normal and CF subjects, whether data were taken at the pharynx or airway opening, during inspiration or expiration, through the nose or mouth. These figures, however, illustrate differences between the inspiratory and expiratory gas conditions at the airway opening and at the pharynx. (Note that the vertical bars span the range of all data points). The sublingual temperature ranged from 36.5 – 36.8°C for the normal subjects and from 36.3 – 36.9°C for the CF subjects.

At the pharynx, the temperature difference between inspired and expired gas is about 4°C for nose breathing and 7°C for mouth breathing. Also, the temperature of inspired gas increased only 5°C through the oral path, but 9°C through the nasal path. Furthermore, the expired gas temperature for nose breathing is less than body temperature (sublingual) by 1 – 2°C , whereas for mouth breathing it is 2 – 3°C less. For both subject groups, the wall temperature varied negligibly at the pharynx during the breathing cycle. The wall temperature at the pharynx is lower than the local gas temperature on expiration. For nose or mouth breathing the temperature difference between inspired and expired gas at the airway opening is about 10 – 11°C . The H_2O partial pressure shows differences corresponding to those of the gas temperature.

During inspiration, the relative humidity (RH), at the pharynx is higher ($\sim 95\%$) for nose breathing than for mouth breathing ($\sim 75\%$). This is reflected in both the T and P_{H_2O} of the gas. During expiration the RH values are approximately the same for nose and mouth breathing at both the pharynx ($\sim 95\%$) and the airway opening ($\sim 90\%$).

Inspiring hot air

Flow-averaged data for the same subjects breathing hot air are shown in figures 5A, 5B and 5C. For all subjects, expired gas was usually within 1 – 2°C of body temperature for both pathways and both measurement locations. Typically, the wall temperature at the pharynx averages about 1 – 2°C less than the local expired gas temperature. By the end of inspiration, the wall temperature at the airway openings is 4 – 8°C less than inspired gas temperature. On average, these wall temperatures are higher for CF subjects than for normal subjects. At the pharynx, gas inspired through the nose was cooled several degrees below body temperature in both sets of subjects. Gas entering the airway opening may differ from the input source of the hot air because of tubing losses, mixing of inspired gas with residual gas in the face mask, and an inadequate seal of the mask for some experiments.

During expiration the P_{H_2O} at the pharynx (fig. 5B) is less than the saturation value at body temperature

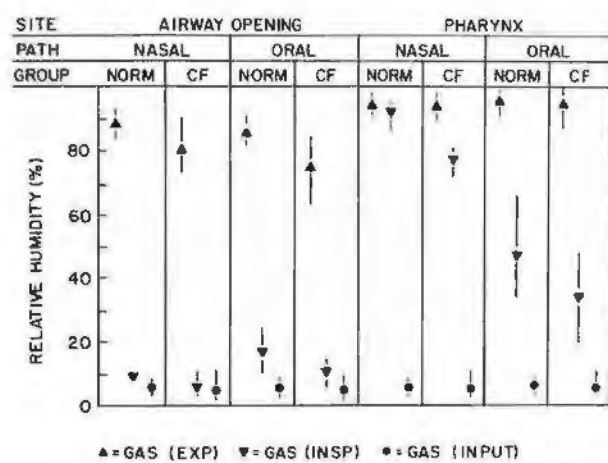
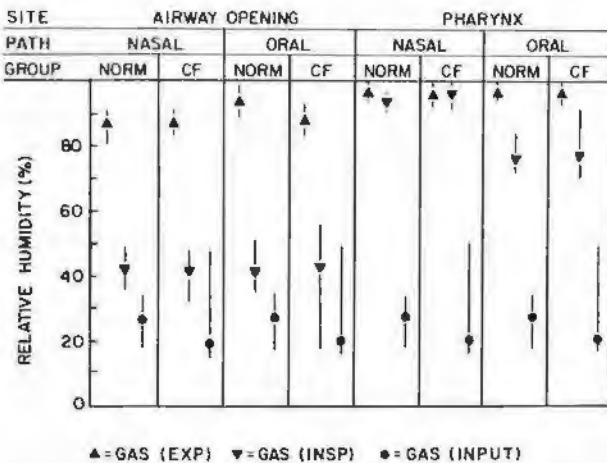
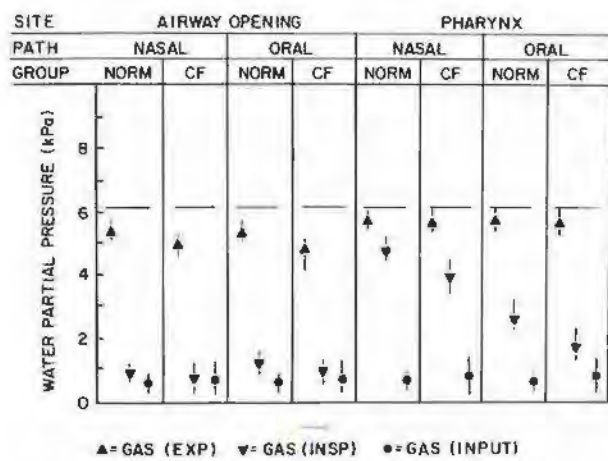
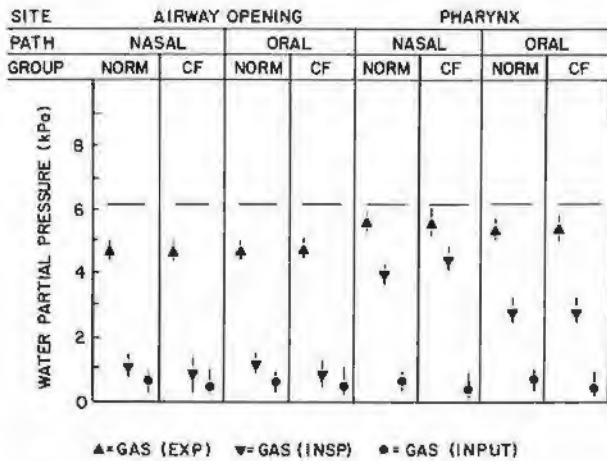
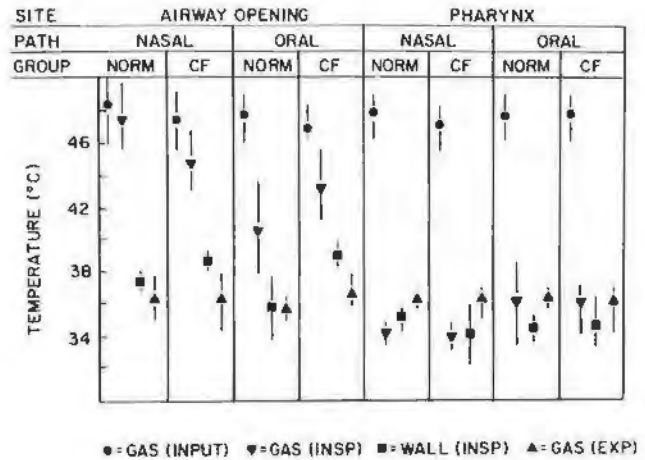
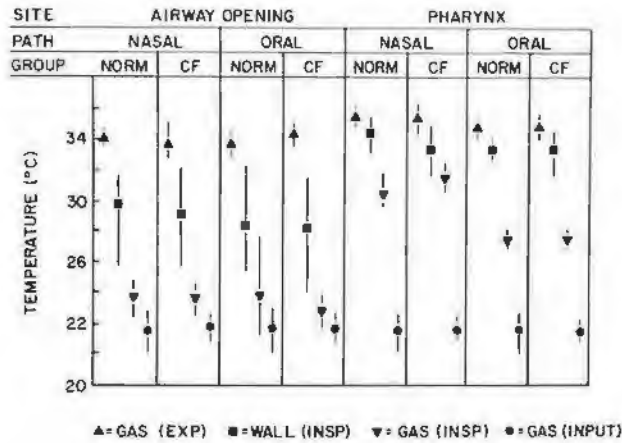


Fig. 4. Upper airway humidification in normal and CF subjects breathing ambient air through the nose and mouth. (Symbols represent mean values and vertical bars span the range of all data points): A. Temperature: local gas on inspiration and on expiration, local airway surface (wall) and inhaled gas (input); B. Water vapour partial pressure: local gas on inspiration and on expiration, and inhaled gas (input). Equilibrium water vapour pressure at 37°C indicated by the horizontal line; C. Relative humidity (at gas temperature): local gas on inspiration and on expiration, and inhaled gas (input).

Fig. 5. Upper airway humidification in normal and CF subjects breathing hot air through the nose and mouth. (Symbols represent mean values and vertical bars span the range for all data points). A. Temperature: local gas on inspiration and on expiration, local airway surface (wall), and inhaled gas (input); B. Water vapour partial pressure: local gas on inspiration and on expiration and inhaled gas (input). Equilibrium water vapour pressure at 37°C indicated by the horizontal line; C. Relative humidity (at gas temperature): local gas on inspiration and on expiration, and inhaled gas (input).

and still less at the airway opening in both subject groups. On inspiration through the nose or mouth, the P_{H_2O} of pharyngeal gas is lower in CF subjects than in normal subjects. (Although the trend is apparent, the number of data points is not sufficient to establish statistical significance.) As shown in figure 5C, the groups exhibit no great differences in the RH of expired gas at both measurement locations or of gas in the pharynx during inspiration through the mouth. But for hot air inspired through the nose, the RH at the pharynx is higher in normal than in CF subjects.

Discussion

Flow and duration

When instantaneous flow (or gas velocity) through the airways is increased, the rate of water and heat transfer between the gas and mucosal surface is expected to increase. Over the range of experimental conditions examined, however, the effects of flow on gas temperature (T) and H_2O partial pressure (P_{H_2O}) are less important than the condition of the inspired gas. Typically, the peak flow range for our subjects varied by a factor of three or four, corresponding to an average flow (or ventilation) of about 10–30 $l \cdot \text{min}^{-1}$. In this ventilation range, MCFADDEN *et al.* [8] found that the temperature at the glottis changes by about 1°C. This is a relatively small change compared to the differences produced by the different inspired gases of our experiments.

Furthermore, in studies of bronchoconstriction during dry air breathing, ESHENBACHER and SHEPARD [12] found significant changes in airway resistance mainly when the ventilation exceeds 30 $l \cdot \text{min}^{-1}$. Since this value is about the upper limit of average flow in our studies, it is not unreasonable to expect that the effect of flow is relatively small. In general, however, this is not true. With higher average flows (or ventilation), the effect of flow is not negligible and must be taken into account.

Another factor that may have reduced the effect of flow is the relatively short duration of breathing of the test gas in our protocol. As reported by TABKA *et al.* [13], gradual changes take place over minutes (a much longer duration than allowed in our studies). Nevertheless, they found no significant effect of an increase of ventilation on the rate of water loss.

Inspired air effects

When ambient air is breathed, the extent of its conditioning on arrival at the pharynx is evident by the changes in T and P_{H_2O} between the airway opening and the pharynx. These changes are much larger for nasal breathing than for oral breathing. Also, the differences between inspired and expired gas temperature and H_2O partial pressure measured at the pharynx are smaller for nasal breathing. This implies that the water and heat exchange loads on the

lungs are less for nasal as compared with oral breathing.

For all subjects, our data indicate that with a higher inhaled air temperature, the exhaled temperature will be higher as reported by ANDERSON *et al.* [14]. This is caused by the warming of the mucosal surface during inhalation. Relatively dry inhaled air leads to evaporation and cooling of the mucosal surface, which counters the sensible heat transfer from the inhaled gas to the surface. Although the temperature of the inspired hot air was more than 10°C above body temperature, the temperature of the subsequent expired air was around body temperature.

As found by other investigators [5, 7], the expired gas was not saturated (based on the vapour pressure of pure water) after inspiration of either ambient or hot air. This can be related to the cooling of the mucosal wall by evaporation during inspiration so that the temperature at the wall was less than the local gas temperature. Theoretically, a decrease of 2°C of the mucosal lining reduces the H_2O vapour pressure at the airway wall by almost 10% [3].

Comparison of normal and CF subjects

Although the H_2O partial pressure of expired gas is about the same for CF and normal groups, this can mistakenly lead to the conclusion that no difference in humidification exists. This conclusion, however, ignores the fact that the transport processes reach equilibrium locally during expiration which can camouflage humidification differences that occur on inspiration. During inspiration of ambient air, the normal and CF groups did not show any significant differences with respect to gas temperature or H_2O partial pressure at the pharynx or airway opening. By contrast, on inspiration of hot air through the nose or mouth, even though the gas temperature in the pharynx was the same for both groups, P_{H_2O} at the pharynx was lower for the CF subjects than for normal subjects. As a consequence, the relative humidity of the CF subjects is also lower at the pharynx.

This difference in H_2O transport, which is the major distinction we found between the two groups, may be associated with drying of the mucosal lining. Although we could not directly verify that drying occurred when hot air was inspired, indirect evidence can be obtained from the wall temperature. By the end of inspiration the wall temperature at the airway openings was higher for CF than for normal subjects. This could indicate less evaporation and therefore less surface cooling along the inspiratory pathway leading to the pharynx.

For a higher inspired air temperature, the rate of evaporation is greater unless the rate of water transport from the tissue interstitium to the surface of the mucosa becomes rate limiting. Other investigators have also suggested the importance of water loss during hot air breathing [14]. In our experiments with acute changes of inhaled gas conditions, the mucosal

water transport in the upper airways responds differently for CF subjects than for normals. This can be seen from the change of P_{H_2O} in the pharynx from ambient to hot air breathing. In normal subjects, this change is small; for the CF subjects there is a noticeable decrease under the corresponding conditions.

Water transport rate

A possible reason for this difference is that the rate of water transport through the mucosal tissue and/or secretions is less for the CF subjects. This is consistent with the hypothesis of BOUCHER *et al.* [15] that airway epithelia in CF have decreased permeability to chloride and increased sodium reabsorption from the airway lumen. Because water tends to follow sodium, the water content in mucosal secretions might be less in CF subjects than in normals. The difference in humidification between normal and CF subjects would be even greater when the subjects inhale hotter and drier air. This can be validated only by making simultaneous measurements of airway surface temperature, gas temperature, and water vapour partial pressure. Temperature measurements alone are insufficient to infer the extent of water transport under such conditions [12, 14].

Although water transport through the mucosa is a possible rate-limiting step, another possibility is the limitation of water transport as a consequence of decreased blood perfusion to the airway tissue. MCFADDEN [16] has suggested this occurs when cold air is inhaled, because it might cause blood vessel constriction. Recently, BAILE and co-workers [17, 18] showed in hyperventilated anaesthetized dogs that cold air or warm dry air tends to increase tracheobronchial blood perfusion, which is not mediated by the autonomic nervous system. To distinguish between possible mechanisms under different inhaled gas conditions (hot, cold and dry), investigators will have to make simultaneous measurements not only of temperature and water vapour, but also *in situ* measurements of mucus water content and of blood flow to the airway tissues.

Significance for CF

The greatest potential problem for CF subjects would occur from inhaling dry air through the mouth. This is suggested by the data of FREED *et al.* [19] who found that concentrations of epithelial cells and prostaglandins in the lavage subsequent to a dry air challenge were much greater than those after a humid air challenge. Hot, dry air would require the greatest humidification and rate of water transport from the airway lining into the gas. Our data indicate that CF subjects cannot accomplish this as well as normals, which may be associated with abnormal properties of the mucus. Cold, dry air requires less humidification, but water availability may also be lower. In any case, drying of the mucosa may lead to airway irritation

and reduced mucociliary clearance. This may occur to a greater extent in CF subjects and could contribute to the development of their pulmonary disease.

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RÉSUMÉ: La pression partielle de vapeur d'eau (P_{H_2O}) et la température (T) ont été mesurées ensemble et de façon continue à l'extrémité des voies aériennes (soit les lèvres, soit les narines), ainsi que dans l'oropharynx, chez des sujets humains à poumons normaux ou atteints de fibrose kystique. On n'a trouvé aucune différence apparente dans la P_{H_2O} et la T entre les sujets normaux et les sujets avec fibrose kystique lorsqu'ils respirent de l'air ambiant à

une température de $22 \pm 2^\circ\text{C}$). Au cours de l'inspiration, l'humidité relative au niveau du pharynx est supérieure (95%) pour ceux qui respirent par le nez que pour ceux qui respirent par la bouche (75%). Si l'on respire de l'air chaud ($48 \pm 2^\circ\text{C}$), la PH_2O et l'humidité relative de l'air inspiré au niveau du pharynx sont plus faibles dans le groupe de fibroses kystiques que dans le groupe normal. De plus, le groupe de fibroses kystiques a une température

des surfaces des voies aériennes plus élevée à l'extrémité des voies aériennes au cours de l'inspiration. Ces données suggèrent que lorsque le taux d'évaporation est suffisamment élevé, l'étape limitative pourrait être le transport d'eau au travers du tissu muqueux et/ou des sécrétions. Ce taux de limitation est plus évident, tout au moins dans les voies aériennes supérieures, chez les patients atteints de fibrose kystique que chez les sujets normaux.