have no significant effect on fetal movement. Interestingly, however, the same work did show that when connected to the cardiotocograph the mothers felt 87% more fetal movements than otherwise they did *whether or not* the ultrasound was on. The authors' suggestion that this was due to heightened maternal awareness under monitoring conditions seems highly plausible, and physical causes, such as the presence of the elastic transducer belts, as well as psychological causes may be a factor. In any event this observation is certainly consistent with the impression of many mothers that their baby moves more during cardiotocography; whether this is actually the case, even though ultrasound is not the cause, remains a matter for conjecture.

We thank the consultant obstetric staff of Princess Anne Hospital, Southampton, Royal Hampshire County Hospital, Winchester, and St Mary's Hospital, Portsmouth, for permission to study patients under their care and also the nursing staff and the patients themselves. The random switching device was designed by Russell Gasser and constructed by Geoffrey Westgarth, of the medical physics department, Southampton General Hospital. Much help with the statistical analyses, for which we are greatly indebted, was provided by Malcolm Christie and Alastair Brown, of the School of Mathematics and Computing, Leeds Polytechnic.

A preliminary report of this work was presented at the eighth International Conference on Fetal Breathing and Other Measurements in October 1981.

References

- David H, Weaver JB, Pearson JF. Doppler ultrasound and fetal activity. *Br Med J* 1975;ii:62-4.
- Hertz RH, Timor-Tritsch I, Dierker LeRJ, Chik L, Rosen MG. Continuous ultrasound and fetal movement. *Am J Obstet Gynecol* 1979; **135**:152-4.
- Powell Phillips WD, Towell ME. Doppler ultrasound and subjective assessment of fetal activity. *Br Med J* 1979;ii:101-2.
- Sadovsky E, Polishuk WZ, Mahler Y, Malkin A. Correlation between electromagnetic recording and maternal assessment of fetal movement. *Lancet* 1973;i:1141-3.
- Wood C, Walters WAW, Trigg P. Methods of recording fetal movement. *Br J Obstet Gynaecol* 1977;**84**:561-7.
- Ehrström C. Fetal movement monitoring in normal and high-risk pregnancy. *Acta Obstet Gynecol Scand* 1979;suppl 80.
- Hertogs K, Roberts AB, Cooper D, Griffin DR, Campbell S. Maternal perception of fetal motor activity. *Br Med J* 1979;ii:1183-5.
- Rayburn WF. Clinical significance of perceptible fetal motion. *Am J Obstet Gynecol* 1980;**138**:210-2.
- Thaler I, Goodman JDS, Dawes GS. Effects of maternal cigarette smoking on fetal breathing and fetal movements. *Am J Obstet Gynecol* 1980;**138**:282-7.
- Altman DG. Statistics and ethics in medical research: III—How large a sample? *Br Med J* 1980;**281**:1336-8.
- Barnett V, Lewis T. *Outliers in statistical data*. Chichester: John Wiley and Sons, 1978.
- Weinstein D, Navot D, Sadovsky E. Antepartum ultrasound fetal heart rate monitoring and fetal movements. *Journal of Obstetrics and Gynaecology* 1981;**2**:85-7.

(Accepted 21 January 1983)

Bronchial reactivity in asthmatic adults with normal spirometric values

TIM HIGENBOTTAM, T C STOKES, S JAMIESON, L HILL

Abstract

A comparison was made between airways obstruction produced by exercise, hyperventilation of cold air, hyperventilation of room air, and inhalation of ultrasonically nebulised distilled water. Seven asthmatics with no airflow obstruction were studied together with seven normal controls. All four provocations produced comparable mean reductions in forced expired volume in one second in the asthmatic patients, but no reduction was obtained in the controls. Whereas exercise, hyperventilation of cold air, and hyperventilation of room air were associated with heat loss from airways, inhalation of nebulised distilled water was not.

Inhalation of ultrasonically nebulised distilled water offers a simple additional diagnostic test for asthma. Changes in the osmolality of airway surface liquid may possibly be the common mechanism by which "fog" and hyperventilation produce bronchoconstriction.

Introduction

There is much to support the idea that the fundamental abnormality in asthma is bronchial hyperreactivity to inhaled non-specific stimuli or specific antigens or both.¹ Despite this, provocation testing is rarely used to diagnose asthma in patients with normal spirometry. This may be due to uncertainty about the safety of challenge testing and the time and apparatus needed to do the test. Most adults, unlike children, are not fit enough to undertake sufficiently extreme exercise to induce asthma.²

Hyperventilation of large volumes of inadequately conditioned air,³ which causes loss of heat and water from the airways, induces bronchoconstriction in asthmatic subjects; this response is comparable to that after inhalation of methacholine.⁴ As an alternative to extracting heat and water by hyperventilation to induce bronchoconstriction, a similar effect may be produced in asthmatics by inhalation at tidal breathing⁵ of a fine mist of either ultrasonically nebulised distilled water or hypertonic saline.

To establish comparability between these newer provocation tests we studied the effects on lung function of exercise, hyperventilation of cold and room air, and inhalation of ultrasonically nebulised distilled water in normal adults and asthmatics with normal spirometric values.

Subjects and methods

We studied seven patients (mean age 32) with clinically recognised asthma.⁶ None was receiving continuous treatment, and six were taking a β -sympathomimetic aerosol intermittently to control

Respiratory Physiology Laboratory, Addenbrooke's and Papworth Hospitals, Cambridge

TIM HIGENBOTTAM, MD, MRCP, consultant physician
T C STOKES, MD, MRCP, senior registrar
S JAMIESON, senior technician
L HILL, MB, MRCP, senior registrar

Correspondence to: Dr Tim Higenbottam, Respiratory Physiology Department, Papworth Hospital, Cambridge CB3 8RE.

symptoms. All treatment was stopped for 12 hours. We also studied seven normal subjects (mean age 29). All subjects gave their informed consent, and the study had the approval of the local hospital ethics committee.

FIG 1—Mean percentage change in forced expired volume in one second (FEV_1) from baseline value in asthmatic patients (★) and normal subjects (●). Mean $\pm$ SEM changes in each group also shown.

FIG 2—Mean respiratory heat exchange in asthmatic patients (★) and normal subjects (●). Mean $\pm$ SEM in each group also shown.

Conversion: SI to traditional units—Heat exchange: 1 kJ/min $\approx$ 239 cal/min.

MEASUREMENT OF RESPIRATORY HEAT LOSS

In all provocation tests the subjects breathed through a low resistance two way valve. The temperature of the inspired and expired air was continuously recorded by a fast response copper and copper nickel thermistor sited 1.5 cm from the mouth. This was intermittently heated to prevent frosting or misting, which blunts the temperature response. Carbon dioxide pressure was continuously monitored in the mouth piece with a capnograph (P K Morgan, England) and the carbon dioxide inspired adjusted to keep the end expired pressure at 4.5 kPa (34 mm Hg).

The volume of exhaled air was measured using a Fleisch pneumotachograph and differential manometer with integrator calibrated for volume before and after each challenge. Records were made on a time based polygraphic recorder (Mingograph, Olema Schönander, Siemens, Germany). Air humidity was recorded continuously with a hygrometer (Shaw, England). Respiratory heat exchange (RHE) was calculated for each provocation using the formula of Deal *et al*⁷:

$$RHE = VE (HC (Ti - Te) + HV (Wci - Wce))$$

where VE = minute ventilation (l/min); HC = heat capacity of air (1.27 J (0.000304 kcal)/l); Ti = temperature of inspired air ($^{\circ}$ C); Te = temperature of expired air ($^{\circ}$ C); HV = latent heat of vaporisation of water (2.42 J (0.00058 kcal)/l); Wci = water content of inspired air (mg/l); and Wce = water content of expired air (mg/l). It was assumed that the water content of cold air (-10 to -20° C) was zero.⁷ The water content of exhaled air was calculated from standard saturated water vapour pressure temperature relations⁸ assuming full saturation.⁹ The same assumptions were applied to calculate the water content of inhaled distilled water mist. The water content of room air was calculated from the relative humidity and temperature of the air.

PROVOCATIONS

The cold air source was an adapted cabinet deep freeze, which could deliver cold air (-20° C) at a rate of 200 l/min. The two way respiratory valve fitted straight into the side of the refrigerator for this provocation.

A Devilbiss 65 ultrasonic nebuliser was used to produce the distilled water mist at a rate of 4 l/min into a one litre reservoir from which the volunteers breathed via the two way valve. This provided an output of 44 mg water/l of mist with a mean particle size of 15.5% of output ($<2 \mu$).

The exercise was performed on an electrically driven treadmill (Avionics, England) set up at a 10% gradient, the speed being adjusted until minute ventilation reached a value roughly 15 times the baseline value of the forced expired volume in one second.²

EXPERIMENTAL DESIGN

Each subject attended the laboratory on four separate days at about the same time of day. In random order they then underwent each of the four provocation tests—namely, exercise on the treadmill for six minutes; hyperventilation of cold air and then room air, at a minute volume of 15 times the forced expired volume in one second, for one minute; and inhalation of distilled water mist such that a dose response curve was produced. When inhaling the distilled water mist the subject was asked to breathe normally for different lengths of time to give a succession of inhaled volumes of mist—namely, 2.5, 5, 15, 30, and 45 litres at intervals of five minutes.

Forced expired volume in one second was recorded in duplicate before and two minutes after each provocation (and, for the exercise and hyperventilation tests, at five, eight, and 10 minutes after the provocation). The lowest mean value after provocation was compared with the baseline value and the respiratory heat exchange of the provocation calculated. The change in forced expired volume and the respiratory heat exchange were analysed by two way analysis of variance.¹⁰

Results

The mean baseline values of forced expired volume in one second in the normal subjects and the asthmatics were similar ($108 \pm \text{SEM } 2.6\%$ and $104 \pm 2.9\%$ of predicted value). There was a significant difference in the mean reduction in forced expired volume between the patients compared with the controls (variance ratio = 8.39; $df = 1,48$; $p < 0.01$). In contrast there were no differences between the provocations in the change in forced expired volume (variance

ratio = 0.05; $df = 3,48$; $p > 0.05$) and no interaction between the effects of each provocation and the presence or absence of a history of asthma (variance ratio = 0.05; $df = 3,48$; $p > 0.05$) (fig 1).

Respiratory heat exchange did not differ significantly between the asthmatics and the controls (variance ratio = 0.38; $df = 1,48$; $p > 0.05$) but did differ significantly between provocation tests (variance ratio = 10.00; $df = 3,48$; $p < 0.005$), with little heat loss occurring with the nebulised distilled water (fig 2). Again, there was no significant interaction between the provocation tests and the presence or absence of a history of asthma (variance ratio = 0.28; $df = 3,48$; $p > 0.05$). Figure 3 shows dose response curves for the inhalation of ultrasonically nebulised distilled water (fig 3).

FIG 3—Dose response curves in one normal subject (★) and one asthmatic patient (●) on breathing ultrasonically nebulised distilled water. SEMs of forced expired volumes in one second (FEV₁) ranged from 0.05–0.15 litres.

Discussion

This study showed that single periods of tidal inhalation of ultrasonically nebulised distilled water to a total volume of around 25 litres is comparable with exercise and hyperventilation tests in inducing bronchoconstriction in asthmatic subjects. This test has the added advantage of being independent of effort and not requiring complicated monitoring apparatus. Moreover, end tidal carbon dioxide pressure does not have to be monitored so long as the subject does not hyperventilate when connected to the apparatus.^{11 12} Such a test could be easily adapted for use in the diagnosis of asthma, particularly in patients in whom spirometric values are normal. The degree of bronchoconstriction produced is comparable with that after an exercise test. In addition, provocation testing using ultrasonically nebulised distilled water may be used to provide a dose response curve (fig 3) in a manner analogous to non-specific chemical challenges with methacholine or histamine. This approach would be of value in research and clinical practice but is time consuming.^{13 14}

The manner in which bronchoconstriction is induced by ultrasonically nebulised water remains unknown. It does not appear to be related to respiratory heat exchange (see fig 2). Isotonic solutions of saline fail to induce bronchoconstriction, unlike hypotonic solutions such as distilled water or hypertonic solutions of saline or glucose.^{5 15} This suggests that changes in the osmolality of bronchial liquid may be important and reduces the probability of a direct effect of mist droplets acting as a particulate stimulus to bronchial and tracheal irritant receptors. During tidal breathing, but not hyperventilation, changing from nose to mouth breathing alters both the osmolality and the electrolyte composition of airways surface liquid.¹⁵ Hyperventilation causes loss of water from the airways³ and, as with hypertonic or hypotonic ultrasonically nebulised solutions, probably also alters the osmolality and electrolyte composition of the airway surface liquid.¹⁵ Such changes might affect directly either epithelial cells or, conceivably, mast cells located superficially on airway epithelium, which react with inhaled antigen to produce bronchoconstriction.¹⁷ This possibility might

account for the unique inhibitory role of disodium cromoglycate not only in antigen induced bronchoconstriction but also on the airway response to hyperventilation in both normal¹⁸ and asthmatic subjects without causing airway cooling.¹⁹

We thank Barbara Minty and David Royston of Northwick Park Hospital for characterising the output of the Devilbiss nebuliser.

References

- Clark TJH. Adult asthma. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1977:373.
- Godfrey S. Exercise-induced asthma. In: Clark TJH, Godfrey S, eds. *Asthma*. London: Chapman and Hall, 1977:60.
- McFadden ER, Ingram RH. Exercise induced asthma. *N Engl J Med* 1979;**301**:763-9.
- O'Bryne PM, Ryan G, Morris M, et al. Asthma induced cold air and its relation to non-specific bronchial responsiveness to methacholine. *Am Rev Respir Dis* 1982;**125**:281-5.
- Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of distilled water and saline. *Br Med J* 1981;**283**:1285-7.
- American Thoracic Society. Committee on Diagnostic Standards. Definition and classification of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev Respir Dis* 1962;**85**:762-8.
- Deal EC, McFadden ER, Ingram RH, Jaeger JJ. Hypernea and heat flux: initial reaction sequence in exercise-induced asthma. *J Appl Physiol* 1979;**46**:476-83.
- Weast RC, ed. *Handbook of chemistry and physics*. 58th ed. Cleveland, Ohio: Chemical Rubber Co, 1978: PE41, 45.
- Ferrus H, Guerard H, Vardon G, Varence P. Respiratory water loss. *Respir Physiol* 1980;**39**:367-81.
- Armitage P. *Statistical methods in medical research*. Oxford: Blackwell Scientific, 1971:223.
- Tweedall PLM, Godden DJ, Grant IWB. Hyperventilation or exercise to induce asthma. *Thorax* 1981;**36**:596-8.
- Kenneal JA, McLennan JE, London RG, McLaurin RL. Hyperventilation induced central hypoxia. *Am Rev Respir Dis* 1980;**22**:407-12.
- Juniper EF, Frith PA, Durrett C, Cockcroft DW, Hargreaves FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;**33**:705-10.
- Chai H, Farr RS, Froehlich LA, et al. Standardisation of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975;**56**:323-7.
- Elwood RK, Hogg JC, Pare PD. Airway response to osmolar challenge in asthma (Abstract). *Am Rev Respir Dis* 1982;**125**:61.
- Boucher RC, Stutts MJ, Bromberg PA, Gatzky JT. Regional differences in airway surface liquid composition. *J Appl Physiol* 1981;**50**:613-20.
- Richardson JB, Hogg JC, Bouchard T, Hall DL. Localization of antigen in experimental bronchoconstriction in guinea pigs. *J Allergy Clin Immunol* 1973;**52**:172-81.
- Fanta CH, McFadden ER, Ingram RH. The effects of cromolyn sodium on the response to respiratory heat loss in normal subjects. *Am Rev Respir Dis* 1981;**123**:161-4.
- Breslin FJ, McFadden ER, Ingram RH. The effects of cromolyn sodium on the airway response to hypernea and cold air in asthma. *Am Rev Respir Dis* 1980;**122**:11-6.

(Accepted 20 January 1983)

YARROW, CALLED NOSE-BLEED, MILFOIL AND THOUSAND-LEAF hath many long leaves spread upon the ground, finely cut, and divided into many small parts. Its flowers are white, but not all of a whiteness, and stayed in knots, upon divers green stalks which rise from among the leaves. It is frequent in all pastures. It flowers late, even in the latter end of August.

It is under the influence of Venus. An ointment of them cures wounds, and is most fit for such as have inflammations, it being an herb of Dame Venus; it stops the terms in women being boiled in white wine, and the decoction drank; as also the bloody flux; the ointment of it is not only good for green wounds, but also for ulcers and fistulas, especially such as abound with moisture. It stays the shedding of hair, the head being bathed with the decoction of it; inwardly taken it helps the retentive faculty of the stomach: it helps the gonorrhea in men, and the whites in women, and helps such as cannot hold their water; and the leaves chewed in the mouth eases the tooth-ache, and these virtues being put together, shew the herb to be drying and binding. Achilles is supposed to be the first that left the virtues of this herb to posterity, having learned them of this master Chiron, the Centaur; and certainly a very profitable herb it is in cramps, and therefore called *Militaris*. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)