Respiratory heat loss in exercise-induced asthma
Measurement and clinical application

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Summary
The theoretical considerations of conditioning inspired air and the application of the respiratory heat loss (RHL) formula are discussed. An on-line method for measuring RHL is described together with the apparatus for generating frigid dry and warm humid air. Exercise-induced asthma (EIA) was studied using these methods. Thirteen asthmatic and 6 normal children and adolescents participated in the study. Each subject undertook two submaximal exercise tests consisting of 6 minutes' ergometric cycling against a fixed load. One test was done while breathing cold dry air (mean temperature -22°C and 0% relative humidity) and the other while breathing warm humid air (mean temperature 36°C and 100% relative humidity). All the other exercise parameters (e.g. heart rate, minute ventilation, oxygen uptake) were carefully matched between the two tests. In the cold dry air tests with a mean RHL of 1.43 kcal/min, all asthmatic subjects developed EIA with a mean fall in forced expiratory volume in the 1st second (FEV) of 48% from baseline. In the warm humid air tests with negligible RHL (0.02 kcal/min) none of the asthmatics developed EIA (mean fall in FEV, 5%). The difference between the two tests was highly significant (P < 0.001). Neither air condition caused bronchospasm in the normal subjects. A dose-response relationship was obtained between the degree of RHL and corresponding fall in FEV1.

In recent years growing medical awareness of the problems associated with exercise-induced asthma (EIA) has encouraged investigation into its mechanisms. Current evidence suggests that the initial stimulus responsible for EIA is heat loss from the respiratory tract. Unlike other stimuli such as antigens or histamine, which have been well studied and defined, there was until recently no similar definition of the relation between respiratory heat loss (RHL) and EIA. A large number of studies have since appeared addressing this problem. The measurement of RHL has emerged as an additional clinical tool in the understanding of mechanisms responsible for bronchoconstriction and has also led to a new method of diagnosing asthma (eucapnic hyperventilation with cold air).

The theoretical considerations of RHL and the on-line method for its measurement developed at the J. G. Strijdom Hospital, Johannesburg, are described. The results of a study confirming the role of RHL in EIA, as originally described by Deal et al., are reported.

RHL — theoretical considerations
During inspiration the air drawn into the lungs is heated and humidified so that by the time it reaches the alveoli it is at body temperature and fully saturated with water vapour (BTPS), i.e. 1 litre of air at 37°C contains 44 mg of water which exerts a pressure of 47 mmHg. This requires evaporation of water and transfer of heat from the mucosal surface lining the airways to the incoming air. The inspired air is heated primarily by convection and as the air is warmed, so its capacity to hold water increases. Humidification is achieved by evaporation of water from the mucosa, which in turn results in further cooling of the latter. During expiration the process reverses along the thermal gradient. As the air is expelled from the lung, heat is convected to the previously cooled mucosa and as air temperature falls so does its ability to hold water vapour. As a result condensation occurs on the cooler mucosa. However, since the respiratory tract is not a perfect heat exchanger, the loss of heat and water from the airways during inspiration is greater than that recovered during expiration. Less than half the heat lost to the incoming air during inspiration is reclaimed during expiration, resulting in a net loss of heat and water from the respiratory tract. The magnitude of this heat loss depends primarily on the conditions of the inspired air and the minute ventilation. The colder and drier the inspired air, the greater will be the amount of heat and water lost. Similarly, when large volumes are exchanged, for example during exercise, the heat and water transfer required to condition the inspired air will be greater. These two components of heat and water loss from the respiratory tract, namely loss due to convection and that due to evaporation, can be calculated and are collectively referred to as RHL.

The overall RHL is expressed as the sum of the convective and evaporative losses multiplied by the minute ventilation:

\[ RHL = VE \times [HC_{t_{exp}} - HC_{t_{in}}] + HV \times (W_{c_{exp}} - W_{c_{in}}) \]

where RHL is respiratory heat loss*, VE expired minute ventilation (l/min), BTPS, HC the heat capacity of air (3.04 x 10⁻³ kcal/l/°C), t_{exp} the expired air temperature (°C), t_{in} the inspired air temperature (°C), HV latent heat of vaporization (0.58 x 10⁻³ kcal/mg), W_{c_{exp}} the water content of expired air (mg/l) and W_{c_{in}} the water content of inspired air (mg/l).

The equation shown, first used by Deal et al., was modified from Chen and Horton and is now generally used in the study of RHL in asthma.

RHL — measurement
Following from equation [1], the parameters to be measured in order to calculate RHL are: VE, t_{exp}, t_{in}, W_{c_{exp}} and W_{c_{in}}. The overall scheme used to measure RHL, including the cold air

* kcal = 4.2 J.
Fig. 1. Schematic representation of the cold air generator and technique for measuring respiratory heat loss on-line.

generator and measurement of exercise parameters, is shown in Fig. 1.

Expired minute ventilation was measured with a pneumotachograph (linear through peak flows of 600 l/min at normal exercise frequencies) connected to the expiratory port of a low-resistance two-way non-rebreathing valve by a 700 mm length of wide-bore (38 mm internal diameter) corrugated tubing. For the cold air tests the expired air was heated to 37°C before reaching the pneumotachograph by blowing hot air from a hair dryer into a 600 mm long sleeve of nylon surrounding the corrugated tubing. By adjusting the temperature of the air surrounding the corrugated tubing leading to the pneumotachograph, the temperature of the expired air passing through the pneumotachograph was controlled at 37°C.

Expired air temperature was measured by a resistance temperature detector (RTD) which protruded through the mouthpiece of the breathing valve into the oral cavity, approximately 1 cm behind the teeth. It was carefully positioned to avoid mucosal contact. Inspired air temperature was measured by an RTD situated in the inspiratory port of the breathing valve, 10 cm from the mouthpiece. The RTDs (response time 300 - 600 msec) were used without their normal protective shields to keep response time as short as possible, a quality essential for breath-by-breath temperature measurement. The outputs from the RTDs were continuously relayed to an analogue-to-digital converter by an RTD transmitter. A computer sampled the temperature signals and calculated the average of the highest values recorded over each 15-second period.

The water content of expired and inspired air was calculated from the equation:

\[ W_c = R_h \cdot W_{cs} \]  

where \( R_h \) is the relative humidity (%) of the sample and \( W_{cs} \) is the water content of fully saturated air. Since the water content of air varies with temperature, the measured temperature was used to derive \( W_{cs} \). The relative humidity of inspired air was measured before each test with an electronic humidity meter and expired air was assumed to be fully saturated.

RHL as defined in equation [1] was calculated on-line every 15 seconds by the computer. The program also calculated total RHL accumulated during exercise and the rate of water loss from the respiratory tract.

For cold dry air tests (CD), frigid air was generated by a custom-built heat exchanger (Fig. 1). The cooling chamber consists of an insulated metal cylinder 58 cm long with an internal diameter of 10 cm into which a thin (0.6 cm internal diameter) copper coil has been inserted. Liquid nitrogen, stored at -198°C, is circulated through the copper coil and eventually comes out of the exhaust as inert gas. Air is drawn through the cooling chamber by the subject via the two-way non-rebreathing valve from a 200 l reservoir bag previously filled with dry compressed medical air. The temperature of the inspired air is a function of the inspired minute ventilation and the flow rate of liquid nitrogen through the cooling coil. The flow rate of liquid nitrogen is regulated by a temperature controller unit receiving an input from an RTD situated in the inspiratory port of the breathing valve. The output from the controller unit operates a cryogenic solenoid valve, which regulates the flow of liquid nitrogen through the cooling coil. Using this negative feedback control system it was possible to regulate the inspired temperature within a 5°C range during exercise.

For warm humid air tests (WH), warm air from a hair-drier was blown through a commercially available humidifier into a reservoir bag, which in turn was connected to the inspiratory port of the non-rebreathing valve. The temperature of the humidifier was adjusted to maintain the temperature of the inspired air at the mouth between 35° and 40°C.

**RHL — clinical application**

**Subjects and methods**

Nineteen children and adolescents volunteered to participate in exercise testing under different conditions of inspired air; 13 (9...
boys and 4 girls, mean age 14 years, range 10 - 18 years) were asthmatic patients known to develop EIA clinically and in the laboratory and 6 (2 boys and 4 girls, mean age 16 years, range 15 - 18 years) were normal subjects (controls) recruited from a nearby school. Anthropometric data for all the subjects are shown in Table I. The asthmatic subjects were younger, lighter and shorter than the controls but only the difference in age was significant \( P < 0.05 \). Eleven of the asthmatic subjects were taking sympathomimetic bronchodilators, 6 were taking sodium cromoglycate, 4 were using inhaled beclomethasone dipropionate, 2 were on long-acting theophylline and 2 were not on regular medication. None of the normal subjects was taking any medication. Medications were withheld before exercise testing as recommended: sympathomimetics for at least 12 hours, sodium cromoglycate for 24 hours and long-acting theophylline for 48 hours. 

Beclomethasone inhalation was continued and subjects took their medication at the same time interval before each test. At the time of testing, all subjects were clinically stable and asymptomatic with no history of asthmatic exacerbation or respiratory tract infection in the month preceding the study. Approval of the Hospital Ethics Committee and long-acting theophylline for 48 hours. Beclomethasone inhalation was continued and subjects took their medication at the same time interval before each test. At the time of testing, all subjects were clinically stable and asymptomatic with no history of asthmatic exacerbation or respiratory tract infection in the month preceding the study. Approval of the Hospital Ethics Committee and informed consent were obtained.

The study consisted of two exercise tests which differed only in the conditions of the inspired air. In one test, the subjects breathed CD air generated by the heat exchanger and in the other they breathed WH air generated as described above. The tests were done in a randomized fashion at the same time of day on two non-consecutive days within a 7-day period. The exercise consisted of 6 minutes’ pedalling on an electrically braked bicycle ergometer at a fixed load, calculated to achieve approximately two-thirds of the subject’s maximal predicted oxygen uptake. The same workload was used for both tests. In order to familiarize the subjects with the test protocol and equipment, each subject performed a preliminary test identical to that done during the study except that they breathed ambient air. This preliminary test was also used to exclude asthmatic subjects who had a greater than 10% fall in the 1-second forced expiratory volume (FEV\(_1\)) induced by repeated forced expiratory manoeuvres.

On arrival in the exercise laboratory the subject was seated comfortably on the bicycle ergometer, fitted with a nose clip and then commenced breathing ambient air through the non-rebreathing valve. Expired ventilation, heart rate and oxygen uptake were measured continuously and RHL was calculated as described above (Fig. 1).

A forced vital capacity manoeuvre (FVCM) was done under ambient conditions and repeated after inspiring the test air for 5 minutes (baseline). The subject then began pedalling against the predetermined workload and the FVCM was repeated 2 minutes after the start of exercise and again at 3, 5, 10, 15 and 20 minutes after stopping exercise. All measurements were performed using the on-line pneumotachograph with the subject seated on the bicycle ergometer and in such a way as not to interrupt the continuity of breathing the test air, including the recovery period. At least 2 - 3 FVCMs were attempted at each time and the highest value for the FEV\(_1\), and peak expiratory flow rate (PEFR) were used for subsequent analysis.

The severity of EIA was expressed as \( \Delta FEV_1 \), the maximum percentage fall in FEV\(_1\), after exercise, calculated as follows:

\[
\Delta FEV_1(\%) = \frac{\text{pre-exercise FEV}_1 - \text{lowest post-exercise FEV}_1}{\text{pre-exercise FEV}_1} \times 100
\]

where the pre-exercise value was that measured immediately before starting exercise while breathing the test air (baseline).

Results

Exercise data for both groups are summarized in Table II. There was no significant difference in minute ventilation, heart rate or oxygen uptake between the CD and WH tests within the groups. However, both ventilation and heart rate were higher in the asthmatic than in the controls in both tests, but only the difference in heart rate during the CD tests was significant \( P < 0.05 \).

The RHL data are summarized in Table III. The mean RHL in the CD tests was 1.43 ± 0.07 kcal/min for the asthmatics and 1.25 ± 0.06 kcal/min for the controls. There was almost no respiratory heat loss in the WH tests (mean RHL of 0.02 ± 0.04 kcal/min for the asthmatics and 0.05 ± 0.06 kcal/min for the controls). The differences in RHL between asthmatics and normals for the CD and WH tests were not significant. However, comparing all RHL indices (RHL, total RHL, inspired temperature and water loss) within the groups, the differences between the CD and WH tests were highly significant \( P < 0.001 \).

Mean values of FEV\(_1\) and PEFR before exercise are shown in Table IV. The normal subjects had higher values than the asthmatics \( P < 0.001 \). Lung function measurements under ambient conditions were similar for the CD and WH tests within each group. There was no significant change after breathing the test air for 5 minutes.

The changes in PEFR during exercise and the maximal changes in FEV\(_1\), after exercise are shown in Fig. 2. During the CD and WH tests, the mean PEFR at 2 minutes of exercise was higher than baseline in both groups. The mean increase in PEFR

<table>
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<th>TABLE I. ANTHROPOMETRIC DATA</th>
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ISB = intermittent sympathomimetic bronchodilators; SCG = sodium cromoglycate; BDP = beclomethasone dipropionate; LAT = long-acting theophylline.
during exercise was similar in the CD and WH tests within both groups and there was no significant difference between asthmatics and controls. All the asthmatic subjects developed EIA after the CD test but not after the WH test (mean % fall in FEV₁; 48.2 ± 5.2 v. 5.3 ± 1.0; P < 0.001). None of the normal subjects developed EIA.

By combining the data obtained from the preliminary exercise tests under ambient conditions with the CD and WH tests, the dose-response relationship between RHL and EIA could be examined. Fig. 3 shows the percentage fall in FEV₁ plotted against RHL for 8 asthmatic subjects in whom adequate data from the ambient tests were available. The fall in FEV₁ after exercise is linearly related to RHL (r = 0.75; P < 0.001). When RHL is corrected for body size (expressing RHL per predicted total lung capacity) the correlation improves (r = 0.81; P < 0.001). However, in spite of this generalized pattern there was still a large variation within the group with respect to the dose-response relationship. For the same change in FEV₁, the degree of respiratory heat loss varied significantly from subject to subject and this variation could not be accounted for by body size.

Discussion

Although EIA was recognized in the 1st century AD16 and the susceptibility of asthmatics to cold air has been known for 120 years,17 the initial stimulus which triggers this asthma has only recently been clearly identified. The hypotheses proposed in the past to explain the mechanism for EIA were reviewed in detail in 1979 by McFadden and Ingram.18 These included hypocapnia, increased minute ventilation, lactic acidosis, stimulation of carotid bodies or pharyngeal receptors, release of stored chemical mediators and imbalance of α- and β-sympathetic discharge. Since 1976 a number of laboratories have studied the combined effects of climate and exercise in asthmatic subjects.8,19,20 Stated briefly, the common denominator of these experiments is that increasing airway cooling induces an increasing degree of EIA. Chen and Horton8 were the first to demonstrate the quantitative relationship between the fall in FEV₁ and RHL and this relationship was subsequently refined by Deal et al.3 over a wide range of temperatures and humidities of inspired air.

Our results confirm that EIA can be prevented in susceptible subjects by breathing warm humid air, whereas the identical exercise matched for oxygen uptake, minute ventilation and heart rate done while breathing cold dry air readily triggers asthma. The typical response of asthmatics to exercise consists of initial bronchodilation during exercise, followed by bronchoconstriction after exercise (Fig. 2). The bronchodilation during exercise is presumed to be due to increased sympa-tho-adrenal discharge. The observed rise in circulating catecholamines during exercise21 may be protective against bronchoconstriction in normal subjects, but recent work has shown that asthmatics have a blunted sympatho-adrenal response to exercise.22,23 If the bronchodilation observed during exercise is related to sympa-tho-adrenal discharge, our results (Fig. 2) would suggest a similar sympatho-adrenal response in asthmatic and normal subjects since they both showed similar rises in PEFR during exercise, irrespective of the conditions of the inspired air. This does not preclude the possibility of sympa-tho-adrenal imbalance occurring at a later stage in asthmatic subjects. Further understanding of the sympatho-adrenal response to exercise will require direct measurement of catecholamines.

The mechanism whereby airway cooling, brought about by RHL during exercise, induces bronchospasm is as yet unknown. Of the mechanisms proposed, release of mediators from mast cells24,25 and vagal reflexes26 have been widely investigated. However, both are still controversial.
However, in spite of the hypersensitivity of the asthmatics to RHL there was still a large variation between individuals within the group. For a given fall in FEV₁, the RHL varied by a factor of 3, even after correction for body size. This variability in airway reactivity to the RHL stimulus is similar to that seen with histamine or methacholine challenges.²⁸

Employing the principles of RHL, a new bronchial challenge test using isoosmotic hyperventilation with cold air is now used in the diagnosis of asthma.²² This technique uses RHL as the inciting stimulus and substitutes controlled voluntary hyperventilation for the hyperpnoea of exercise. The amount of RHL can be accurately measured and controlled and, unlike aerosol inhalation challenge, it avoids issues regarding particle size, deposition, retention and clearance. It is an easily repeatable and reproducible test, using a naturally occurring stimulus with less patient discomfort. In addition to detecting airway hyperreactivity, this technique could also be useful in assessing efficacy of therapy²⁹ and the protective effects of new drugs in the treatment of asthma.³⁰

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REFERENCES

Smoking in inflammatory bowel disease and the irritable bowel syndrome

D. G. BURNS

Summary

The smoking habits of 145 patients with irritable bowel syndrome (IBS) were compared with those of 63 patients with ulcerative colitis and 25 patients with Crohn's disease. Patients with IBS and ulcerative colitis smoked significantly less than those with Crohn's disease. There was no significant difference in the smoking prevalence between ulcerative colitis and IBS patients. There were significantly more ex-smokers in the ulcerative colitis group and two-thirds of these patients developed their colitis within a year of stopping smoking. It is suggested that any protective role postulated for smoking in the pathogenesis of ulcerative colitis should also be considered for IBS.

The association of non-smoking and ulcerative colitis (UC) was first reported in 1982 and subsequently confirmed by others. Four of these reports showed that this association was not shared by patients with Crohn's disease (CD). On the basis of these reports it has been suggested that smoking may in some way be protective against the development of UC while it may predispose to the onset of CD. In view of this suggestion, the prevalence of smoking in patients with inflamatory bowel disease has been compared with that in patients with the irritable bowel syndrome (IBS).

Patients and methods

A series of 145 consecutive patients with IBS referred during the period 1981-1983 was compared with a similar series of 88 patients with inflammatory bowel disease referred during 1980-1985. Only patients over the age of 17 years were included and information on the smoking status and number of cigarettes smoked was analysed retrospectively. A non-smoker was defined as a patient who had never smoked, and an ex-smoker as one who had not smoked for at least 3 months before entry into the study. The criteria for the diagnosis of IBS have been reported elsewhere and 62% of these patients were classified as having diarrhoea predominantly. The diagnosis of UC was confirmed by rectal biopsy in every case. Proctosigmoiditis was present in 76% of patients, left-sided colitis in 16% and extensive colitis in 8%. CD was diagnosed according to conventional criteria of clinical course, radiological features of the large and small bowel, and histological examination of the resected specimen or colonoscopic biopsies in 16 cases. The small bowel alone was involved in 48% of these patients, small and large bowel in 32%, and colon or rectum in 20%. More than 70% of patients in each group were categorized as of social class 1 or 2 according to the criteria of Schlemmer and Stopforth. All statistical analyses were performed by the chi-square test, with Yates's correction where appropriate.

Results

Patients with UC and IBS were well matched for age, although there was a higher proportion of men in the group with UC (Table I). There was no significant difference between the number of non-smokers or ex-smokers with UC (84.1%) and those with IBS (77.9%). However, there were significantly fewer non-smokers or ex-smokers with CD (44%) (Table II). There were significantly more ex-smokers in the UC group than in the IBS group (Table III) and 8 of the 12 ex-smokers with UC claimed to have developed their disease within 1 year of stopping smoking. Patients with UC who smoked tended to smoke less cigarettes per day than smokers in the other two groups (Table IV). In the three groups of patients, there were no significant differences in smoking rates between the sexes.