CLINICAL RESEARCH

Diminished bronchial reactivity to cold air in diabetic patients with autonomic neuropathy

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Abstract

To investigate the role of neural pathways in the non-asthmatic response to eucapnic hyperventilation with below freezing air five diabetic patients with severe symptomatic autonomic neuropathy were studied. Their responses were compared with those shown by five diabetic patients without autonomic neuropathy and five non-diabetic controls. After bronchial provocation testing with cold air the diabetic patients with autonomic neuropathy did not show a significant fall in specific airways conductance (mean (SE) maximum percentage fall 2.0 (3.0)%), whereas conductance fell in the diabetic patients without neuropathy by 30.8 (2.0)% ($p < 0.001$) and in the non-diabetic controls by 22.7 (4.6)% ($p < 0.02$).

In subjects who do not have asthma the bronchial response to cold air is mediated largely via neural mechanisms.

Introduction

Human airways respond to various stimuluses by constriction. Because the airways of patients with bronchial asthma are particularly sensitive to such stimulation airway "hyper-reactivity" is included in many definitions of asthma¹ and testing airway responsiveness may be used to aid diagnosis.² Pharmacological agents such as histamine or methacholine may

be used to test airway reactivity, but more recently hyperventilation with air at below freezing temperatures has been shown to be a comparable alternative.³ Using a naturally occurring stimulus enables possible mechanisms of bronchial responses to be studied.

Bronchoconstriction may be induced by one of three principal mechanisms: a direct effect on airway smooth muscle; a neural reflex bronchoconstriction via vagal pathways; or release of chemical mediators by degranulation of mast cells. Studies using anticholinergic agents to investigate neural mechanisms have produced conflicting results. Some workers have found that such agents offer good protection, especially in non-asthmatic subjects,^{4,5} whereas others have reported a less appreciable effect.^{6,7} Anticholinergic agents are bronchodilators, making interpretation of such studies difficult because of differences in airway calibre before the challenge test.

To investigate further the role of vagal pathways in mediating the bronchial response to cold air in non-asthmatic subjects, we studied the response to provocation with cold air in a group of diabetic patients with severe, symptomatic, autonomic neuropathy and cardiovascular evidence of vagal damage. Diabetic patients with autonomic neuropathy have been shown to have a normal resting airway calibre but decreased resting vagal tone.⁸

Subjects and methods

We studied two groups of insulin dependent diabetic patients and one group of non-diabetic controls. The first group of diabetics consisted of five patients, all less than 45 years old, selected because of their severe symptomatic neuropathy defined as a variability in heart rate of less than 10 beats/minute. The other group of diabetics consisted of five patients of similar age and duration of diabetes, with no autonomic features, who were randomly selected from the clinic. The control group consisted of five subjects without diabetes.

None of the subjects had a recent or remote history of respiratory disease and none was tested within six weeks after an upper respiratory tract infection. All were non-smokers. All subjects yielded results to resting lung function tests that were within their normal predicted range.⁹ They all gave their informed consent to the study, and the study was approved by the ethics committee of this hospital.

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TESTS OF AUTONOMIC FUNCTION

Testing for the presence of neuropathy was done by one of us, who subsequently did not take part in the bronchial provocation tests. Diabetic autonomic symptoms were defined as follows: diabetic diarrhoea was defined as intermittent and especially nocturnal diarrhoea, usually with faecal incontinence preceded by borborygmi with no other gastrointestinal pathological abnormalities; bladder paresis was defined as delayed micturition with a residual volume on either intravenous urography or ultrasonic scanning of the bladder, with no mechanical obstruction; postural hypotension was defined as symptoms of hypotension on standing, with a drop of 30 mm Hg or more in the systolic blood pressure; and gustatory sweating was defined as facial sweating precipitated by eating specific foods, especially cheese or yoghurt.

Autonomic function tests were done after five minutes of rest in the supine position. Each subject's heart rate was recorded with a Lectromed ratemeter, MX2P amplifier, and MX212 chart recorder. The response of the heart rate to standing and the variability in heart rate at six breaths a minute were measured as previously described.¹⁰ The Valsalva ratio was calculated as the ratio of the maximum tachycardia to the maximum bradycardia during a standard Valsalva's manoeuvre.¹¹ Blood pressure was measured supine and at 60 seconds after standing. Diastolic blood pressure was measured at Korotkoff phase IV.

BRONCHIAL PROVOCATION TESTING

Our apparatus and technique for performing bronchial provocation testing with air at below freezing temperatures have been described elsewhere.⁴ Bronchial responses were assessed in terms of specific airways conductance measured in a constant volume whole body plethysmograph (W E Collins Inc). Bronchoconstriction was shown by a fall in specific airways conductance. Subjects rested in the laboratory before baseline determinations of lung function were made. Three recordings of forced expiratory volume in one second were made with a Vitalograph spirometer, and the best value was taken for each subject. Specific airways conductance was determined with five readings made at both five and 10 minutes after the end of hyperventilation. After baseline measurements had been made the subjects hyperventilated below freezing air for three minutes at a minute ventilation of $25 \times$ resting forced expiratory volume in one second. Specific airways conductance was again determined at five and 10 minutes after the end of hyperventilation and the maximum bronchoconstriction recorded. All subjects were thoroughly trained in the necessary techniques before undergoing testing.

STATISTICAL ANALYSIS

Results were analysed with Student's *t* test for paired and unpaired data. The level of significance was taken at $p < 0.05$.

Results

The table shows the symptoms and results of autonomic function tests for the diabetic patients. All neuropathic patients had severe

autonomic neuropathy. The results of the investigation in the non-neuropathic diabetic patients are also shown; none had postural hypotension. The normal variability in heart rate in this age range is over 15 beats/minute, heart rate increase on standing over 20 beats/minute, and Valsalva ratio over 1.2.¹² Of the subjects with autonomic neuropathy, three had proliferative retinopathy, one background retinopathy, one no retinopathy, and two proteinuria. Of the diabetic subjects without neuropathy, two had background retinopathy, three no retinopathy, and none proteinuria.

Mean resting specific airways conductance did not differ between the three groups (figure). Responses to bronchial provocation challenges were the same in each group with no differences in mean minute ventilation or temperatures of inspired or expired air.

Change in airway conductance after hyperventilation of cold air. (Horizontal bars represent mean specific airways conductance.)

After eucapnic hyperventilation of air at -20°C the diabetic patients with neuropathy did not show a significant fall in specific airways conductance (mean (SE) 2.37 (0.2)/kPa/s before challenge; 2.31 (0.2)/kPa/s after challenge). The diabetics without neuropathy and the controls without diabetes, however, both showed highly significant falls in airway conductance (2.56 (0.3) to 1.77 (0.2)/kPa/s ($p < 0.001$) and 2.53 (0.1) to 1.96 (0.2)/kPa/s ($p < 0.01$) respectively, (figure). Diabetic patients with neuropathy showed a mean fall in specific airways conductance of 2.0 (3.0)% whereas those without neuropathy showed a fall of 30.8 (2.0)% and subjects without diabetes a fall of 22.7 (4.8)%.

Discussion

Autonomic function tests established the presence of severe autonomic neuropathy in five patients with diabetes and indicated vagal denervation of the heart.¹⁰ In these five patients bronchial provocation with eucapnic hyperventilation of air at below freezing temperatures did not produce significant bronchoconstriction. In contrast, the diabetic patients with no

Results of autonomic function tests in diabetic patients with and without autonomic neuropathy

Case No	Age (years)	Duration of diabetes (years)	Autonomic symptoms	Resting heart rate (beats/minute)	Increase in heart rate on standing (beats/minute)	Variability in heart rate	Valsalva ratio	Lying blood pressure (mm Hg)	Standing blood pressure at 60 s (mm Hg)
<i>Diabetic patients with autonomic neuropathy</i>									
1	29	9	Postural hypotension, bladder dysfunction	104	13	3	1.1	144/110	70/60
2	22	18	Postural hypotension, diabetic diarrhoea	92	4	1.8	0.93	130/80	100/60
3	40	15	Postural hypotension, diabetic diarrhoea, gustatory sweating	112	2	1.5	1.0	114/98	80/70
4	43	15	Postural hypotension, diabetic diarrhoea, gustatory sweating	86	8	1	1.0	160/80	70/46
5	37	25	Gustatory sweating	104	4	2	1.08	144/94	114/78
Mean	34.2	16.4		99.6	6.2	1.86	1.0		
<i>Diabetic patients without neuropathy</i>									
Mean (range)	29.3 (23-35)	17.6 (6-26)	None	69.3 (55-80)	32.1 (23-45)	22.4 (17.2-28.9)	1.63 (1.35-1.73)		

autonomic symptoms and in whom all autonomic function tests yielded normal results showed considerable falls in airway conductance after matched challenges. Their response did not differ from that of the non-diabetic controls. The results confirm that vagal pathways have a major role in the non-asthmatic response to bronchial cooling.

Autonomic neuropathy occurring in diabetic subjects may produce severe symptoms relating to the cardiovascular, gastrointestinal, and genitourinary systems, and objective testing can readily confirm dysfunction. Symptoms relating to the respiratory system are less apparent. Douglas *et al* have shown, however, that, in subjects in whom the respiratory system is affected, anticholinergic agents do not have a bronchodilator effect, implying that resting airway vagal tone is reduced owing to the respiratory branches of the vagus nerve being affected by the neuropathy. As baseline airway calibre is not affected in these subjects neurally mediated mechanisms of bronchoconstriction may be investigated without the use of pharmacological agents.

Attempts to study the role of vagal pathways in bronchial reactivity using anticholinergic agents have produced conflicting results. Different groups have used widely different doses or routes of administration of either atropine or ipratropium bromide, and all such studies are open to the criticism that any protection afforded by cholinergic blockade is due entirely to the change in baseline airway calibre produced by the bronchodilator action of the drugs.¹³ We have previously suggested that, in subjects who do not have asthma, bronchial responses to cold air are vagally mediated,^{4 14} and the present study confirms this view. Also, in a recent study, Jammes *et al* showed that in anaesthetised cats the increase in lung resistance induced by the inhalation of cold air could be abolished by sectioning the superior laryngeal and vagus nerves,¹⁵ further confirming our conclusion.

Finally, we have speculated that impaired, protective respiratory reflexes such as we have shown in this study may perhaps be implicated in the unexpected cardiorespiratory arrests that have been reported to occur in diabetic subjects with autonomic neuropathy.¹⁶

References

- 1 American Thoracic Society. A statement by the committee on diagnostic standards for non-tuberculous respiratory diseases. *Am Rev Respir Dis* 1962;**85**:762-8.
- 2 Hargreave FE, Ryan G, Thomson NC, *et al*. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J Allergy Clin Immunol* 1981;**68**:347-55.
- 3 O'Byrne PM, Ryan G, Morris M, *et al*. Asthma induced by cold air and its relation to non-specific bronchial responsiveness to metacholine. *Am Rev Respir Dis* 1982;**125**:281-5.
- 4 Heaton RW, Henderson AF, Gray BJ, Costello JF. The bronchial response to cold air challenge: evidence for different mechanisms in normal and asthmatic subjects. *Thorax* 1983;**38**:506-11.
- 5 Sheppard D, Epstein J, Holtzman MJ, Nadel JA, Boushey HA. Dose-dependent inhibition of cold air induced bronchoconstriction by atropine. *J Appl Physiol* 1982;**53**:169-74.
- 6 Griffen MP, Fung KF, Ingram RH, McFadden ER. Dose-response effects of atropine on thermal stimulus response relationship in asthma. *J Appl Physiol* 1982;**53**:1576-82.
- 7 O'Byrne PM, Thomson NC, Morris M, Roberts RS, Daniel EE, Hargreave FE. The protective effect of inhaled chlorpheniramine and atropine on bronchoconstriction stimulated by airway cooling. *Am Rev Respir Dis* 1983;**128**:611-7.
- 8 Douglas NJ, Campbell IW, Ewing DJ, Clarke BF, Flenley DC. Reduced airway vagal tone in diabetic subjects with autonomic neuropathy. *Clin Sci* 1981;**61**:581-4.
- 9 Cotes JE. *Lung function*. 4th ed. London: Blackwell Scientific Publications, 1979.
- 10 McKay JD, Page MMcB, Cambridge J, Watkins PJ. Diabetic autonomic neuropathy. The diagnostic value of heart rate monitoring. *Diabetologia* 1980;**18**:471-8.
- 11 Levin AB. A simple test for cardiac function based upon the heart rate changes induced by the Valsalva manoeuvre. *Am J Cardiol* 1966;**18**:90-9.
- 12 Wieling W, van Brederode JFM, de Rijn RCG, *et al*. Reflex control of heart rate in normal subjects in relation to age: a data base for cardiac vagal neuropathy. *Diabetologia* 1982;**22**:163-6.
- 13 Benson MK. Bronchial hyper-reactivity. *Br J Dis Chest* 1975;**69**:227-39.
- 14 Henderson AF, Heaton RW, Costello JF. Effect of nifedipine on bronchoconstriction induced by inhalation of cold air. *Thorax* 1983;**38**:512-5.
- 15 Jammes Y, Barthelemy P, Delpierre S. Respiratory effects of cold air breathing in anaesthetised cats. *Respir Physiol* 1983;**54**:41-54.
- 16 Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980;**49**:95-108.

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Anti-Jo-1 antibody: a marker for myositis with interstitial lung disease

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Abstract

An autoantibody known as anti-Jo-1 antibody is found in 25% of patients with myositis. Its prevalence in patients

with both myositis and cryptogenic fibrosing alveolitis was 68% (13 out of 19 patients), compared with 7.5% in patients with myositis alone (four of 53) and 3% in patients with cryptogenic fibrosing alveolitis alone (two of 62).

Anti-Jo-1 antibody may be useful in indicating patients with myositis and cryptogenic fibrosing alveolitis. Raynaud's phenomenon, the sicca syndrome, and mild arthritis are also often part of the syndrome.

Introduction

Anti-Jo-1 antibody, an autoantibody directed at the cellular enzyme histidyl-tRNA synthetase,¹ is found in 25% of patients with myositis but not in other myopathies² and only rarely in other connective tissue diseases.^{2 3} It has long been recognised that a subset of patients with myositis have other features such as serositis and Raynaud's phenomenon, but, until a recent report associating anti-Jo-1 antibody with interstitial pulmonary fibrosis,⁴ lung disease was thought to be uncommon.⁵

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