

LETTERS TO THE EDITOR

Respiration in dystrophia myotonica

The interesting paper by Dr JE Clague *et al* (March 1994;49:240-4) contains some results and conclusions which are at variance with earlier studies.

Firstly, their results showed that the ventilatory response to carbon dioxide in these patients was lower than in the controls, but the difference was not significant. Several earlier studies showed clear evidence of a reduction in the slope of the ventilatory response.^{1,2} In addition, one study showed that the magnitude of this reduction was related to the severity of respiratory muscle weakness.² I would therefore submit that the first conclusion in the abstract of the paper that "moderately severe global respiratory muscle weakness does not appear to influence the ventilatory response to rising carbon dioxide tension" is incorrect.

It should also be pointed out that the authors do not actually quote data confirming "global respiratory weakness" as they only report maximum inspiratory pressures (MIP). In this condition this may lead to underestimation of the severity of muscle weakness since previous studies in dystrophia myotonica have shown that maximum expiratory pressures tend to be relatively more impaired than inspiratory pressures.^{2,3} Weakness of expiratory muscles might also be relevant to the sensation of discomfort during carbon dioxide rebreathing. Clague *et al* assessed this by asking the question "how difficult is it to breathe?" They equate the answers with inspiratory effort sensation and go on to examine the relation between this index and various factors including MIP. In the unnatural situation of ventilation stimulated by carbon dioxide both inspiratory and expiratory muscles are usually active, and therefore the sensation may not be determined solely by inspiratory effort. It might have been worth also exploring the relation between the effort sensation and expiratory muscle weakness.

A further point where the results appear to be at variance with earlier data relates to the variability of the timing of resting breathing. The authors found no difference from normal in the variation of the duration of individual breaths. Previous work has, however, commented on patients with marked variation from breath to breath. The explanation for the discrepancy may lie in the technique used, since subjects in the study of Clague *et al* used a mouthpiece and noseclip, while studies showing marked variability of breath timing^{2,3} used more surreptitious monitoring of chest wall movement which probably gives a fairer reflection of undisturbed resting breathing.

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- 1 Begin R, Bureau MA, Lupien L, Bernier J-P, Lemieux B. Pathogenesis of respiratory insufficiency in myotonic dystrophy. *Am Rev Respir Dis* 1982;125:312-8.
- 2 Serisier DE, Mastaglia FL, Gibson GJ. Respiratory muscle function and ventilatory control. I. In patients with motor neuron disease. II. In patients with myotonic dystrophy. *Q J Med* 1982;51:502-26.
- 3 Gillam PMS, Heaf PJD, Kaufuren L, Lucas BGB. Respiration in dystrophia myotonica. *Thorax* 1964;19:112-20.

AUTHOR'S REPLY We were interested to read Professor Gibson's letter which raises several important points. He is quite correct in stating that we did not include the maximum expiratory pressure data as we followed the normal convention of relating inspiratory effort sensation to maximum inspiratory pressures. This approach has been developed in Hamilton (Canada) and Cleveland (USA) but the subject table should certainly have contained the MEP data which was 56 (16) cm H₂O for the myotonic group compared with 156 (23) cm H₂O for our normal subjects. As can be seen the patient values are significantly below the age-matched controls and are very similar for both inspiration and expiration. This is the basis for the statement about global respiratory muscle weakness and we apologise for this omission.

We were surprised to see no significant difference in the ventilatory responses to carbon dioxide between our patients and the control subjects. We suspect this reflects the selection of our patients which we specified in the methods section. As can be seen, we did not study the most severely affected myotonic patients and, in particular, there were no subjects with diaphragm weakness - a difference between our patient group and that of Professor Gibson which he cites in his reference 2.

We have conducted a subsidiary analysis adopting the same approach of pooling data that we used in our analysis of effort sensation. If this is done with the independent variable being ventilation, then a just significant effect of maximum inspiratory pressure can be seen ($p > 0.05$) and this explains a very small amount of the variability in the ventilatory response to carbon dioxide. This analysis was removed for reasons of space during the revision of the paper.

Our point is that the ventilatory response to carbon dioxide is likely to be a continuum, with the most severely affected patients certainly having a reduced ventilatory response but many patients who are affected by dystrophia having preserved responses. Hence the problem is one of degree and other complicating factors, rather than an intrinsic defect always associated with the disease.

We have analysed the inspiratory effort sensation for both global and expiratory muscle weakness and found no difference in the conclusions from those listed in the paper. This is not surprising, given the similarity of the MIP and MEP results. We know of no data looking at the patterns of activation of the expiratory muscles during carbon dioxide rebreathing in patients with dystrophia myotonica. However, we doubt if this is substantially different from that seen in healthy humans.

Finally, we agree that the breathing pattern data we report are different from those obtained using non-invasive means of monitoring ventilation and we have suggested in paragraph 2 of the discussion why this may be so. Some of our patients showed substantial variability in their respiratory cycle duration when monitored awake as part of a sleep study

described elsewhere. We were impressed by how easily these effects were abolished by a modest dead space. This may reflect an influence of a different set point for the apnoeic threshold in these patients that might be worth further systematic study.

However, these intriguing changes in ventilatory control do not seem to influence the capacity of the individual to assess sensation unless that patient is confronted by an increased inspiratory load to breathing.

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Sympathomimetics and airway hyperreactivity

In commenting upon whether the use of sympathomimetics is associated with hyperreactivity of asthmatic airways to inhaled spasmogens, Drs Taylor and Sears and Drs van Schayck and van Herwaarden (February 1994;49:190-1) categorise the effect of sympathomimetics (at therapeutic dose levels) as small. Their opinions may be valid when histamine or methacholine are used for assessment of airway responsiveness, but it is possible that larger effects might have been observed if other test spasmogens had been used. For instance, it is known that regular use of terbutaline resulted in an increased sensitivity to the spasmogenic actions of adenosine monophosphate that was greater than the corresponding change in sensitivity to methacholine.¹ Recently, similar differential changes have been observed in allergic patients whose sensitivity to allergen, after regular use of salbutamol, was exaggerated to a greater extent than to methacholine.²

Clinical observations of differential changes in sensitivity of intact airways to spasmogens were anticipated by an experimental analysis of the changed responsiveness of the airways in sensitised guinea pigs during exposure to antigen.³ In these animals, responsiveness of the airways to seven distinct spasmogens was measured before and after infusion of antigen. As in humans,⁴ the magnitude of increased responsiveness was greater for some spasmogens than for others, with peptidoleukotrienes (LTC₄ and LTE₄) and bradykinin being particularly sensitive indicators of increased responsiveness during an acute allergic reaction in the guinea pig. Of possible interest to clinical investigators was the finding that, following prolonged exposure to salbutamol, the exaggerated responsiveness of the airways to LTC₄ and LTE₄ that accompanies a mild allergic reaction was further intensified. Thus, a substantial proportion of animals (78 of 235) became either too responsive for evaluation or died during exposure to antigen or LTC₄, even though concomitant responsiveness to histamine, acetylcholine, serotonin, and prostaglandin F_{2α} was diminished significantly.⁵ A reduced response to certain spasmogens reflected a continued bronchodilator response to infused salbutamol, and these findings therefore explain the paradox of hyperreactivity to inhaled antigen without corresponding hyperreactivity to histamine as had been reported earlier but not understood.⁶ No mechanism has been established to account for this differential; however, it may be a manifestation of the properties of the (supposedly inert) enantiomer that comprises 50% of salbutamol, since induction of ex-

aggerated sensitivity to LTC₄ has been observed to be a characteristic of s-salbutamol in allergic animals.⁷

There can be no doubt that allergic hyperreactivity in the guinea pig is spasmogen selective, with LTC₄, LTE₄, and histamine being sensitive indicators of this phenomenon. However, following protracted (six days) exposure to salbutamol (1 mg/kg/day) there is a divergence of changed responsiveness such that it might be concluded from studies using LTC₄ or LTE₄ that airway responsiveness had increased whereas, at the same time and in the same animal, reduced responsiveness to histamine would favour a contrary conclusion. Hence, before categorising changes in airway responsiveness due to sympathomimetics as being small in asthmatic subjects, it would be prudent to examine a wider range of test spasmogens. When first investigated by use of sophisticated recording techniques, it was concluded that allergic airway hyperreactivity did not occur in the guinea pig.⁸ By giving consideration to alternative test spasmogens it is now possible to demonstrate substantial increased airway responsiveness during a modest allergic reaction in this species.³ Furthermore, it is possible to define circumstances whereby sustained exposure to sympathomimetics heightens susceptibility to certain allergic mediators so that the response to a low dose of antigen is transformed from a source of mild discomfort to sudden death. In the absence of experimental data, it cannot be presumed that this phenomenon cannot occur in asthma.

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- 1 O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled beta₂-agonists in asthma. *N Engl J Med* 1992; 327:1204-8.
- 2 Cockcroft DW, McParland CM, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1994;342:833-7.
- 3 Hoshiko K, Morley J. Allergic bronchospasm and airway hyperreactivity in the guinea-pig. *Japan J Pharmacol* 1993;63:151-7.
- 4 Djukanovic R. Is airways hyperreactivity selective or non selective? *Agents Actions [Suppl]* 1993; 43:231-9.
- 5 Hoshiko K, Morley J. Exacerbation of airway hyperreactivity by racemic salbutamol in sensitized guinea-pigs. *Japan J Pharmacol* 1993;63: 159-63.
- 6 Chapman ID, Mazzoni L, Morley J. An anomalous effect of salbutamol in sensitized guinea-pigs. *Br J Pharmacol* 1990;99:66P.
- 7 Morley J, Chapman ID, Foster A, Hoshiko K, Mazzoni L. Effects of (+) and racemic salbutamol on airway responses in the guinea-pig. *Br J Pharmacol* 1991;104:295P.
- 8 Popa V, Douglas JS, Bouhuys A. Airway responses to histamine, acetylcholine and propranolol in anaphylactic hypersensitivity in guinea pigs. *J Allergy Clin Immunol* 1973;51:344-56.

AUTHORS' REPLY We thank Dr J Morley for his meaningful comment. We agree that our statement that the effect of sympathomimetics on bronchial hyperresponsiveness is relatively small was based upon studies in which histamine or methacholine were used. Other test spasmogens may indeed have other effects. Moreover, we believe that the clinical significance of the effects of spasmogens which are inhaled in natural circumstances (such as allergens) is much greater than that of provocative agents such as histamine or methacholine. The recently published study of Cockcroft *et al* points to this difference.¹ The results of the study of Cockcroft *et al*

and the other studies mentioned by Morley may be explained not only by the fact that other spasmogens were used, but also by the fact that the subjects involved were clearly sensitive to allergens. In other words, an increased bronchial hyperresponsiveness during continuous use of a bronchodilator may occur especially in allergic asthmatic patients. We have some information which supports this suggestion. In a secondary multivariate analysis of our study which showed an increased decline in lung function during continuous bronchodilator use² it was observed that only asthmatic patients who were both allergic and had a high reversibility of obstruction after a bronchodilator had an increased decline in lung function during continuous use of the sympathomimetic drug salbutamol. As this effect was independent of all other important characteristics (for example, baseline bronchial hyperresponsiveness, baseline lung function, peak flow variability, and smoking), it seems probable that reversibility and allergy were not merely measures of the severity of the disease but were real determinants of an increased decline in lung function during bronchodilator use. The enhanced airway response to allergens may be caused by enhanced mediator release from mast cells, possibly due to mast cell β -receptor downregulation.¹ This would mean that regular use of sympathomimetics in conjunction with exposure to allergens would induce inflammation, which in turn is an important determinant for an increased decline in lung function.³ It would also explain why β_2 agonists induce an increase in hyperresponsiveness in some patients and not in others in our study.

It seems paradoxical that particularly allergic patients should be careful in using sympathomimetics chronically, as these patients will in general benefit most from the acute bronchodilating effect of these drugs. This allows for a second explanation for the possibly deleterious effects of bronchodilators, namely a masking effect of the drug.⁴ If a patient is sensitive to an antigen and wheezes or gets dyspnoea on exposure, his natural tendency will be to stay away from it. The bronchoconstrictive reaction to antigens will warn him against repeated exposure. If, however, the patient is given effective bronchodilator medication that allows him to "carry on a normal life", he will quickly learn to get rid of the wheezing when it starts or to prevent it altogether by taking the bronchodilator in advance. Since the sympathomimetic drug does not interfere with the late reaction to the inhaled substance, patients may eventually develop a progressive inflammatory airway disease with increasing bronchial hyperresponsiveness. We observed earlier that there was a correlation between the decline in lung function and the increase in bronchial symptoms in patients who had been treated on demand, but that there was no correlation at all in patients who were treated with bronchodilators continuously.⁵ A poor perception of the severity of asthma seems to be a predictor of severe asthma, and it may be possible that these drugs have an influence on afferent signalling and its processing in the brain.⁶

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- 1 Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
- 2 Schayck CP van, Dompeling E, Herwaarden CLA van, *et al*. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. *BMJ* 1991;303:1426-31.
- 3 Schayck CP van, Dompeling E, Herwaarden CLA van, Wever AMJ, Weel C van. Interacting effects of atopy and bronchial hyperresponsiveness on the annual decline in lung function and the exacerbation rate in asthma. *Am Rev Respir Dis* 1991;144:1297-301.
- 4 Whitelaw WA. Asthma deaths. *Chest* 1991;99: 1507-10.
- 5 Schayck CP van, Folgering H, Otter JJ den, Tizimanna P, Weel C van. Does the continuous use of bronchodilators mask the progression of asthma or chronic bronchitis? *Fam Pract* 1992;9:397-404.
- 6 Barnes PJ. Blunted perception and death from asthma. *N Engl J Med* 1994;330:1329-34.

Bronchodilators in COPD

In their recent paper (April 1994;49:332-4) Fink and coworkers found, in a group of 22 patients with severe COPD (FEV₁ <50% predicted), that theophylline therapy induced a small but statistically significant increase in maximal voluntary ventilation (from 43.0 l/min with placebo to 46.7 l/min) resulting in an improvement in peak exercise capacity. Since at the same time there was no change in FEV₁ (from 1.05 to 1.1 l), they speculated that theophylline was probably acting on the respiratory muscles, either directly or via a central stimulatory pathway. The finding of a statistically significant improvement in arterial blood gases at rest favoured the second hypothesis.

However, we think that they have not paid enough attention to another of their findings - namely, the increase in FVC from 2.28 l to 2.38 l. Although of small magnitude, this change may well indicate beneficial bronchodilating effects of theophylline not reflected in FEV₁. Other workers have previously shown a reduction in the work of breathing,¹ a decrease in trapped gas volume, and an increase in slow vital capacity² without concomitant change in FEV₁ in patients with COPD receiving theophylline. We have also recently found such dichotomous responses to bronchodilators in COPD after betamimetic inhalations^{3,4}; significant decreases in specific airway resistance and sometimes increases in maximal inspiratory flows can occur in the absence of significant increases in FEV₁. Such a finding should not come as a surprise, however, since no change or only a small change in FEV₁ after administration of bronchodilators is somewhere included in the definition of COPD!

We suggest that, for evaluating bronchodilators, we should stop concentrating only on FEV₁ measurements and should look at other indices of airway function such as specific airway resistance, maximal inspiratory flows, and even the slow vital capacity.⁵

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