

# Impaired voluntary drive to breathe: a possible link between depression and unexplained ventilatory failure in asthmatic patients

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## Abstract

**Background** – Although psychological distress predicts mortality in asthma, an underlying physiological link has not been shown. This study examined relations between impaired voluntary drive to breathe and measures of mood states.

**Methods** – The level of maximal voluntary activation of the diaphragm and elbow flexors was measured in a previous study using a sensitive modification of the twitch interpolation technique in 11 asthmatic and 10 control subjects. In this study psychological distress was assessed using the Profile of Mood States questionnaire and measures of distress were compared with the muscle voluntary activation results.

**Results** – For the asthmatic subjects, depressed mood increased the risk of impaired maximal voluntary activation of the diaphragm by 3.5 times (95% CI 1.09 to 11.3). No such association was observed in control subjects.

**Conclusions** – These results suggest that depressed mood may predispose an asthmatic patient to impaired voluntary activation of the diaphragm. Such individuals would be at increased risk of rapidly developing ventilatory failure if faced with severe airway narrowing.

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Although the development of ventilatory failure during severe asthma is usually attributed to inspiratory muscle fatigue,<sup>1</sup> death may be sudden without obvious exacerbation of airflow obstruction shortly before the fatal episode. Furthermore, there may be relatively little inflammation or inspissated mucus in the bronchi at post mortem examination.<sup>2,3</sup>

Identified risk factors for death from asthma include patient underestimation of the severity of airway narrowing, the use of sedative or psychotropic drugs, and the presence of psychological symptoms, notably anxiety and depression.<sup>4,5</sup> Anxiety and depressive symptoms are common in patients with asthma<sup>6,7</sup> and potential explanations include: (1) that the experience of asthma precipitates psychological distress; (2) that psychological factors precipitate airway narrowing; and/or (3) that some patients with asthma have a concurrent central nervous system vulnerability to psychological disorders.<sup>7</sup>

We have shown previously that some asth-

matics, while in remission, have impaired voluntary drive to the unfatigued diaphragm during maximal voluntary inspiratory efforts.<sup>8</sup> In this study we examined in the same subjects the relation between the degree of maximal voluntary activation of the diaphragm and self-reported measures of psychological distress obtained with a validated questionnaire.

## Methods

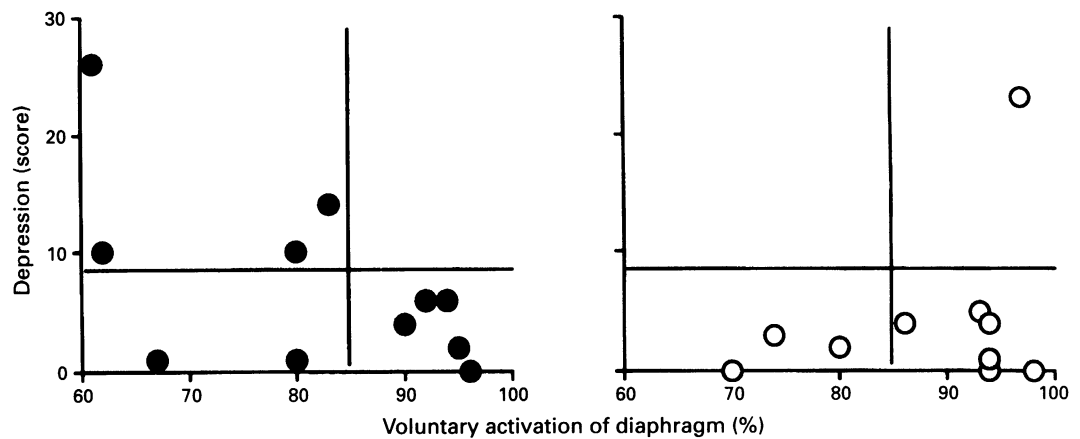
Twenty one subjects (11 asthmatics, 10 controls) were recruited by advertisements in hospital and university newsletters. None had participated in respiratory muscle testing or training. Informed consent was obtained and the study was approved by the appropriate institutional ethics committee. The asthmatic subjects were unselected other than the requirement to respond to histamine challenge with a 40-50% decrease in FEV<sub>1</sub>. Each asthmatic patient completed a questionnaire detailing the history and treatment of their asthma (frequency of episodes of wheezing, admissions to hospital, current and past medications). On these criteria the clinical severity of asthma was rated by a respiratory physician (DM, who was unaware of the muscle test results or the psychological scores) on a 10 point scale and ranged from 0.5 to 8.<sup>8</sup> Three patients had been admitted to hospital for a severe exacerbation of asthmatic airway narrowing within the previous five years, and another in childhood. Three had only intermittent need for medication. The remaining eight were taking inhaled steroids at a prescribed dose ranging from 1000 to 2400 µg/day. Three patients had taken a short course of oral steroids in the previous 18 months; none was taking oral theophylline. Bronchial reactivity was quantified as the concentration of histamine required to produce a 20% reduction in FEV<sub>1</sub> and varied from 0.6 to 14 mg/ml histamine. The subject groups were well matched for age, height, weight, and level of physical activity.<sup>8</sup>

Voluntary activation was assessed during maximal voluntary contractions of the diaphragm and elbow flexors using the technique of twitch interpolation which has been described previously.<sup>4</sup> In brief, subjects performed two sets of 10 maximal voluntary contractions (MVCs) of the diaphragm and an identical protocol for the elbow flexors. Each set of MVCs was preceded by an incremental inhalational challenge (doubling concentrations of histamine from 0.125 mg/ml up to 32 mg/ml, nebulised for one minute) or a sham chal-

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Relative risks of impaired diaphragmatic activation as a consequence of depression in asthmatic (●) and control (○) subjects. For asthmatics the relative risk was 3.5 times (95% CI 1.09 to 11.3). No such trend was apparent for controls (relative risk = 0.7, 95% CI 0.42 to 1.06). Activation score was the mean of 20 estimates for each subject.

lenge (3–4 inhalations of isotonic phosphate buffered saline). During each MVC, at the peak force, a single supramaximal electrical stimulus was delivered either to both phrenic nerves or over the biceps brachii. A second supramaximal stimulus was delivered with the muscles relaxed approximately five seconds later. The degree of failure of voluntary drive is indicated by an increment in force (or pressure) evoked by the stimuli during the contraction. The “superimposed” increment for each trial is expressed as a percentage of the response evoked by the same stimuli in the relaxed muscles and subtracted from 100 to give the final activation percentage. A 100% activation score is thus derived for no increment in force with interpolated stimuli (indicating complete neural activation), while a 50% score indicates that the interpolated twitch was half the amplitude of the resting twitch – that is, only half of the absolute maximal force from the stimulated muscle was generated voluntarily.

All subjects completed the Profile of Mood States (POMS) questionnaire to assess current psychological distress.<sup>9</sup> This is a validated “self-report” questionnaire with 65 items and it

provides separate numerical scores for six mood or affective states: anxiety, depression, anger, vigour, fatigue-inertia, and confusion. Each item is scored on a five-point scale with responses ranging from “not at all” (0) to “extremely” (4).

Pearson correlations were calculated between mean voluntary activation of the diaphragm and elbow flexors and the key psychological variables. The relative risk of depressed mood (POMS depression subscale score >9) associated with an impaired voluntary drive to breathe (mean activation score of diaphragm <85%) was calculated for both asthmatic and control subjects.

## Results

As reported previously<sup>8</sup> asthmatic subjects showed lower and more variable voluntary activation of the diaphragm and elbow flexors than control subjects: diaphragm 82.0% (18.4%) *v* 87.8% (12.0%),  $p < 0.01$ ; elbow flexors 91.3% (7.6%) *v* 95.8% (4.1%),  $p < 0.01$ . These findings confirm the previous observation that the diaphragm is more difficult to activate than elbow flexors.<sup>10</sup>

Impaired voluntary activation of the diaphragm (defined as <85%) was 3.5 times (95% CI 1.09 to 11.3) more common in asthmatics with depressed mood (defined as POMS score >9) (figure). No such association was apparent among control subjects (relative risk = 0.7; 95% CI 0.42 to 1.06), but only one control subject had a depression score >9 (figure). Asthmatic subjects showed a moderate negative correlation between depressed mood and voluntary activation of the diaphragm ( $r = -0.56$ ,  $p = 0.07$ ) but not between depressed mood and voluntary activation of the elbow flexors ( $r = -0.11$ ). There was no significant correlation in control subjects between depressed mood and mean activation of the diaphragm ( $r = 0.32$ ) or elbow flexors ( $r = 0.18$ ). A correlation was also seen between ability to activate the diaphragm and ability to activate the elbow flexors ( $p < 0.01$ ).<sup>8</sup>

The pattern of correlations across the POMS

Pearson correlations between impaired voluntary activation of the diaphragm and psychological distress, bronchial reactivity, and clinical severity of asthma

	Mean voluntary activation score for the diaphragm	
	Asthmatics (n = 11)	Controls (n = 10)
(A) Psychological measures:		
(i) Profile of Mood States:		
(a) Total score	-0.39	0.29
(b) Subscales		
Depression	-0.56*	0.32
Anxiety/tension	-0.19	0.39
Vigour	0.17	-0.06
Fatigue	-0.09	0.25
Confusion	-0.40	0.31
Anger	-0.48	0.28
(B) Illness measures:		
(a) Bronchial reactivity <sup>1</sup>	-0.13	
(b) Clinical severity <sup>2</sup>	-0.17	

\*  $p = 0.07$ .

<sup>1</sup>  $\text{Log}_{10}$  transformation of  $\text{PC}_{20}$  for histamine.

<sup>2</sup> Bronchial reactivity and clinical severity were not significantly correlated ( $r = -0.40$ ,  $p = 0.22$ ).

subscale scores was consistent with the view that increasing psychological distress, notably in the form of depressed mood, was associated with impaired voluntary activation of the diaphragm (table). Neither the clinical severity of asthma nor the degree of bronchial reactivity correlated with impaired voluntary activation of the diaphragm. Similarly, there were no associations between clinical severity ( $r = -0.11$ ) or bronchial reactivity ( $r = -0.17$ ) and total POMS scores.

### Discussion

This study reveals an association between depressed mood and impaired voluntary activation of the diaphragm in asthmatic patients. It complements our previous detailed report that voluntary diaphragmatic activation was reduced in a group of asthmatics compared with healthy controls.<sup>8</sup>

It could be argued that healthy subjects may not have been an appropriate control group. However, all the asthmatics studied here were in remission, had relatively normal lung function, and several were involved in competitive sports such as swimming and triathlon. While four asthmatic subjects had depression scores well above the control subjects, their level of depression would only be rated in the "mild" to "moderate" range. Only one asthmatic had a relatively high score for depression.

Few data are available on voluntary activation in other patient groups. Impaired voluntary activation of limb muscles has been reported in patients with joint pathology but this was attributed to inhibition of the alpha motoneurone pool by nociceptive inputs.<sup>11</sup> Patients with post-infection fatigue syndrome have normal voluntary activation of their elbow flexor muscles but correlates with depressed mood were not examined.<sup>12</sup> Conversely, patients previously affected by the polio virus have variable activation but no evidence of depressed mood.<sup>13</sup>

Most normal subjects find it easier to achieve full activation of the elbow flexors than the diaphragm.<sup>8</sup> The neural mechanisms which underly this difference have not been investigated. It could simply reflect a lack of familiarity with maximal contractions of the diaphragm but, if so, it is surprising that voluntary activation of the diaphragm of asthma patients is impaired, given that it is intermittently loaded. It is also possible that the diaphragm receives less facilitation from descending and spinal inputs such as muscle spindles.

The difference in voluntary activation of the diaphragm between asthmatic and control subjects is unlikely to be due simply to variation in lung volume because there was no significant difference between the groups in total lung capacity and functional residual capacity.<sup>8</sup> Although the absolute lung volume for the maximal inspiratory pressure manoeuvres was higher in the asthmatic group, there was no correlation between lung volume and voluntary activation. Furthermore, end expiratory lung volume increased in the asthmatic group following histamine, but this did not influence their voluntary activation.<sup>8</sup>

Confidence in our results is limited by the small number of subjects assessed and considerable inference has been drawn from the differences in the pattern of correlations between asthmatic and control subjects. The deficit in voluntary activation of the diaphragm in asthmatic patients was revealed by twitch interpolation in a laboratory, rather than clinical, situation. Clearly the low voluntary drive to the diaphragm, and its specific association with depressed mood, require confirmation in a larger group of patients with varying asthma severity, especially those with a history of life threatening episodes complicated by alveolar hypoventilation. Retesting of diaphragmatic activation after resolution of the depressive symptoms could also help to establish the specificity of the result.

Neither clinical severity of asthma nor the degree of bronchial hyperresponsiveness appears to be a major determinant of depressed mood in asthmatic subjects, nor do these characteristics predict impaired voluntary activation of the diaphragm. One explanation may be that certain individuals are predisposed to respond to the development of some types of chronic illness with depressive ideation. Since it is unlikely that impaired voluntary activation of the diaphragm causes depressed mood, we suggest that either depressed mood leads directly to impaired voluntary activation of the diaphragm, or both are the consequence of another unmeasured (central nervous system) factor.

Depressed mood is classically associated with feelings of hopelessness and "giving up" and failure to achieve complete voluntary activation could be a relevant physiological correlate of these feelings. While impaired voluntary activation of the diaphragm may be of little physiological significance during remission, it might contribute to ventilatory failure during a severe episode of asthmatic airway narrowing. The deficit in voluntary drive documented here was in the absence of diaphragmatic fatigue. The development of inspiratory muscle fatigue in the face of extreme loading might be associated with a decline in voluntary activation (central fatigue).<sup>10</sup> This proposed physiological consequence of a psychological state may explain why some asthmatic subjects develop ventilatory failure precipitously, while others maintain ventilation in the face of extreme airway narrowing.

In conclusion this study suggests that even minor levels of depressed mood in asthmatic subjects may be of physiological significance. In addition, it presents a possible explanation for the known association between depression and risk of death from asthma.

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