PostScript

LETTERS TO THE EDITOR

Improvement of respiratory failure with NIV

In their recent paper Nickol *et al*[1] studied the possible mechanisms by which non-invasive ventilation (NIV) improves ventilatory failure in patients with a restrictive defect due to either neuromuscular disease or kyphoscoliosis. They investigated three possible hypotheses for reduction in daytime hypercapnia—namely, increased ventilatory sensitivity to CO_2, improved respiratory muscle function, and increased respiratory system compliance. They showed that the reduction in diurnal $Paco_2$ after treatment was accompanied by an increase in hypercapnic ventilatory response (HCVR), with no changes in non-volitional tests of respiratory muscle strength or respiratory mechanics. They conclude that an increased ventilatory response to CO_2 is the principal mechanism underlying the long term improvement in gas exchange associated with NIV.

Interpretation of HCVR in patients with lung disease is often difficult and, as the authors point out, the measurement is highly variable. In attempting to minimise this variability they report the mean of two tests, but the finding of no significant difference between the first and second test is insufficient evidence to assess repeatability. Furthermore, acknowledging that an association between HCVR and $Paco_2$ has been demonstrated, there is a danger of over-interpreting this as cause and effect (increased HCVR resulting in lower $Paco_2$), and I would suggest that reverse causality (lower $Paco_2$ resulting in higher HCVR) is at least equally (and probably more) likely.

Studies over many years[2–4] have shown that the ventilatory response to CO_2 is dependent on the prevailing $Paco_2$ and bicarbonate concentration. The law of mass action dictates that, in patients with chronic hypercapnia and raised blood and CSF bicarbonate levels, a given change in $Paco_2$ during stimulated breathing will result in a smaller than normal increase in hydrogen ion concentration (the fundamental stimulus to the respiratory centres) and consequently a smaller increase in ventilation. When a chronically raised $Paco_2$ is lowered (as occurs with NIV), the bicarbonate concentration also falls (as clearly shown in this study) and an increase in the ventilatory response to CO_2 would be expected.

I therefore question the conclusion of Nickol *et al* that the ventilatory control mechanism is "fundamental" in determining the improvement in ventilatory failure accompanying NIV. As they explain, gas exchange improves as a result of optimising the "load/capacity/drive balance of the respiratory system" but, in my view, the "drive" is likely to be of secondary importance. The authors produce good evidence, as have others, that changes in load are probably not relevant. As they acknowledge, however, they have examined only one aspect of "capacity". It remains likely that, by relieving the load for several hours per day, some aspect of respiratory muscle function is improved, allowing $Paco_2$ to be maintained closer to normal for the remainder of the 24 hour period. Whether this improvement relates to better endurance, less fatigue, or an aspect of strength which is incompletely assessed by the tests used remains to be determined. I submit that, when considering the mechanisms of improved gas exchange with NIV, the focus should remain on the respiratory muscles rather than on the ventilatory control mechanism.

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Authors' reply

We thank Professor Gibson for his comments on our paper[1] and, indeed, acknowledge that an association between increased HCVR and reduced $Paco_2$ following NIV does not prove cause and effect, but that there may be co-dependency. We speculate that the heightened HCVR will help to maintain a lower $Paco_2$ during spontaneous breathing, even if the heightened HCVR is merely arising secondary to a lower $Paco_2$ and bicarbonate level. However, the mechanisms responsible for increasing the ventilatory response to CO_2 during chronic changes in blood gas and pH status remain unresolved, so the increased HCVR may also be only a correlation with the lower $Paco_2$. The relationship between the HCVR and $Paco_2$ or bicarbonate level can vary under different conditions (such as during chronic hypoxia), which makes it difficult to establish cause and effect. As Dempsey pointed out over 20 years ago,[2] it is no longer justifiable to consider ventilatory adaptations as the result of presumed changes in stimulus levels while assuming the gain of the reflexes is constant with only linear interactions. From a practical point of view, we would see our paper as supporting efforts to obtain the greatest possible reduction in daytime $Paco_2$ consistent with patient comfort.

We also acknowledge that, theoretically, a change in an unmeasured aspect of muscle function such as endurance may contribute towards improved daytime gas exchange, although it is of interest to note that inducing diaphragm fatigue by maximum voluntary ventilation or by inspiratory resistance loading does not alter neural drive to the diaphragm as indicated by electromyography.[3] Measuring respiratory muscle endurance is difficult because traditional techniques are either incremental tests (and therefore, in effect, tests of strength) or may be influenced by the breathing pattern adopted. To resolve these issues we recently described a novel test of respiratory muscle endurance[4] which could be used to test Professor Gibson's hypothesis.

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Consideration of palivizumab not justified

Broughton and colleagues[1] state that consideration should be given to the use of prophylactic palivizumab to infants born at less than 32 weeks in the case of maternal smoking or even if they have siblings. However, the authors present no data from their own or other studies to indicate that this would be in any way cost effective or justified. Certainly the word "consider" is fortunate, given the stated funding provided to one author by the manufacturer.

The study demonstrated a relationship between lower respiratory morbidity from respiratory syncytial virus (RSV) and smoking which has been widely shown elsewhere. The numbers of smokers were in fact very small—surprisingly so at 18 per 126 babies, given both their prematurity and the catchment population for this hospital, although 28 experienced smoking in the home. One wonders if the 61 non-consenters and non-attenders may have comprised a higher proportion.

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