LETTERS TO THE EDITOR

Mechanical ventilation of the newborn

EDITOR,—Drs Baumer, Beresford, Shaw, Manning, and their co-investigators in the two recent studies on mechanical ventilation of the newborn are to be congratulated for their hard work and persistence in performing these difficult clinical trials. In both, the authors conclude that patient-triggered ventilation (PTV) provided no added benefit; in Baumer’s trial, there was a trend towards more pneumothorax in infants below 28 weeks gestation. Both studies attempted to assess important clinical outcomes, such as the duration of mechanical ventilation, the incidence of chronic lung disease, and potential neurological injury. Their inability to tease out any of the potential benefits of PTV suggested by smaller studies is disappointing. Still, I would suggest that we do not conclude from these works that no benefits are possible, nor that these techniques should be abandoned.

An inescapable limitation of a large randomised trial is characterised by the Heisenberg uncertainty principle. Like the electron, optimal clinical treatment is a moving target. By its very nature, a study protocol will no longer reflect the clinical arena as well at the outset. In these studies, the authors evaluate PTV as a new and unproven clinical modality. Unfortunately, in neither study were they able to incorporate intermittent or continuous tidal volume measurement during ventilation. Like PTV, volume targeting is a new and relatively untested technique, although there is evidence that it may improve outcomes.1 Current neonatal ventilators commonly include tidal volume monitoring as a standard feature; some have the ability to provide volume controlled ventilation during a variety of patient triggered modes. One may speculate that the trend toward increased pneumothorax in the Baumer trial and the similarity in duration of ventilation and intracranial haemorrhage in both trials between the control and PTV groups may in part be due to underestimated fluctuations in tidal volume during pressure preset mechanical ventilation.

Another major problem faced by clinicians today is the difficulty in performing studies large enough to detect differences in meaningful outcomes. The authors of both current studies comment on their inability to realistically recruit the thousands of patients needed to delineate further differences between these treatments. Thus, at a time when the technology is finally available to measure tidal volume changes in volume and pressure at the bedside, and to reasonably estimate the impact of these changes on individual pulmonary functions, our clinical outcomes are good enough to make assessment of these new techniques exceedingly difficult. The authors of these studies have done an admirable job. I hope we can avoid the temptation to conclude that the PTV systems are the best ways, and that the new techniques available for neonatal mechanical ventilation are just “bells and whistles”.

MARK C MAMMEL Department of Neonatal Medicine Children’s Hospital of St. Paul 345 N Smith Ave, Room 2100 St Paul, MN 55102, USA


PTV: should it be patient triggered and patient terminated ventilation?

EDITOR,—We were surprised at the results of the two studies published in your journal by Baumer,1 and Beresford et al.2 Our experience with triggered ventilation over ten years is shown in table 1.

In comparison with the outcome figures in the articles, some underlying complications of pneumothoraces (PTX), intraventricular haemorrhage (IVH) and retinopathy of prematurity (ROP) were significantly less. As explained in our original article3 and subsequently shown by others, pressure and flow triggered systems perform suboptimally in infants less than 1500 g. While bench testing may suggest an adequate response time, clinical practice indicates that these systems are compromised by the following: (1) chest wall and lung compliance, (2) airway resistance, (3) leak around the endotracheal (ET) tube, (4) ET tube resistance, and (5) systems compliance. The trigger delay may be aggravated by each of these factors, especially in the very low birth weight infants.

We believe that the inability of the patient to terminate the insufflation of gases at the onset of exhalation leads to increased intra thoracic pressure and even intra cranial pressure. Thus, if there is trigger delay as postulated above, the ventilator continues to force gases into the infant during the expiratory phase causing active exhalation and with consequent deleterious effects.

The system used in our unit is triggered by modified impedance technology. Peak detectors within the system detect onset of inspiration and exhalation with sensitivity and rapidity. Furthermore, since the sensitivity depends on the rate of change of impedance, it is more sensitive when applied to very low birth weight infants or with increased rate of respiration. This may explain the marked difference in outcome, compared with the pressure triggered system, as shown by the application of the system in 1701 infants weighing less than 1500 g over ten years. There were 1270 infants in the same group weighing less than 1500 g. The only problem we have encountered is that of some cardiorespiratory monitors are incompatible with the triggering device. The signal processing through the monitors is optimal in the optimal performance of the respiratory analog input signal to the trigger/terminator. Prototypes of the system were used initially but since 1993, the commercially available system (Sechrist SAVI, Sechrist Industries, Anaheim, CA, USA) was used exclusively.

In large multicentre studies, derivation of consensus and consistent application of a standardised ‘conventional ventilation’ protocol is very difficult. This may skew some of the outcome data. Perhaps the limitations of flow and pressure triggered systems need to be considered prior to abandoning triggered systems in the respiratory support of new borns. Active exhalation predisposes some of these infants to the complications cited. The incidence of ROP in our experience is less than that reported in the literature. Possibly the same mechanism described above also predisposes the infants to ROP.

Given all of the above, further studies and analysis may be prudent. Such studies of patient triggered ventilation should also incorporate the capability of patient terminated ventilation.

N VISVESHWARA Department of Paediatrics, UCSF Fresno Valley Children’s Hospital, Fresno, CA, USA

niveshwara@valleychildrens.org

Table 1 Complications of prematurity 1991–1999

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;1500 g</th>
<th>Retinopathy of prematurity ≥3%</th>
<th>Intraventricular haemorrhage ≥3%</th>
<th>Pneumothorax (%)</th>
<th>Retinopathy of prematurity ≥4%</th>
<th>Intraventricular haemorrhage ≥4%</th>
<th>Pneumothorax (%)</th>
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</table>

To trigger or not to trigger?

**EDITOR,—**The international randomised controlled trial by Dr Baumer concluded that there was no benefit of patient triggered ventilation (PTV), but an added risk of increased pneumothorax in those less than 28 weeks gestation. In the same issue, Beresford et al concluded in a similar trial (with slightly more mature newborns 29 weeks + 27), that PTV was feasible with no significant differences noted in medium term outcomes. Chronic lung disease (CLD) is multifactorial in origin and in Baumer’s trial significant differences noted in medium term outcomes. Intrauterine growth retardation has been found in a study of 40 infants and a further 110 uncontrolled cases from one centre. A multicentre randomised controlled trial of sufficient power is needed to demonstrate benefit from the impedance technique and treatments applied to the infants (ventilation pressures, use of postnatal steroids and of continuous positive airway pressure (CPAP)).

In a large randomised controlled study, individual patients will have varying degrees of risk for the outcomes being measured. The purpose of the study design is to allocate patients in such a way that the overall risk for each arm is the same. However, the study, the less likely that there will be an unequal balance of risk, assuming that the randomisation process is performed correctly. We reported very similar birthweights and gestations in the two groups. The proportion of growth retarded infants was therefore allocated equally, and will not have biased the results.

A study comparing two modes of ventilation cannot be conducted with the attendant clinicians blind to treatment allocation. The study protocol required all other treatments to be applied equally to infants in both arms of the study. There were written treatment protocols for each arm. However, it is still possible that other treatments could have been applied unequally, with the possibility of bias resulting.

Patients were ventilated for an average of 8 days and 29% of infants died during ventilation. In summary, the research is unconvincing, based as it is on a controlled study of 40 infants and 110 uncontrolled cases from one centre. The trial therefore shows no evidence of benefit from the trigger trial, as infants recruited were by definition already being ventilated.

**Dr Baumer responds on behalf of the trigger trial collaborators:**

Visveshwara emphasises that the results of the trigger trial should not be interpreted as demonstrating lack of benefit for patient triggered ventilation using sensors or ventilators. I concur with this statement, which was emphasised in the paper. However, Visveshwara should not be surprised to find different outcome rates in the patients whose results he presents, as they are a different group of infants from those reported in either study. The evidence for benefit from the impedance technique is unconvincing, based as it is on a controlled study of 40 infants and 110 uncontrolled cases from one centre. A multicentre randomised controlled trial of sufficient power is needed to demonstrate benefit from the impedance and patient terminated ventilation techniques he describes. To date, such a study has not been performed.

Yadav suggests that important risk factors have not been compared in the study. He describes two different types of risk factor, namely inherent factors in the infant (intrauterine growth retardation) and treatments applied to the infants (ventilation pressures, use of postnatal steroids and of continuous positive airway pressure (CPAP)).

In a large randomised controlled study, individual patients will have varying degrees of risk for the outcomes being measured. The purpose of the study design is to allocate patients in such a way that the overall risk for each arm is the same. However, the study, the less likely that there will be an unequal balance of risk, assuming that the randomisation process is performed correctly. We reported very similar birthweights and gestations in the two groups. The proportion of growth retarded infants was therefore allocated equally, and will not have biased the results.

A study comparing two modes of ventilation cannot be conducted with the attendant clinicians blind to treatment allocation. The study protocol required all other treatments to be applied equally to infants in both arms of the study. There were written treatment protocols for each arm. However, it is still possible that other treatments could have been applied unequally, with the possibility of bias resulting.

Interpretation of ventilator pressures is difficult, as in the trigger ventilation technique weaning was undertaken at lower peak inspiratory pressures. In Plymouth, trigger ventilated infants entered in the trial had slightly lower peak inspiratory pressures in the first 72 hours, consistent with the different weaning policy. However, as the duration of ventilation did not differ between the groups, it is reasonable to conclude that there was no systematic bias in the application of ventilation.

Information on the postnatal use of steroids was collected in the trial. There was no difference in the proportion of infants receiving postnatal steroids (25.5% v 26.0%), nor in the postnatal age at which they were first administered (median 15 v 17 days). There is therefore no evidence of bias resulting from their use.

The use of CPAP for weaning from ventilation has not been demonstrated to reduce chronic lung disease in randomised controlled trials. The paper Yadav cites discusses the possibility of a policy of early use of nasal CPAP. This is not relevant to the trigger trial, as infants recruited were by definition already being ventilated. I would also like to qualify Yadav’s statement that we found an increased risk of pneumothorax in infants less than 28 weeks gestation. The difference was not statistically significant, suggesting that the ventilator technique may have occurred as a result of chance.

The trial therefore shows no evidence of bias, and the finding that patient triggered ventilation has no additional benefit over intermittent mandatory ventilation using the ventilators and techniques studied remains valid. The trial cannot assist clinicians in their choice of other modalities of support such as early use of CPAP or postnatal steroids and is applicable both to growth retarded as well as appropriately grown preterm infants.

**J H BAUMER**
Department of Paediatrics, Derriford Hospital, Devon, UK

harry.baumer@phht.west.nhs.uk

Patient triggered ventilation

**EDITOR,—**We read with great interest the recent study by Baumer which compared patient triggered ventilation (PTV) and a trend towards a higher incidence of pneumothorax in infants less than 28 weeks of gestation. Methological problems in this study, however, prompt us to question the validity of these conclusions.

While an open trial is perhaps the fastest means of achieving a large sample size, it has inherent problems of unequal experience and exposure among participating centres and unequal enrolment of patients. This study had a rather high rate of non-enrolment of eligible patients and a significant number of patients were not even offered the assigned mode of ventilation. Baumer provides little information regarding the experience of each centre with PTV and one might infer that some of the centres had little or none. Perhaps this might also be an explanation as to why more PTV patients were candidates for non-ventilatory intermittent mandatory ventilation (IMV) in preterm infants with respiratory distress syndrome. Baumer’s trial is the largest to date. He concludes that there is no observed benefit to PTV and a trend towards a higher incidence of pneumothorax in infants less than 28 weeks of gestation. Methological problems in this study, however, prompt us to question the validity of these conclusions.

In summary, the research is unconvincing, based as it is on a controlled study of 40 infants and 110 uncontrolled cases from one centre. The trial therefore shows no evidence of benefit from the trigger trial, as infants recruited were by definition already being ventilated.

**M YADAV**
Department of Paediatric Gastroenterology, Booth Hall Children’s Hospital, Charlestown Road, Blackley, Manchester M9 7AA, UK
myprateek@hotmail.com

References:

chronic lung disease could be confidently detected; no such effect was demonstrated. Although we applaud Baumer’s effort in organising a trial of this magnitude, we must caution that the conclusions should be confined to the specifics of this trial and may not be representative of PTV in this population.

STEVEN M DONN
Professor of Pediatrics, Interim Director, Division of Neonatal-Perinatal Medicine.
University of Michigan Health System, Ann Arbor, Michigan, USA

ANNE GREENEROUGH
Children Nationwide Professor of Clinical Respiratory Physiology, Deputy Head of Division of Women’s & Children’s Health, Guy’s, King’s & St Thomas’ School of Medicine, London, UK

SUNIL K SINHA
Senior Consultant in Paediatrics and Neonatology, Director of Neonatology, South Cleveland Hospital, Middlesbrough, UK


Dr Baumer comments on behalf of the trial collaborators:

It was heartening to see the interest shown in the trigger ventilation trial, and I share the correspondents’ caution that this trial can only show the effectiveness or otherwise of this mode of ventilation using the ventilators and techniques adopted for the trial.

The correspondents suggest that some of the participating centres were inexperienced or inept in the technique. As was dis- cussed in the paper, the trial coordinator vis- ited each participating centre and briefed staff in the technique; written protocols on both modes of ventilation were available in all centres; most participating centres already had experience of the technique (typically up to two to three years before entering the trial); centres were enrolling patients for up to four years. In addition, those few centres without prior experience were advised not to start randomising patients until they were confident with the technique. This was a pragmatic trial. If the technique of patient triggered ventilation (PTV) cannot be ap- plied successfully even with the education and support offered in this trial, it is reason- able to conclude that it is not likely to be any more effective in widespread use.

On reviewing the dataset, 139 infants were enrolled within three months of their centre’s first infant being randomised. There was no significant difference in rates of death or chronic lung disease, duration of ventilation, cerebral ultrasound abnormality, or depar- ture from the assigned mode of ventilation between these infants and those enrolled after the first three months. There was, however, a significantly lower rate of pneumothorax in the first three months of each centre starting the trial (5.0% versus 13.0%, p < 0.02), but with no observed difference in pneumothorax rate between the two modes of ventilation. This effect does not take into account other possible confounding factors (such as centre effects). This difference in pneumothorax rate was no longer apparent if the infants enrolled within the first year at their centre were considered separately.

The finding of an apparent time effect should be interpreted with great caution. It might suggest that the education provided by the trial coordinator had a short term benefit in reducing pneumothorax rates. If so, this is an important finding that could point to the need for improved ongoing education pro- grammes in neonatal intensive care units, and which also needs to be considered in the design of randomised controlled trials involving comparison of different techniques of ventilation.

The rate of non-enrolment (33%) is not surprising when one considers the difficulties of obtaining informed consent in such circumstances. In addition, the patient char- acteristics of non-enrolled patients were reported, showing similar gestation and birth weight. It is therefore reasonable to conclude that the results of the trial should be general- isable to the population served by the partici- pating centres. The proportion of infants ini- tially ventilated with the incorrect mode of ventilation was very small (1%). These infants were appropriately analysed on an “intention to treat” basis, and even when infants receiving only their assigned mode of ventilation were considered, the results were the same. It should be emphasised that the trial protocol allowed clinicians to change the mode of ventilation at their discretion. This was interpreted more liberally by one or two centres. It is therefore of note that 79% of infants only received their assigned mode of ventilation throughout. Thirteen per cent of infants in the trigger-arm of the Beresford study were changed to an alternative mode of ventilation, even when the study design precluded crossover of treatment strategy. As reported, the most immature infants and those subsequently dying were more likely to be switched to the other mode of ventilation. This does not suggest that centres were lack- ing in experience.

It is not possible to draw any inferences from the observed mortality rate. This study was conducted in the surfactant era, and the median duration of ventilation (six days) attests to the severity of the respiratory prob- lems, including the more mature infants, despite surfactant therapy in 93% and antenatal steroid administration in 63%. The lower rate of adverse outcomes in the study of Beresford and colleagues’ was not surprising given that the fact that infants below 1000 grams were excluded.

The hypothesis advanced by the corre- spondents about the consequences of too slow a rate of weaning of inspiratory pressures in PTV mode is intriguing. However, it is unsupported by any reference, suggesting that it is a purely hypothetical explanation for the development of pneumothorax.

The suggestion that the pressure triggering device may be less able to achieve synchrony than the Dräger babylog 8000 was unequivoc- al in the discussion (reference 31). We found no significant difference in pneumo- thorax rates. There was also no observed ben- efit in the more mature infants in the study, as also reported by Beresford et al.

No modification to the trigger ventilation technique used in this study has been shown to be required based on the available research evidence from the intervening seven years. Until further evidence is published that shows a better method of PTV than the one used in this trial, it is reasonable to conclude that a similar study conducted now using the SLE 2000 would reach a similar conclusion. The limited information from this study on the Dräger babylog 8000 does not suggest that different results would have been found if the trial had used only this ventilator.

The corresponding concerns about methodology therefore are very unlikely to account for the disappointing lack of ob- served benefit from PTV.

Morphine was used frequently or routinely in both the PTV trials, and theophyllines were not used except during weaning. This differs from the practice at the time of our initial report in 1993, and could have had a significant impact on the success of PTV, especially in the more immature infants. Further research is also needed to improve triggering devices, to find better methods for detecting asynchrony, and to investigate the use of different approaches to PTV such as the ones suggested by the correspondents.

I would like to use this opportunity to pay tribute to the two trial coordinators (Sue Ellis and Tom Mill), to the trial statistician (David Wright), and to the data monitoring committee (David Field and Diana Elbourne), whose details were inadvertently omit- ted from the final paper, and without whom, together with the trial collaborators, the study would not have been possible.

J H BAUMER
Department of Paediatrics,
Derriford Hospital,
Devon, UK

harry.baumer@phnt.wst.nhs.uk

To trigger or not to trigger?

M YADAV

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