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 newborns 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 as the study’s completion as it did at the outset. In these studies, the authors evaluate PTV as a new and unproven clinical mode. 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. 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 undermeasured 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 tiny 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 old ways are the best ways, and that the new techniques available for neonatal mechanical ventilation are just “bells and whistles.”

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1 Baumer JH. International randomized controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 2000;83:F2-F5.10

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, our group has found complications of pneumothoraces (PTX), intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP) to be significantly less. As explained in our original article1 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) system compliance. The trigger delay may be aggravated by each of these factors, especially in the very low birthweight infant.

We believe that the inability of the patient to terminate the insufflation of gases at the onset of exhalation leads to increased intrathoracic 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 2500 g. The only infants we have encountered is that of some cardiorespiratory monitors are incompatible with the triggering device. The signal processing through the monitors is crucial to the optimal performance of the respiratory ana!og signal input 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 newborns. 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.

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Table 1 Complications of prematurity 1991–1999

| Year | <1500 g n=175 | <1250 g n=130 | <1500 g n=136 | <1250 g n=136 | <1500 g n=133 | <1500 g n=128 | <1500 g n=162 | <1250 g n=160 | <1500 g n=218 | <1250 g n=169 | <1500 g n=169 | <1250 g n=160 | <1500 g n=196 | <1250 g n=203 | <1500 g n=184 | <1250 g n=184 |
|------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| 1991 | 2.2           | 4.7           | 3.8           | 5.5           | 12.3          | 12.8          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          |
| 1992 | 5.2           | 3.4           | 3.2           | 4.6           | 8.7           | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          |
| 1993 | 6.5           | 4.8           | 5.5           | 7.1           | 11.8          | 9.7           | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          |
| 1994 | 4.8           | 5.5           | 7.1           | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            |
| 1995 | 7.1           | 5.5           | 7.1           | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            | <1            |
| 1996 | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          | 12.3          | 11.8          |
| 1997 | 9.7           | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          |
| 1998 | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          | 11.6          |
To trigger or not to trigger?

EDITOR,—The international randomised controlled trial by Baumer et al 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 factors, like ventilation pressures, intrauterine growth retardation, use of postnatal steroids, and nasal continuous positive airway pressure (nasal CPAP) use, have not been compared between the groups.

Intrauterine growth retardation has been shown to be an important risk factor for CLD.1 In a trial where primary outcome is CLD, omission of the data regarding use of postnatal steroid use is quite surprising. Meta-analysis of the use of dexamethasone in very low birthweight infants has shown marked reduction in CLD at 36 weeks postconceptional age.2 The use of nasal CPAP that has been shown to influence the incidence of CLD, is not mentioned in their trial. Beresford et al did not use nasal CPAP in any of their infants, but used synchronised intermittent mandatory ventilation (SIMV) in the weaning phase.

To the clinician, who has to make the choice of using these commonly available tools to reduce death and morbidity in this vulnerable group of infants, is the choice clear or more unclear? I leave the readers to decide.

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Dr Baumer responds on behalf of the trigger trial collaborators:

Vivekshara remarks that the results of the trigger trial should not be interpreted as demonstrating lack of benefit for patient triggered ventilation (PTV). In the present study, the incidence of risk factors for each outcome measured in the infants with PTV were the same as in the conventional group, and there was no evidence of bias resulting from the randomisation process.

The trigger trial collaborators:

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.

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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 the mode of ventilation using the ventilators and techniques adopted for the trial.

The correspondents suggest that some of the participating centres were inexperienced or inexpert in the technique. As was discussed in the paper, the trial coordinators visited each participating centre and briefed staff in the technique; written protocols on detecting asynchrony, and to investigate the use of different approaches to PTV such as the ones suggested by the correspondents.

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 departure 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 programmes 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 characteristics 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 generalisable to the population served by the participating centres. The proportion of infants initially 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 in their own 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 lacking 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 problems, 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 the fact that infants below 1000 grams were excluded.

The hypothesis advanced by the correspondents 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 not well justified in the discussion (reference 31). We found no significant difference in pneumothorax rates. There was also no observed benefit 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 correspondents’ concerns about methodology therefore are very unlikely to account for the disappointing lack of observed benefit from PTV.

Morphine was used frequently or routinely in both the PTV trials and was 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 omitted from the final paper, and without whom together with the trial collaborators, the study would not have been possible.

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