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► **To cite this version:**

David Treacher. Use of the prone position in the acute respiratory distress syndrome: how should we assess benefit?. *Clinical Science*, 2006, 110 (6), pp.641-643. 10.1042/CS20060068 . hal-00479323

HAL Id: hal-00479323

<https://hal.science/hal-00479323>

Submitted on 30 Apr 2010

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Use of the prone position in the acute respiratory distress syndrome – how should we assess benefit?

Abstract

Prone positioning of patients with acute respiratory failure was first suggested over 30 years ago. In the present issue of *Clinical Science*, Reutershan and co-workers have studied the changes in end-expiratory lung volume in 12 patients with ARDS (acute respiratory distress syndrome) over an 8 h period following manual turning from the supine to prone position. From the data presented, the authors suggest that baseline end-expiratory lung volume could be used to identify responders, and serial measurements would permit appropriate 'dosing' of the therapy. Although this is an interesting study that provides data that have rarely been collected when assessing the response to prone positioning, there are a number of limitations that need to be considered. However, despite the limitations, the study does stimulate a number of important questions related not only to the use of the prone position, but also to the management of patients with ARDS in general.

Prone positioning of patients with acute respiratory failure was first suggested over 30 years ago¹. Although studies have repeatedly shown improvement in arterial oxygenation in about two-thirds of patients with the acute respiratory distress syndrome (ARDS)², no clear outcome benefit has been demonstrated largely because nearly all the studies have been small, directed at discovering the mechanism of the benefit and at attempting to predict which patients would benefit.

Central to these studies has been the assumption that improvement in oxygenation would equate with outcome benefit. The only two large randomised controlled studies of prone positioning in acute lung injury (ALI) from Italy³ and France⁴ showed the anticipated improvement in oxygenation but there was no survival benefit. Both of these studies have been criticised on the grounds of their design, the heterogeneity of the patients enrolled, protocol violations, for only providing prone position for brief periods (≤ 8 hours per day) and for failing to adjust the ventilator settings in response to the improvement in gas exchange (not 'using the gain'). A Spanish study (Mancebo et al) achieved 20 hours per day in PP, did 'use the gain' to modify the ventilator settings (reduce FIO₂ and PEEP) and demonstrated a 25% relative reduction in ICU mortality and a 19% reduction in hospital mortality but, due to recruitment difficulties, it was terminated prematurely and also failed to achieve conventional significance.

In the study by Reutershan and colleagues⁵ changes in end-expiratory lung volume (EELV) in 12 patients with ARDS were measured over an eight hour period following manual turning from the supine to prone position. To their credit the authors give a clear description of how the patients were supported when in the prone position. Since change in thoraco-abdominal compliance is a major factor in the change in distribution of ventilation that results from proning, the way in which the thorax and abdomen are supported can be of great significance. EELV was measured by manually ventilating the patient on a rebreathing bag containing 1% sulphur hexafluoride in oxygen and values were derived for relative FRC (EELV/predicted FRC). Even in this small study the baseline data reveal a group of patients that is heterogeneous in regard to the aetiology of lung injury (pulmonary vs

extrapulmonary), the time from onset of ARDS and the level of positive end-expiratory pressure (PEEP) used. There was also a surprising variation in the relative FRC with the majority showing the expected significant volume loss but with some patients at or above predicted values. Eight patients (66%) were defined as 'responders' on the basis of $\geq 30\%$ increase in oxygenation index (PaO₂/FIO₂) but the time course of this improvement and the associated increase in EELV was variable with three patients achieving maximum recruitment within a few hours while in the other five patients recruitment continued through the entire proning period. Of the baseline parameters measured it was only EELV that predicted the gas exchange response to proning but the time course of the changes was patient specific and not predictable. The authors suggest that baseline EELV could be used to identify responders and serial measurements would permit appropriate 'dosing' of the therapy.

This is an interesting study that provides data that have rarely been collected when assessing the response to prone positioning but some issues need to be highlighted. The technique described to measure EELV is neither practical in routine clinical practice nor arguably desirable in view of the risk of de-recruitment associated with removing patients with severe lung injury from the ventilator, notwithstanding the authors' practice of clamping the endotracheal tube at end expiration in an attempt to maintain PEEP. The patients were also paralysed for the procedure. The fact that duplicate measurements showed no difference between the first and second measurement does not necessarily exclude the possibility that the procedure influenced the measurement, only that the effect, however large or small, is consistent. Most of the previous studies that have explored the baseline characteristics that may be predictive of benefit from proning have used a lesser ($\approx 20\%$) improvement in oxygenation to define a 'responder'. As an observational study it is understandable that the clinically determined ventilator settings were not changed during the study period but the tidal volumes used were consistently above the 6ml/kg demonstrated to have survival benefit in the ARDSnet study⁶ published in 2000 and the higher levels of PEEP used in some of the patients would not be supported by a more recent study from the same group⁷. Furthermore, improvements in gas exchange achieved in the responders were not used to permit more lung friendly ventilation by reducing the inspired oxygen concentration, tidal volume and PEEP. Although no mortality benefit would be expected in such a small study, it is interesting to note that survival was higher (75%) in the 'non responders' & than in the 'responders' (63%).

Despite its limitations this paper stimulates a number of important questions related not only to the use of the prone position but also to our management of patients with ARDS in general:

- (i) How should we determine the 'optimum' ventilator settings particularly with regard to PEEP? Should we be guided by gas exchange benefit alone or, as the evidence increasingly suggests, beware of producing high airway pressures and overinflating normal lung? Would measurement of EELV be an appropriate way of assessing the need for and the impact of recruitment manoeuvres?
- (ii) Which measurement should be used to define a 'responder' to a therapy such as proning and which intermediate measurements are the best surrogates for outcome benefit? If we become obsessed with an inappropriate intermediary endpoint the assessment of new therapies and the design of subsequent outcome studies will be seriously compromised. Could our fixation on improvement in indices of oxygenation be

flawed? A previous therapy for ARDS, inhaled nitric oxide, produced dramatic improvements in gas exchange in the short term but proved to have no long term benefit⁸ and may even have been harmful. The concept of ventilator induced lung injury (VILI) has now focussed our management not only on avoiding mechanical trauma due to high alveolar pressures and lung overdistension but also on avoiding ventilatory strategies that may cause increased cytokine release which may produce distant organ damage and contribute to multiple organ failure^{9,10}. Surely any gain in gas exchange obtained with proning should be used to reduce both the inspired oxygen concentration and PEEP to the level at which maximum recruitment of collapsed lung is achieved but without causing damaging overdistension of more normal lung

- (iii) Should we rely on large randomised controlled studies to decide how to manage patients with ARDS and thereby adopt a 'one size fits all' policy ignoring the heterogeneity of this patient population or attempt to tailor management to the individual patient using measurements such as EELV?

The recently introduced technique of electrical impedance tomography promises the opportunity of the bedside measurement not only of lung volumes but also the distribution of ventilation and perfusion within the lung in the ventilated patient and may prove to be a more feasible way of collecting the data that this paper suggests is important in assessing and titrating the use of prone positioning and other therapies that will hopefully improve the outcome from ARDS.

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