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What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome?

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Abstract *Objective*: To evaluate the effects of prone ventilation on respiratory parameters and extravascular lung water (EVLW) in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in order to characterise the optimal duration of ventilation in the prone position. *Design*: Prospective, observational study. *Setting*: Nine-bed general intensive care unit. *Patients*: Eleven patients with refractory hypoxaemia due to ALI/ARDS were prospectively investigated during 12 consecutive episodes of prone ventilation. *Interventions*: Ventilation in the prone position for 18 h. *Measurements and main results*: Measurements were obtained supine and after 1, 2, 6, 12 and 18 h in the prone position and 1 h after returning supine. There was a progressive improvement in PaO_2/fraction of inspired oxygen (FIO_2) ratio which reached significance after 12 h [121 (81–151) to 258 (187–329) torr; $p<0.05$]. EVLW index increased transiently at 1 h [14.2 (7.6–20.8) to 15.1 (9.0–20.2); $p=0.05$] and thereafter declined progressively and was significantly decreased at 18 h [12.1 (7.2–17.0); $p=0.043$]. The shunt fraction showed an early fall [0.41 (0.40–0.42) to 0.31 (0.30–0.32) at 1 h; $p<0.001$] preceding a subsequent progressive fall [0.22 (0.21–0.23) at 18 h; $p<0.001$]. *Conclusions*: Over the 18h period studied there was progressive improvement in gas exchange, pulmonary shunt and EVLW. Although it is not possible to exclude that improvement over this period was unrelated to prone positioning, these findings suggests that ventilation in the prone position for more prolonged periods may be required for optimal improvement and warrants further study.

Keywords Prone position · Acute respiratory distress syndrome · Hypoxia · Gas exchange · Mechanical ventilation · Extravascular lung water

Introduction

Prone positioning has been suggested since 1974 as a ventilatory strategy to improve oxygenation and pulmonary mechanics in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Considerable evidence exists to demonstrate the early beneficial effect of ventilation in the prone position in ALI or ARDS [1, 2, 3, 4, 5, 6]. Although this mode of ventilation can improve gas exchange, knowledge regarding the optimal duration of the prone position is uncertain. The early increase in oxygenation has been shown to be associated with a reduction in pulmonary shunt, probably due to more uniform regional ventilation and alveolar recruitment [1]. It has been suggested that alternative mechanisms may account for the benefit seen with more prolonged prone ventilation. Additional putative mechanisms include reduction in physiological and alveolar dead space, alteration in EVLW or pulmonary capillary permeability.

As no study to date has prospectively examined the duration of prone ventilation to achieve maximum benefit in patients with ALI and ARDS, the objective of this study was to evaluate the effect on respiratory parameters and EVLW to characterise the optimal duration of ventilation in the prone position.

Materials and methods

Study population

During a 6month period, patients with ALI or ARDS according to the criteria of the American European Consensus Conference [7] were prospectively studied. Subjects were enrolled if the ratio of PaO_2/FIO_2 was less than 300 torr despite 2:1 inverse ratio pressure-controlled ventilation with positive end-expiratory pressure (PEEP) greater than 10 cmH_2O. Patients with cardiogenic pulmonary oedema and spinal instability were excluded. All patients were studied while sedated with morphine and midazolam and paralysed with atracurium. The ventilatory settings and PEEP were maintained constant throughout the study period. Only FIO_2 was adjusted according to the clinical needs. Fluid support was unchanged throughout the study period and no diuretic therapy was used. The study was approved by the local research institute and consent was obtained from next of kin.

Measurements

Measurements were obtained supine (baseline), after 1, 2, 6, 12 and 18 h in the prone position and 1 h after returning to the supine position. All patients had a radial artery cannula and a pulmonary artery (PA) catheter (CCOmbo; Baxter Health Care, Irvine, Calif., USA). The PA catheter was attached to a monitor (Vigilance VGS2; Baxter Health Care) which measured continuous cardiac output.

A 5Fr fiberoptic thermistor catheter (Pulsiocath; Pulsion Medical Systems, Munich, Germany) was advanced into the descending aorta via a femoral artery and connected to the integrated fiberoptic monitoring system. A thermodilution curve was recorded in the aorta with the thermistor-tipped fiberoptic catheter. A computer (PiCCO; Pulsion Medical Systems) determined the thermal dilution curve and calculated intrathoracic blood volume index (ITBVI) and EVLW index (EVLWI). Mean thermal indicator dilution was calculated from three successive measurements [8]. Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 3 min of these measurements. Samples were analysed immediately using a blood gas analyser with integrated co-oximeter.

Statistics analysis

Parametric and non-parametric data are given as means (SD) or medians (IQR), respectively. Data were analysed using analysis of variance followed by the appropriate test for multiple comparisons between the supine position (as baseline control) and after 1,2,6,12 and 18 h in the prone position and 1 h after returning to the supine position. A value of p less than 0.05 was considered as statistically significant.

Results

Twelve consecutive episodes of prone ventilation in 11 patients were studied. One patient underwent prone ventilation on two occasions. The clinical characteristics of the patients are summarised in Table 1.

There was an initial marked improvement in PaO_2/FIO_2 ratio (Fig. 1) which was followed by a further progressive improvement that reached significance after 12 h [121 (81–151) to 258 (187–329) torr; $p<0.05$] and persisted after returning to the supine position [264 (205–337) torr; $p<0.05$]. Patients are classified as non-responders if the PaO_2/FIO_2 ratio does not increase by

Table 1 Patient characteristics (*BSI* body surface index, *MV* mechanical ventilation, *ARDS* acute respiratory distress syndrome, *PPH* post-partum haemorrhage)

Patient	Sex (M/F)	Age (years)	APACHE II	APACHE II predicted mortality	BSI (kg/m^2)	Duration of MV (days)	PaO_2/FIO_2 ratio	PEEP (cmH_2O)	Cause of ARDS	Outcome
1a	F	17	14	14	19	3	40.67	15	Meningococcal sepsis	Survivor
1b						12	16	15		
2	F	66	16	16	18	9	33.83	10	Peritonitis	Survivor
3	F	28	14	19	18	5	14.66	10	PPH/massive transfusion	Survivor
4	M	65	19	21	29	3	10.13	12	Post-lobectomy	Survivor
5	M	28	22	29	24	11	10.1	10	Pneumonia post-chemotherapy	Non-survivor
6	F	38	19	21	52	1	5.9	18	Eclampsia	Survivor
7	M	48	12	47	22	2	16.77	14	Pneumonia	Survivor
8	M	61	14	11	26	1	19.5	10	Post-pneumonectomy	Non-survivor
9	F	65	11	29	28	4	20.33	15	Faecal peritonitis	Survivor
10	F	42	13	28	21	8	15.85	15	Variceal bleed alcoholic liver disease	Non-survivor
11	M	49	20	35	32	1	11.04	15	Sepsis/massive transfusion	Survivor
Median (IQR)		48 (33–65)	14 13.5–19.5	21 17.5–32	24 20–30.5	3.5 (1.5–8.5)	15.9 (10.5–19.9)	14.5 (10–15)		

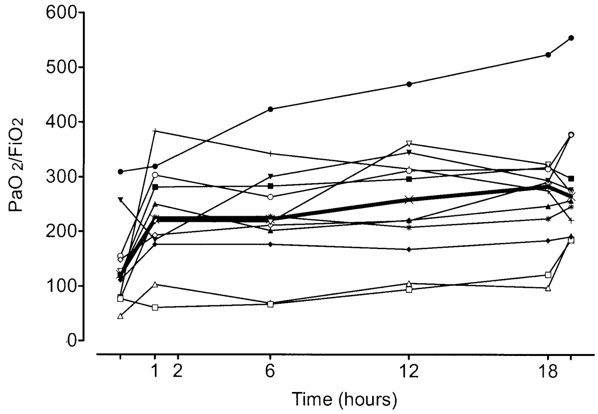

Fig. 1 Change in PaO_2/FIO_2 ratio during the study period. Individual data points with median (*v. bold line*). For clarity 2h data has been excluded from figure

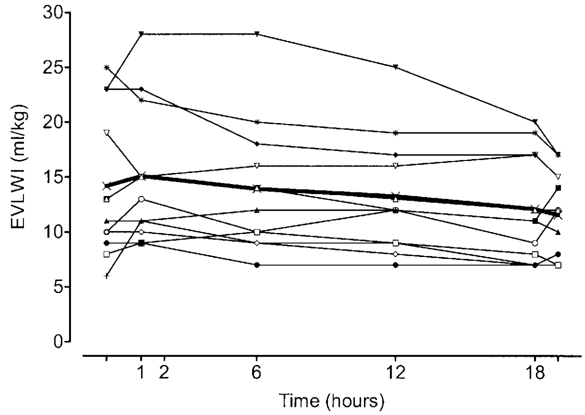

Fig. 2 Change in extravascular lung water index during the study period. Individual data points with mean (*v. bold line*). For clarity 2h data has been excluded from figure

Table 2 Haemodynamic and oxygen transport variables (*EVLWI* extravascular lung water index, Q_S/Q_T right to left intrapulmonary shunt, *HR* heart rate, *MAP* mean arterial pressure, *PAOP* pulmonary artery occlusion pressure, *CI* cardiac index, DO_2 oxygen delivery index, VO_2 oxygen consumption index)

	Baseline	Prone 1 h	Prone 2 h	Prone 6 h	Prone 12 h	Prone 18 h	Supine 1 h
PaO_2/FIO_2[a]	121	222	205	222	258[b]	282[b]	264[b]
(torr)	(81–151)	(180–292)	(186–260)	(188–292)	(187–329)	(203–315)	(205–337)
EVLWI[c]	14.2	15.1	14.0	13.9	13.3	2.1[b]	11.5[b]
(ml/m^2)	(7.6–20.8)	(9.0–20.2)	(7.9–20.1)	(8.0–19.8)	(8.1–18.5)	(7.2–17.0)	(7.7–15.3)
Q_S/Q_T[c]	0.41[d]	0.31[d]	0.29[d]	0.28[d]	0.23[d]	0.22[d]	0.21[d]
(0.40–0.42)	(0.30–0.32)	(0.28–0.30)	(0.27–0.29)	(0.22–0.24)	(0.21–0.23)	(0.20–0.22)	
HR[a]	111	115	117	114	109	115	107
(beats/min)	(96–128)	(101–126)	(97–126)	(100–126)	(95–118)	(95–116)	(90–114)
MAP[c]	78	82	83	79	87	84	84
mmHg	(66–80)	(66–98)	(72–94)	(69–89)	(75–99)	(70–98)	(70–98)
PAOP[c]	15	17	17	17	19	18	16
(mmHg)	(11–19)	(12–22)	(12–22)	(11–23)	(13–25)	(12–24)	(11–21)
CI[c]	4.7	4.9	4.9	4.7	4.6	4.1	4.0
($l/min/m^2$)	(3.5–5.9)	(3.4–6.4)	(3.4–6.4)	(3.7–5.7)	(3.4–5.8)	(3.1–5.1)	(2.8–5.2)
DO_2[c,e]	575	641	653	634	578	503	490
($ml/min/m^2$)	(435–715)	(480–802)	(504–802)	(514–753)	(441–715)	(416–590)	(361–619)
VO_2[c,e]	135	141	152	154	135	130	129
($ml/min/m^2$)	(108–162)	(105–177)	(122–182)	(110–198)	(114–146)	(107–153)	(99–159)

[a] Data median (IQR) and comparison performed with Friedman repeated-measures ANOVA
[b] $p<0.05$
[c] Data mean (SD) and comparison performed with one-way repeated measures ANOVA with Bonferroni correction
[d] $p<0.001$; [e] Data not available on one patient

more than 20%. There were three non-responders at 1 h, two at 2 h and one at 6 h, but by 12 h all patients had responded.

The EVLWI (Fig. 2) transiently increased at 1 h [14.2 (7.6–20.8) to 15.1 (9.0–20.2); $p=0.05$], thereafter declined progressively and was significantly decreased at 18 h [12.1 (7.2–17.0); $p<0.05$]. A consistent reduction in shunt fraction was seen in all patients (Table 2) with an initial early fall [0.41 (0.40–0.42) to 0.31 (0.30–0.32) at 1 h; $p<0.001$] preceding a subsequent progressive fall [0.22 (0.21–0.23) at 18 h; $p<0.001$]. As shown in Table 2, other measured parameters remained unchanged during the period in the prone position.

In terms of complications and outcome, dependent facial oedema was seen in all patients but was reversible once the patient was returned supine. Apart from minor cutaneous injury in two patients, no other complications occurred.

Discussion

This study showed an early improvement in oxygenation following prone positioning, as has been previously demonstrated. This study also provides additional findings. There is continuing improvement in gas exchange after this initial improvement, which does not appear to reach a plateau. Furthermore, this improvement is associated with progressive reduction in EVLW and pulmonary shunt which only become apparent after a more prolonged period in the prone position. The finding of progressive improvement in gas exchange is consistent with the findings from studies where patients have been ventilated prone for longer periods [2, 4, 5, 6]. However, these studies were methodologically flawed in that not all patients had ALI or ARDS and the frequency and duration of prone ventilation was variable. Furthermore, it was unclear from these studies if a plateau of improvement was reached, as changes in respiratory parameters were not prospectively measured.

An increase in gas exchange at 1–2 h has been used to predict response to prone positioning, however the validity of using this parameter can be questioned. In this study we demonstrated that although three patients were classified as non-responders at 1 h, by 12 h all patients had responded. Several studies have also reported delayed response to prone positioning [4, 5, 6]. Stocker [6] identified two groups, those showing an immediate response and those with a gradual response over a longer time period up to 24 h. On the basis of these findings it is suggested that it is not appropriate to use this test to predict response to prone positioning.

In our study all patients responded to ventilation in the prone position. Response rates as low as 58% [3] have been reported after 2 h in the prone position. With prolonged ventilation in the prone position, response rates of 100% [2, 6] have been reported. This suggests prolonged prone positioning is associated with increased response rates. As a result of a reduction in dependent atelectasis and pleural pressure gradient, regional ventilation is more homogeneous in the prone position. This causes a consequent reduction in ventilation and perfusion mismatch and a reduction in intrapulmonary shunt. Early increase in oxygenation has been shown to be associated with a reduction in pulmonary shunt, as was demonstrated in this study.

The significance of the alteration in EVLW in ARDS remains to be defined. Management of fluid balance based on an algorithm incorporating measurement of EVLW reduces the duration of mechanical ventilation and length of stay in intensive care [9]. In this study there was progressive reduction in EVLW after an initial transient increase. The mechanism of alteration in EVLW is uncertain. It may be related to progressive diuresis, which has been recently reported in a study of children with acute respiratory failure placed in the prone position for 12 h [10] although this was not examined in our study. Given EVLW is dependent on pulmonary perfusion [11], it is also possible that the reduction in EVLW may be due to changes in pulmonary perfusion which occur in the prone position [12]. The reduction in EVLW may contribute to the ongoing improvement in gas exchange and pulmonary shunt.

Some potential limitations of this study are worth mentioning. It is possible that improvement in the underlying disease process, unrelated to ventilation in the prone position, may account in part for the improvement seen over the study period. Equally, it is possible that the improvement was related to an intervention other than prone positioning, however, given that all patients received standardised management which was unchanged during the study period, this is less likely. Due to the small sample size of this pathophysiological study in which the majority of patients had extrapulmonary ARDS, it is uncertain if these results are applicable to a larger population and this requires further study.

In conclusion, our results show that, over the period studied, there was progressive improvement in gas exchange, pulmonary shunt and EVLW. Although it is not possible to exclude that improvement over this period was unrelated to prone positioning, these findings suggest that ventilation in the prone position for more prolonged periods may be required for optimal improvement. A randomised, controlled trial has recently demonstrated that prone ventilation for only 6 h daily for up to 10 days does not improve outcome [13]. Further studies examining prolonged ventilation in the prone position are warranted to determine whether outcome can be improved.

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