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Effect of positive end expiratory pressure and mean airway pressure on respiratory compliance and gas exchange in children with liver disease

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Abstract The effect of positive end expiratory pressure (PEEP) and mean airway pressure (MAP) on respiratory compliance and gas exchange was assessed in children with liver disease. In the first study of 12 patients, PEEP was decreased either by 3 cmH_2O below the baseline level (the child's original level) or to 0 cmH_2O and then increased to 3 cmH_2O above the baseline. Decreasing PEEP impaired compliance ($P < 0.01$), and oxygenation ($P < 0.05$), whereas increasing PEEP improved compliance ($P < 0.05$) and oxygenation ($P < 0.05$). Neither increasing nor decreasing PEEP caused significant changes in the carbon dioxide levels. In the second study, 24 children were studied at their baseline settings and then after increasing the PEEP by 3 cmH_2O while simultaneously lowering the peak inspiratory pressure (PIP) to maintain MAP constant (12 children had lung function measurements). In the group overall increasing PEEP while decreasing PIP resulted in an insignificant change in p_aO_2, but a significant increase p_aCO_2 ($P < 0.01$) and reduction in tidal volume ($P < 0.01$), the change in compliance was not significant. After a second period at the baseline settings, in 12 children inspiratory time (T_I) was increased while keeping MAP constant by reducing PIP. No significant change in p_aO_2 or compliance was experienced, but p_aCO_2 increased ($P < 0.05$) and tidal volume decreased ($P < 0.01$). In the other 12 children MAP was increased by prolonging T_I. Increasing MAP had a variable effect and the changes in p_aO_2 and p_aCO_2 were not significant. No critical MAP level with regard to oxygenation was demonstrated. We conclude that in children with liver disease, increasing PEEP can improve oxygenation and compliance, but the MAP level alone does not determine oxygenation.

Key words Compliance
Mechanical ventilation
Mean airway pressure
Positive end expiratory pressure

Abbreviations *FRC* functional residual capacity · *MAP* mean airway pressure · p_aO_2 arterial oxygen tension p_aCO_2 arterial carbon dioxide tension *PEEP* positive end expiratory pressure *PIP* peak inflating pressure T_I inspiratory time

Introduction

During mechanical ventilation, addition of positive end expiratory pressure (PEEP) recruits atelectatic areas and improves gas exchange, but if too high a level is used this will overdistend alveoli. In adults, it has been demonstrated that changes in gas exchange are paralleled by changes in compliance, the maximum compliance produced by increasing PEEP coincides with optimum lung function [13]. The reverse relationship has been demon-

strated in neonates in that even a modest elevation of PEEP level can both impair oxygenation [9] and cause a deterioration in compliance [2]. In contrast, in children with severe liver disease, increasing PEEP to 6 cmH_2O improved oxygenation [11]. Children with that diagnosis have low functional residual capacities (FRCs) [8] and thus elevation of PEEP may have improved oxygenation [11] by recruiting alveoli, hence increasing compliance. The aim of our first study was to test that hypothesis by documenting the effect of changes in PEEP level on compliance and gas exchange in children with severe liver disease.

Mean airway pressure (MAP) may be altered by changing the inspiratory time, flow, positive end expiratory or peak inspiratory pressure (PIP) level. In neonates oxygenation relates to the MAP level, regardless of how it is achieved [1]. Thus to improve oxygenation in that population, manoeuvres can be employed to increase MAP other than by altering PIP, which may consequently reduce complications due to barotrauma [6]. Limitation of barotrauma is also highly desirable in the ventilation of children, but unfortunately no data are available to assess the importance of MAP in determining oxygenation in the paediatric population. The aim of our second study was to provide such information.

Methods

Children with liver disease admitted to the intensive care unit at King's College Hospital were eligible for entry into the study. Patients were recruited once haemodynamically stable and when their blood gases had been within the desired range (pH 7.3–7.5, p_aO_2 10–20 kPa, p_aCO_2 3.5–7 kPa) for at least a 2-hour period without any change in ventilator settings. All patient care (physiotherapy, turning etc.) was completed 15 min prior to the commencement of each study.

Study 1

The children were initially studied at their original ventilator settings (baseline PEEP). PEEP was then decreased by 3 cmH_2O, in children whose baseline PEEP was less than 3 cmH_2O, the PEEP level was reduced to 0 cmH_2O (low PEEP level). The level was subsequently increased to 3 cmH_2O above baseline (high PEEP level). After each change to a new PEEP level the child was returned to the baseline PEEP. The patient remained at each setting for 20 min. During the study period no change was made in the other ventilator settings.

Study 2

The children were initially studied at their original ventilator settings (baseline). In the first phase of the protocol PEEP was increased by 3 cmH_2O and the PIP reduced so that the MAP remained at the baseline value. During these manoeuvres chest wall movement was observed to ensure that this remained adequate. After 20 min the patient was then returned to the baseline settings for a further 20-min period.

The study population was then divided into two, the first subgroup followed the protocol as outlined in study 2 (a) and the second subgroup the protocol as outlined in study 2 (b).

Study 2 (a)

The inspiratory time (T_I) was increased from 25% to 33%, but the MAP was kept constant by reducing the PIP. PEEP and rate remained at the baseline settings. The patient remained at the new T_I for 20 min and was then returned to the baseline settings.

Study 2 (b)

The MAP was increased by lengthening the inspiratory pause time from 10% to 20%. The PIP, PEEP and rate remained at the baseline values. Ventilator rate was kept constant. The patient remained at the new MAP level for 20 min and then was returned to the baseline settings.

Blood gas measurements

All patients had indwelling arterial catheters which had been sited for clinical purposes. From these lines arterial blood gases were sampled after each 20-min period and analysed immediately.

Compliance measurements

Compliance was measured, at the end of each 20-min period, by determining the volume change resulting from a positive pressure inflation. A pneumotachograph (Mercury F100L) attached to a Validyne pressure transducer (range ± 2 cmH_2O) was inserted between the endotracheal tube and ventilator circuit. The pneumotachograph measured flow changes which were electronically integrated to give volume (Gould 13-4615-70). Airway pressure was measured from the child's side of the pneumotachograph using a Validyne pressure transducer (range ± 88 cmH_2O). Flow, volume and pressure changes were recorded simultaneously on a Polygraph (Gould 3000). The volume change from the positive pressure inflation was divided by the pressure difference between the PIP and the PEEP and thus compliance was determined. Expiratory volumes were used in the calculation. Only positive pressure inflations occurring during a period of apnoea were considered. Compliance was calculated from the mean of ten such inflations. Compliance was not measured in the patients who took part in study 2 (b) i.e. patients 13–24 (inclusive).

Analysis

Compliance, p_aO_2 and p_aCO_2 at the study settings were compared to the mean achieved at the baseline levels. Differences were assessed for statistical significance using the paired Wilcoxon signed rank test.

Trial size

A study population of 12 children was required to detect a change in compliance of 0.1 ml/cmH_2O per kilogram with 80% power at the 5% level and a difference of 1 kPA in p_aO_2 with 90% power at the 5% level between different ventilator settings.

Patients

Twenty-four children were recruited into the study, all suffered from liver disease (Table 1) and none had a primary pulmonary disorder. The children were all ventilated by volume controlled ventilators. The patients had uncuffed endotracheal tubes. Thirteen

Table 1 Patient characteristics (+ Paralysed, –, non-paralysed, *bpm* breaths per minute, *ARDS* adult respiratory distress syndrome)

Patient	Age (years)	Diagnosis	Paralysed	PIP (cmH_2O)	MAP (cmH_2O)	PEEP (cmH_2O)	Rate (bpm)	I:E
1	13.3	Orthotopic liver transplantation	+	22	8.0	3	12	1:3
2	3.9	Orthotopic liver transplantation	–	20	7.8	3	18	1:3
3	3.7	Portal hypertension/ARDS	+	26	11.0	5	20	1:3
4	7.9	Orthotopic liver transplantation	+	21	7.2	3	18	1:2
5	9.5	Orthotopic liver transplantation	–	20	6.3	3	15	1:3
6	3.1	Orthotopic liver transplantation	+	24	8.2	2	30	1:3
7	0.1	Hepatitis	+	23	10.5	3	30	1:2
8	1.3	Fulminant hepatic failure	+	25	9.5	5	32	1:3
9	13.6	Orthotopic liver transplantation	–	24	10.0	3	15	1:2
10	3.6	Chronic active hepatitis	+	20	6.7	2	27	1:3
11	0.9	Orthotopic liver transplantation	+	26	8.6	2	20	1:3
12	3.4	Orthotopic liver transplantation	+	26	9.3	4	26	1:3
13	12.0	Extrahepatic biliary atresia, portal hypertension	+	35	18.7	10	16	1:2
14	10.9	Orthotopic liver transplantation	–	20	9.2	4	16	1:3
15	10.1	Hepatocellular failure, typhoid	–	22	8.7	4	25	1:2
16	4.8	Orthotopic liver transplantation	–	25	8.5	5	22	1:2
17	2.5	Hepatocellular failure, pneumococcal sepsis	+	27	7.8	0	16	1:3
18	2.4	Septicaemia, post orthotopic liver transplantation	–	36	14.6	6	20	1:2
19	2.4	Orthotopic liver transplantation	–	29	11.6	4	19	1:2
20	13.0	Congenital hepatic fibrosis	–	16	4.9	2	14	1:3
21	9.8	Hepatocellular failure, haemolytic uraemic syndrome	–	32	8.4	3	16	1:3
22	1.3	Hepatocellular failure	+	25	8.2	3	30	1:2
23	0.3	Hepatocellular failure	+	28	14.0	3	35	1:2
24	0.8	Hepatocellular failure, immune deficiency	–	23	9.3	3	40	1:2

Table 2 Changes in p_aO_2 and compliance related to PEEP level

Patient no.	p_aO_2 (kPa)			Compliance ($ml/cmH_2O/kg$)		
	PEEP: low level	PEEP: baseline	PEEP: high level	PEEP: low level	PEEP: baseline	PEEP: high level
1	16.2	16.4	17.7	0.40	0.44	0.47
2	13.5	16.0	15.3	0.49	0.52	0.56
3	10.0	10.6	10.9	0.50	0.46	0.43
4	12.4	15.3	20.8	0.22	0.42	0.53
5	10.3	11.2	11.7	0.32	0.47	0.43
6	13.0	16.9	17.7	0.33	0.42	0.89
7	7.5	9.8	11.1	0.15	0.25	0.22
8	13.8	15.2	15.9	0.38	0.42	0.49
9	19.0	18.9	18.4	0.20	0.30	0.28
10	19.0	20.0	20.5	0.39	0.48	0.62
11	10.8	11.6	12.8	0.24	0.28	0.32
12	18.0	13.7	14.0	0.30	0.33	0.37
Median	13.7	15.2	15.6	0.32	0.42	0.43

children were receiving neuromuscular blocking agents and all the patients were sedated with either fentanyl or propofol throughout the study.

This study was approved by the King's College Hospital Ethics Committee.

Results

Study 1

Compared to baseline, reducing PEEP to the low level significantly impaired oxygenation ($P < 0.05$), whereas increasing PEEP to the high level significantly improved oxygenation ($P < 0.05$) (Table 2). Changes in PEEP, how-

ever, caused no significant changes in p_aCO_2; baseline median p_aCO_2 4.4 kPA (range 3.5-5.9 kPa); low level median 4.3 kPA (range 3.5–6.1 kPa); high level median 4.4 kPa (range 3.2–6.1 kPa). Compared to baseline, reducing PEEP to the low level significantly impaired compliance ($P < 0.01$) and increasing PEEP to the high level significantly improved compliance ($P < 0.05$) (Table 2).

Study 2

Patient 13 did not tolerate either the reduction in PIP or increase in PEEP and thus blood gas data was analysed from 23 patients. Decreasing the PIP and increasing PEEP did not result overall in any significant changes in p_aO_2, the median p_aO_2 at the baseline settings was 12.7 kPa (range 7.6–23.5) and at the high PEEP, low PIP level was 13.5 kPa (range 6.9–26.1). One patient (patient 22) had a dramatic fall in oxygenation from 13.2 to 7.6 kPa. The change in PIP and PEEP resulted overall in a significant increase in p_aCO_2 from a median of 4.5 kPa (range 3.3–6.4 kPa) at baseline to a median of 5.7 kPa (range 2.9–8.3 kPa) at the high PEEP, low PIP level ($P < 0.001$). The decrease in PIP and increase in PEEP resulted in a significant reduction in tidal volume ($P < 0.005$) from a median of 7.9 ml/kg (range 5.0–9.1 ml/kg) to a median of 5.8 ml/kg (range 3.3–8.3 ml/kg), but no significant change in compliance from a median 0.42 ml/cmH_2O per kilogram (range 0.25–0.52 ml/cmH_2O/kg) to a median of 0.45 ml/cmH_2O per kilogram (range 0.21–1.07 ml/cmH_2O/kg).

Study 2(a)

Increasing the T_I and decreasing PIP to keep MAP constant did not result in any significant change in p_aO_2. At the baseline settings the median p_aO_2 was 13.6 kPa (range 7.6–23.5 kPa) and at the increased T_I the median p_aO_2 was 15.3 kPa (range 8.4–21.5 kPa). Despite maintaining MAP, on increasing T_I but decreasing PIP a significant increase in p_aCO_2 was experienced from a median of 4.8 kPa (range 3.3–6.3 kPa) at baseline settings to a median of 4.9 kPa (range 4.3–6.1 kPa) at the increased T_I ($P < 0.05$). Lengthening T_I was also associated with a significant reduction in tidal volume from a median of 7.9 ml/kg (range 5.0 to 9.1 ml/kg) at the baseline to 7.0 ml/kg (range 3.0–8.6 ml/kg) at the longer T_I ($P < 0.004$), there was, however, no significant change in compliance being a median of 0.42 ml/cmH_2O per kilogram (range 0.25–0.52 ml/cmH_2O/kg) at the baseline settings to a median of 0.38 ml/cmH_2O per kilogram (range 0.14–0.56 ml/cmH_2O/kg) at the increased T_I.

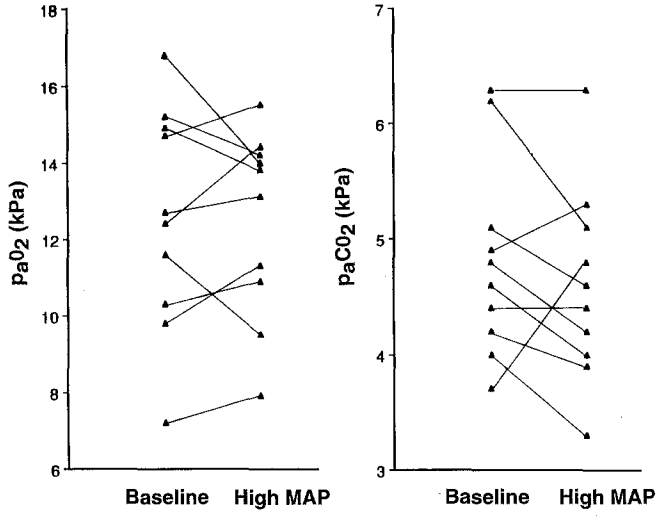

Fig. 1 p_aO_2 and p_aCO_2 at baseline settings and on increasing MAP. Individual data demonstrated by linked data points

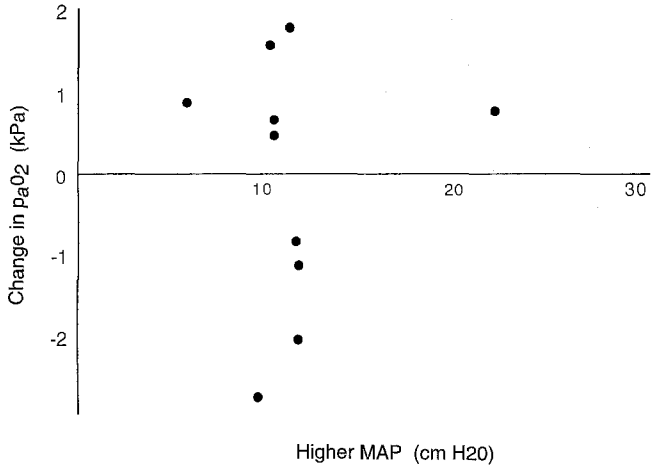

Fig. 2 The change in oxygenation related to the higher MAP level achieved in protocol 2(b). Individual data demonstrated

Study 2(b)

Patients 18 and 23 both became agitated requiring suction when T_I was increased to elevate MAP and this part of the study was not completed in those patients. Thus blood gas data were available from ten patients. Lengthening the inspiratory time resulted in a median increase in MAP of 16% (range 6%–40%), that is a median absolute increase in MAP of 1.6 cmH_2O (range 0.5–3.3 cmH_2O). This maneuvre did not result overall in significant changes in p_aO_2 (median change 0.4 kPa, range –2.8 to 1.7 kPa) or p_aCO_2 (median change –0.5 kPa, range –0.9 to 1.0 kPa), but the effect varied between individuals (Fig. 1). The change in oxygenation was not dependent on the MAP level achieved by lengthening the inspiratory time (Fig. 2).

Discussion

These data confirm our hypothesis as, in the majority of patients, maximum oxygenation was associated with the highest compliance. In 9 of the 12 children increasing PEEP from the baseline to the high level improved both compliance and oxygenation and, in addition, in 6 patients the effect on compliance of changing PEEP levels exactly mirrored the effect on blood gases. Our data thus confirms the findings in adults [13] that compliance measurements may successfully guide the choice of an appropriate PEEP level to optimize gas exchange. Sivan et al. [12] studied the relationship of changes in compliance and FRC to PEEP levels. They found that the PEEP level which normalized FRC did not necessarily result in the maximum compliance. Although the difference between the two levels was usually small, the PEEP level associated with maximum compliance varied from being above or below that which normalized FRC. Those data [12] suggest no additional benefit would be gained from measuring FRC as well as compliance to determine optimum PEEP levels.

An earlier study in children investigated PEEP levels from 0 to 18 cmH_2O [12], the patients suffered from adult respiratory distress syndrome or diffuse pneumonia. We felt the diagnoses of our patients (Table 1) more closely resembled those of the adults examined by Suter et al. [13], that is respiratory failure following major surgical procedures or metabolic processes. In the adult cohort [13], increasing PEEP beyond 6 cmH_2O resulted in a decrease in total respiratory compliance. As we wished to avoid such a complication, we felt it prudent to study the majority of our patients in the range of 0 to 6 cmH_2O of PEEP. The present findings confirm [11] in children with stiff lungs, increased PEEP levels to at least 6 cmH_2O will improve oxygenation. Our results demonstrate this advantageous effect is associated with an increase in compliance.

In the second study we found altering PIP and PEEP, but keeping MAP constant, resulted in no significant overall effect in oxygenation. We do not feel, however, that these results demonstrate that MAP is the key determinant of oxygenation, as the effect of the changes in ventilator settings varied between individual children, one child even experiencing a dramatic fall in p_aO_2. We have previously found that elevation of PEEP with PIP constant, universally increased oxygenation in a population of children with liver disease [11]. Interpreting the present data in the light of those findings [11] would suggest that the reduction in PIP, despite maintaining MAP constant, was responsible for the reduction in p_aO_2 experienced by certain patients.

In some patients, we were able to reduce PIP and by simultaneously increasing PEEP maintain oxygenation. We had tried to avoid an adverse effect on gas exchange by only studying children who had adequate chest wall movement at the new settings. As a consequence patient 13 was not included in the analysis of the results from the first part of the protocol. Yet the other patients experienced an increase in p_aCO_2. Our results thus demonstrate effective ventilation cannot be assumed even though the child's chest is apparently moving well. We previously found increasing PEEP by 3 cmH_2O but keeping constant PIP did not result in significant changes in p_aCO_2 [11]. There was, however, a significant difference in the p_aCO_2 levels at PEEP 0 cmH_2O and PEEP 6 cmH_2O, the same PIP being used at both PEEP levels [11]. In this study we increased PEEP by 3 cmH_2O and decreased PIP by approximately the same increment so that MAP remained constant. This reduced the pressure swing (PIP-PEEP) by approximately 6 cmH_2O and this difference was sufficient to compromise tidal volume which presumably caused the carbon dioxide retention.

Increasing T_I but keeping MAP constant by a compensatory reduction in PIP resulted in a variable change in p_aO_2, again suggesting MAP is not the sole determinant of oxygenation. As in our earlier study the reduction in PIP was associated with a reduction in tidal volume, despite in the later protocol we had increased T_I. The reduction in tidal volume caused a significant increase in p_aCO_2.

In certain patients MAP was allowed to rise by increasing the inspiratory time and a variable effect was noted on oxygenation. Although all of our study patients were sedated, only a minority were paralysed and thus most were capable of making breathing movements during mechanical ventilation. In neonates prolonging the inspiratory time beyond a critical level has been associated with stimulation of active expiratory efforts [3, 4]. Active expiration reduces inspiratory volume [7] and can impair oxygenation [5]. Changes in the nature of the patient's respiratory activity thus might have contributed to the deterioration in blood gases experienced by certain of our patients when the inspiratory time was prolonged.

We chose to study children with severe liver disease, as we expected that group to be relatively homogenous and likely to have similar lung function abnormalities. Children with severe liver disease have small volume, noncompliant lungs [10], that is similar to the abnormalities found in newborns with respiratory distress syndrome. In lambs with severe respiratory distress syndrome, elevation of MAP up to 15 cmH_2O consistently improved oxygenation [1]. In the present study, however, the effect on oxygenation of increasing MAP was independent of the higher MAP level achieved (Fig. 2). For example, elevation to approximately 10 cmH_2O resulted in improved oxygenation in some, but deterioration in other children. These results suggest the effect of raising MAP on lung volume varied between patients; reducing atelectasis and hence improving gas exchange in some, but in others causing overdistension and impairing oxygenation.

Our data demonstrate the effect of raising MAP in the paediatric population requires careful individual assessment. Children requiring paediatric intensive care are het-

erogeneous in diagnosis and age. The present results suggest even in a relatively homogeneous group, the effect of alterations in MAP cannot be predicted. It seems unlikely that policies can be made regarding the attainment of a critical MAP level for a particular disease entity and certainly such a level cannot be predicted from results in neonates [1].

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