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Hydrochloric acid-induced lung injury: effects of early partial liquid ventilation on survival rate, gas exchange, and pulmonary neutrophil accumulation

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Abstract *Objective:* Partial liquid ventilation can improve respiratory functions in acid-induced lung injury. We studied the effects of the interval between induction of injury and initiation of partial liquid ventilation on survival, gas exchange, and pulmonary neutrophil accumulation. *Material and methods:* Anesthetized rats were randomly assigned to one of five groups ($n = 6$ per group). Group 1 served as the control group, in the other groups an extended lung injury was induced by intratracheal instillation of hydrochloric acid. Whereas lungs of group 2 were gas-ventilated, group 3 received an early partial liquid ventilation (5 min after acid instillation) and group 4 a delayed partial liquid ventilation (30 min after acid instillation, 5 ml/kg perfluorocarbon). Group 5 received an additional continuous perfluorocarbon application of 5 ml·kg^{-1}·h^{-1} (30 min after acid instillation). Blood gases were measured with an intravascular blood gas sensor. *Results:* Acid instillation resulted in a marked decrease in PO$_2$-values within 30 min (from 481±37 mmHg to 128±71 mmHg, FiO$_2$ 1.0). Survival rate of the study period (12 h) was higher with early partial liquid ventilation. We observed no differences between groups in peak PO$_2$-values during treatment. Histopathological examination, however, showed less pulmonary neutrophil accumulation in lungs of the early partial liquid ventilation group when compared to the delayed partial liquid ventilation group. *Conclusions:* Our results suggest that early partial liquid ventilation increases survival after extended acid-induced lung injury. While effects on arterial oxygenation appear not to predict acute survival we observed less intrapulmonary neutrophil accumulation with early partial liquid ventilation.

Keywords Rats · Acid aspiration · Partial liquid ventilation

Introduction

Acid aspiration-induced lung injury is recognized as a serious cause of morbidity and mortality in intensive care medicine. The resulting acute respiratory distress syndrome includes pulmonary edema, alveolar collapse, and impairment in gas exchange [1, 2, 3]. It is attributed to direct chemical effects of hydrochloric acid on the alveolar and capillary membranes occurring within the first minutes after the injury as well as to marked inflammatory responses occurring in a later phase [4, 5, 6, 7, 8, 9].

Partial liquid ventilation has been shown to improve gas exchange and lung mechanics in vivo [10, 11, 12] and to reduce the acid-induced increase in capillary filtration coefficients in isolated blood perfused lungs [13]. In adult sheep with acute lung injury following intratracheal administration of hydrochloric acid (2 ml/kg of 0.05 N) the tracheal instillation of 30 ml/kg perfluorocarbon 10 min after induction of the injury resulted in higher arterial

PO$_2$-values when compared to gas-ventilated control animals [10]. Similar results were observed in piglets with a lung injury due to instillation of gastric aspirate. In these animals, partial liquid ventilation (30 ml/kg perfluorocarbon) was started 60 min following lung injury [11]. In addition, rats receiving 7 ml/kg perfluorocarbon 30 min after the injury had significant higher arterial PO$_2$-values compared to a control group [12]. In our own experiments in isolated blood perfused rabbit lungs, filtration coefficients after acid-induced injury were significantly reduced with the instillation of 5 ml perfluorocarbon/kg body weight [13]. These studies thus suggest that the instillation of perfluorocarbons improves gas exchange in the acute phase following acid-induced lung injury. However, the limited study periods of these investigations (4–6 h) do not allow conclusions regarding whether the improved gas exchange during partial liquid ventilation also increases survival rate. In addition, it also remains unclear what role the interval between induction of lung injury and instillation of perfluorocarbons plays regarding effects on survival rate, gas exchange, and pulmonary neutrophil accumulation, which is strongly associated with inflammatory reactions following acid aspiration [4, 5, 6, 7, 8, 9]. Because the developing lung injury following acid aspiration is a rather dynamic process we hypothesize that early initiation of partial liquid ventilation within the first minutes after the injury has superior effects on these variables than a delayed initiation. To study these effects we instilled hydrochloric acid into the trachea of anesthetized and mechanically ventilated rats with the intention to induce an extended lung injury with an expected survival time of less than 3 h. Subsequently, we determined the effects of early (5 min after induction of lung injury) and delayed partial liquid ventilation (30 min after induction of lung injury), as well as a continuous instillation of perfluorocarbons on survival rate and gas exchange for a study period of 12 h. At the end of the experiments, we determined pulmonary neutrophil accumulation to study the effects on neutrophil recruitment into the injured lungs.

Materials and methods

Animal preparation

The study was performed in accordance with the principles of laboratory animal care (NIH publication No. 86–23, revised 1985) and with approval of the local District Animal Investigation Committee. Male adult Wistar rats with a body weight between 362 g and 422 g (388±12 g, mean±standard deviation) were anesthetized with 200 mg/kg s-ketamine (Ketanest S, Parke-Davis, Berlin, Germany) injected intraperitoneally. Thereafter, the trachea was intubated with a 14-gauge cannula (Venflon, Becton Dickinson, Helsingborg, Sweden) and the lungs were ventilated with a small animal ventilator (mod. 40–1003, Harvard Apparatus, Edenbrige, UK) using the following respiratory settings: a tidal volume of 6–8 ml/kg body weight, a respiratory rate of 60–90

breaths/min, an inspiratory/expiratory ratio of 1:1, an end-expiratory pressure of 5 cmH$_2$O, and an inspiratory oxygen concentration of 1.0. Medical gas was supplied by AGA Linde Healthcare (Unterschleissheim, Germany). Anesthesia was maintained by infusion of 25 mg·kg^{-1}·h^{-1} α-chloralose (Sigma Chemical, St. Louis, Mo., USA) via a jugular venous catheter (24 G, Introcan-W, Braun, Melsungen, Germany). In addition, 5 ml/kg body weight/h saline (0.9%, Braun, Melsungen, Germany) was infused intravenously via this catheter to compensate for fluid losses.

Measurements

Blood gases and pH were measured continuously with an intravascular blood gas sensor. For this purpose a 20-gauge cannula (Abbocath-T, Abbott, Sligo, Ireland) was placed in the left carotid artery. Via this cannula the blood gas sensor (Paratrend 7+, Diametrics Medical, High Wycombe, UK) was advanced into the thoracic aorta allowing the tip (approximately 3 cm in length) to float freely in the aortal lumen. This sensor has, according to the manufacturer, a precision of ±10% for PO$_2$-values between 20–500 mmHg and of ±3 mmHg for PCO$_2$-values between 10–80 mmHg. In vivo drift was observed to be 0.03 mmHg/h for PO$_2$ and 0.15 mmHg/h for PCO$_2$. After placement of the sensor a 20-min stabilization period was allowed before the monitor was calibrated in vivo with an arterial blood gas sample (ABL700, Radiometer, Copenhagen, Denmark). Blood temperature (measured with a thermistor integrated in the blood gas sensor) was maintained above 37.5 °C by a heating pad and a warm air ventilator (bair hugger, Augustine Medical, Eden Prairie, Minn., USA).

Experimental protocol

After instrumentation the rats were observed for 20 min. Following this stabilization period the animals were randomly assigned to a control group ($n = 6$) or to a lung-injury group ($n = 24$). Whereas the animals of the control group (group 1) were mechanically ventilated without further injury or treatment, the animals of the lung-injury group received an intratracheal instillation of hydrochloric acid (0.1 N, 2.5 ml/kg body weight). After induction of lung injury these animals were again randomly assigned to different groups. Animals of group 2 were gas-ventilated (FiO$_2$ = 1.0) and animals of group 3–5 received either an early or a delayed partial liquid ventilation. In group 3 (early partial liquid ventilation) a single dose of perfluorocarbon (5 ml/kg) was instilled 5 min after the injury. In group 4 (delayed partial liquid ventilation) the same dose was instilled 30 min after the injury. Animals of group 5 received a continuous instillation of 5 ml/h in addition to the delayed instillation of 5 ml/kg perfluorocarbon. Animals were observed until they died (cardiocirculatory arrest) or the study period of 12 h following the induction of lung injury was over. Animals that survived the 12-h study period were killed with an overdose of α-chloralose.

Partial liquid ventilation

The perfluorocarbon compound used (PF-5080, 3 M, Neuss, Germany) had the following characteristics: chemical structure C$_8$F$_{18}$, specific gravity 1.77 g/ml, surface tension 15 dynes/cm, vapor pressure 44 torr (5.9 kPa) at 25 °C, and dynamic viscosity 1.4 mPa·s. Perfluorocarbon was instilled prewarmed (37 °C) and oxygenated via a side port of the endotracheal tube which was located above the carina. Instillation was performed over a period of 30 s with continued ventilation. A meniscus of perfluorocarbon was present at the completion of the instillation.

Pulmonary neutrophil accumulation

Immediately after the rats died or were killed their chest was opened by sternotomy and lungs and trachea were removed. Lung specimens from different lung regions were fixed in 4% formaldehyde solution, embedded in paraffin wax, cut into sections (3 μm), de-waxed, and stained with hematoxylin and eosin. A duplicate tissue section was stained for naphthol-ASD-chloroacetate esterase. In three random sections per lung region the number of neutrophils was counted in light microscopic images (magnification ×400). For this purpose, five fields per sample were randomly selected, examined, and documented with a digital camera. The investigator determining neutrophil count was blinded to the origin of the section. To quantify pulmonary neutrophil accumulation the mean neutrophil number of five random fields per sample were determined.

Statistical analysis

Data are presented as mean±standard deviation unless otherwise indicated. In the control group we tested differences between initial and final blood gases at the beginning and at the end of the experiments with a t-test. In the acid-injured groups, we tested differences of survival rates between the gas-ventilated and the partial-liquid ventilation groups with Fisher's exact test. Individual time courses of blood gases are shown for all animals because of the heterogeneous courses and variable survival times. We tested differences between groups at three time points: before and after the induction of lung injury, and at the peak PO_2-value during the treatment. For these tests Bonferroni t-test was used to analyze differences between group 2 (gas-ventilation) and groups 3–5. Differences in pulmonary neutrophil number between the partial liquid ventilation groups were tested by t-test. A two-tailed P-value of less than 0.05 was considered statistically significant.

Results

In the non-injured control group we observed no differences between initial and final PO_2- and PCO_2-values (465±39 mmHg versus 505±29 mmHg, 38±3 versus 44±7 mmHg, respectively). There were also no differences between the initial blood gases of the five groups before the induction of lung injury: mean PO_2-values ranged between 465±39 mmHg and 495±45 mmHg, and mean PCO_2-values between 38±4 mmHg and 43±3 mmHg, respectively.

Intrabronchial instillation of hydrochloric acid resulted in a marked decrease in arterial PO_2- and pH-values and an increase in PCO_2 within 30 min in all lung-injured animals. The individual time courses of the blood gases are shown for all animals in Fig 1, Fig. 2, and Fig. 3. Following the initial decrease in arterial oxygen tension, almost all animals showed a subsequent recovery over several hours and a final decrease. Peak PO_2-values during treatment of the three partial liquid ventilation groups (groups 3, 4, and 5) did not differ significantly from the values of the gas-ventilated group (group 2), Table 1.
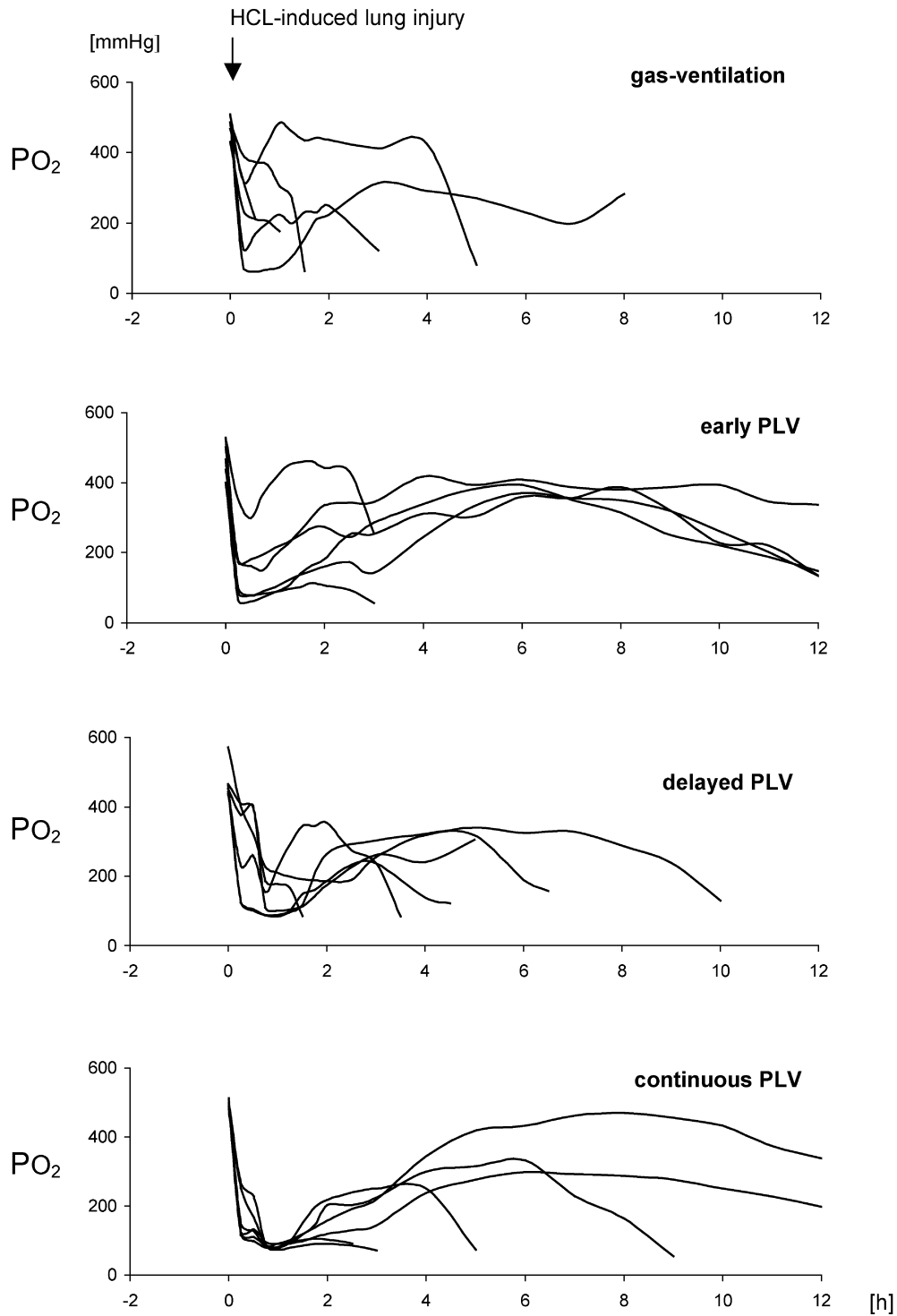
In the non-injured control group (group 1) five of six animals survived the 12-h study period, and one animal died after 11 h (Fig. 4). While no acid-injured gas-ventilated animal survived this period, four of six animals with early partial liquid ventilation (group 3) survived (P=0.03). In contrast, no animal of group 4 (delayed partial liquid ventilation) survived and two animals of group 5 survived.

Pulmonary neutrophil accumulation after acid-induced lung injury at the end of the experiments was most pronounced in the gas-ventilated lungs (Fig. 5 and Fig. 6). Compared to gas-ventilation, fewer neutrophils were counted in lungs of group 3 (early partial liquid ventilation)(P<0.001) and of group 5 (delayed and continued partial liquid ventilation) (P=0.007). We observed a significant difference in neutrophil accumulation between the early and delayed partial liquid ventilation group (P=0.006). Irrespective of the groups, more neutrophils were present in the lungs of the 18 non-surviving animals when compared to the lungs of the six surviving animals (scores 46±14 versus 28±12, P <0.001).

Table 1 Blood gases before (baseline) and after induction of acid-induced lung injury as well as during treatment. Data from anesthetized rats (n = 6 per group), presented as mean±SD; pH-values are given as median and range. The data during treatment refer to the time points with peak PO_2-values during the recovery period following acid instillation. For statistical tests we calculated H^+-concentration from pH = - log (H^+). There were no significant differences between the gas-ventilated group and the three PLV-groups (P >0.05 for all variables).

		Gas-ventilation	Early PLV	Delayed PLV	Continuous PLV
PO_2 (mmHg)	Baseline	481±27	447±46	488±82	495±9
	Lung injury	161±90	140±82	117±40	82±6
	During treatment	350±99	345±113	302±45	258±131
PCO_2 (mmHg)	Baseline	38±4	41±2	41±4	43±3
	Lung injury	62±25	57±13	60±9	64±13
	During treatment	55±8	52±11	61±12	61±14
pH	Baseline	7.39 (7.37–7.47)	7.42 (7.39–7.46)	7.38 (7.34–7.46)	7.42 (7.39–7.47)
	Lung injury	7.20 (7.15–7.33)	7.31 (7.22–7.44)	7.23 (7.18–7.29)	7.26 (7.16–7.31)
	During treatment	7.33 (7.29–7.42)	7.31 (7.24–7.39)	7.25 (7.20–7.30)	7.25 (7.16–7.32)
H^+ (nmol/l)	Baseline	40.9±6.4	37.8±2.7	41.5±3.5	37.8±2.4
	Lung injury	62.5±14.6	49.4±7.3	58.7±5.6	54.9±6.7
	During treatment	51.1±6.2	49.5±5.7	55.9±4.2	55.9±8.1

Fig. 1 Individual time courses of arterial PO$_2$-values of anesthetized and mechanically ventilated rats following acid-induced lung injury. Data from 24 rats assigned randomly to four groups ($n = 6$ in each group). While one group was gas-ventilated the other groups received either a single perfluorocarbon instillation 5 min after acid instillation (early PLV) or 30 min after acid instillation (delayed PLV), or received in addition to a delayed instillation a continuous instillation (continuous PLV) until the animals died.

Fig. 2 Individual time courses of arterial PCO_2-values of anesthetized acid-injured rats. Data from 24 rats assigned randomly to four groups ($n = 6$ in each group).
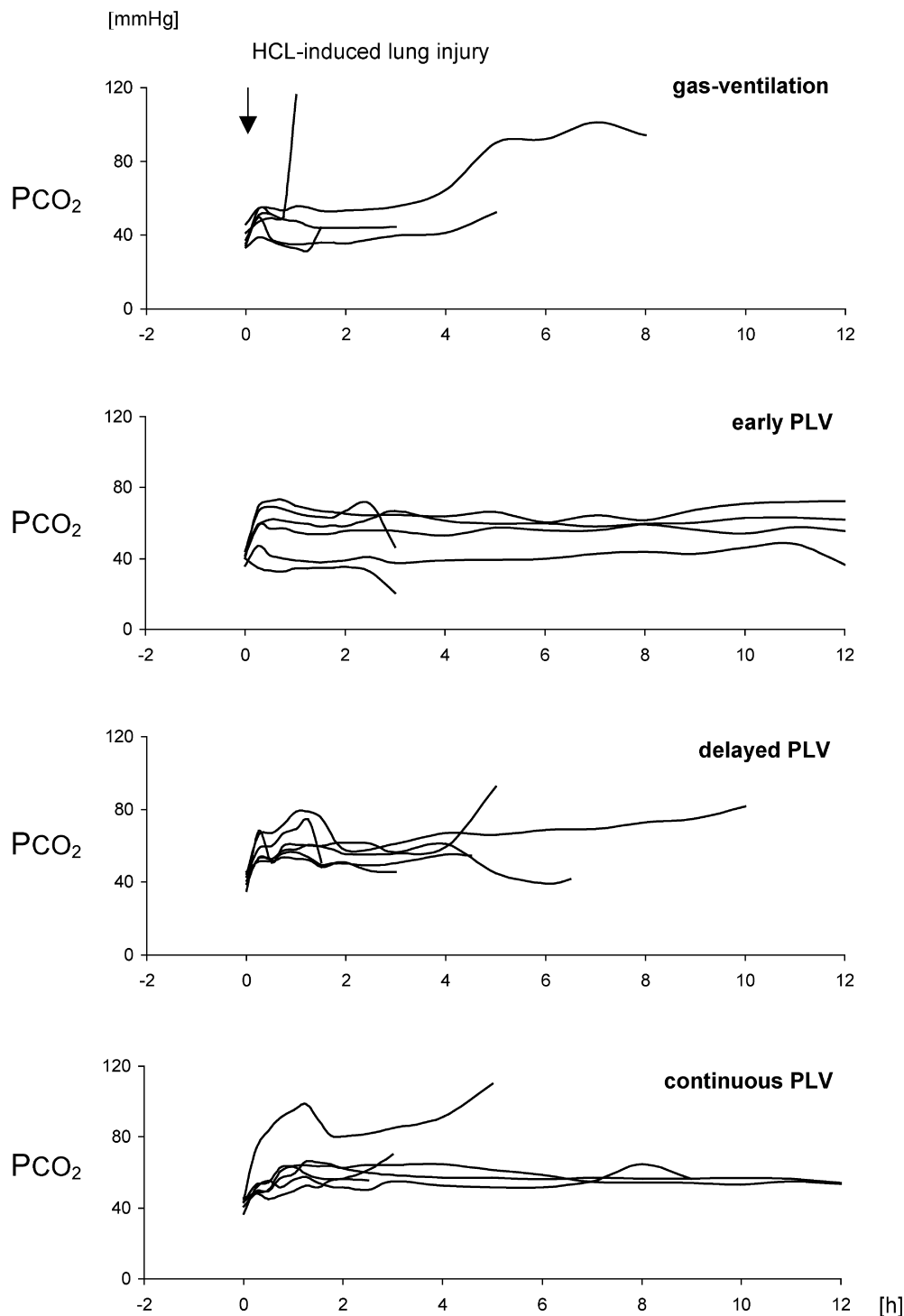

Discussion

The aim of our study was to determine the effects of early and delayed initiation of partial liquid ventilation on survival rate, gas exchange, and pulmonary neutrophil accumulation of rats with an extended acid-induced lung injury. We observed a higher survival rate when partial liquid ventilation was started early. While peak arterial oxygen tensions during the treatment after the injury did not differ between the various groups, we observed a decrease in pulmonary neutrophil accumulation with early partial liquid ventilation suggesting that perfluorocarbon-

Fig. 3 Individual time courses of pH-values of anesthetized acid-injured rats. Data from 24 rats assigned randomly to four groups (n = 6 in each group).
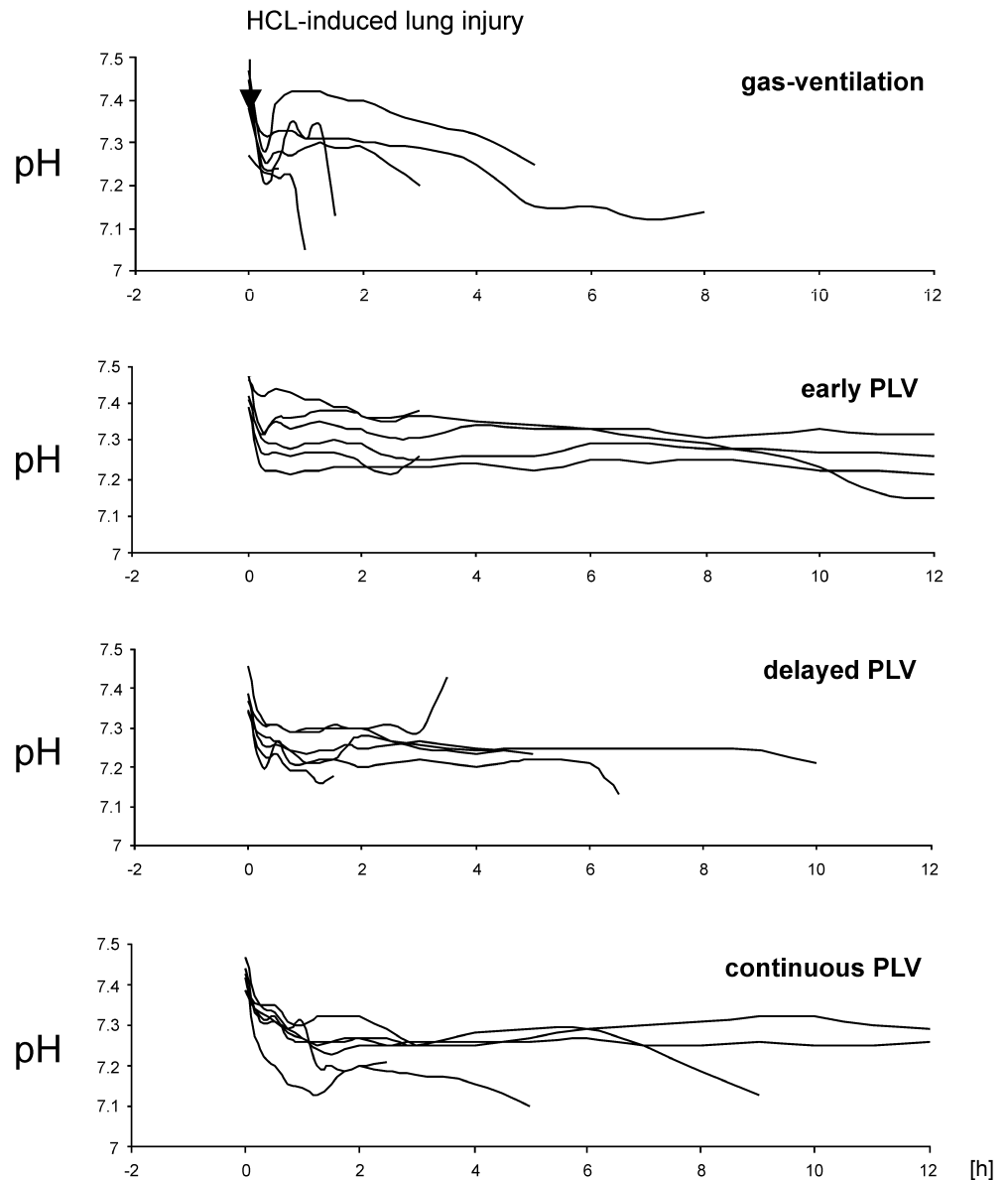
related antiinflammatory effects contribute to the increased survival rate.

Critique of methods

Sub-lethal lung injury

Our results were obtained from rats with a sub-lethal acid-induced lung injury. In pilot experiments we instilled variable amounts of hydrochloric acid into the trachea of anesthetized rats to identify a dose which causes the death of all animals within a few hours. As a result of these experiments we decided to administer 2.5 ml/kg of 0.1 N hydrochloric acid via a catheter placed just above the carina. This volume induced a marked decrease in arterial PO_2 and a mean survival time in the lung-injured and gas-ventilated group. No animal of this group survived the study period of 12 h.

We ventilated the injured lungs with low tidal volumes (6–8 ml/kg) and positive end-expiratory pressures (5 cmH_2O), because ventilatory variables play a crucial role for lung function following acid-induced lung injury. In a recent study in rats the degree of pulmonary edema after intratracheal acid instillation (4 ml/kg HCl, pH 1.25) was significantly less severe when tidal volume was reduced from 12 ml/kg to 6 ml/kg or 3 ml/kg [14]. In this study, rats were ventilated with a positive end-expiratory pres-

Fig. 4 Kaplan-Meier survival curves of 30 anesthetized and mechanically ventilated rats ($n = 6$ in each group). Cumulative survival time after lung injury according to treatment. Animals of the control group were not injured. All other groups received an intratracheal HCl-instillation. Most animals which died after acid instillation died within the first 6 h.
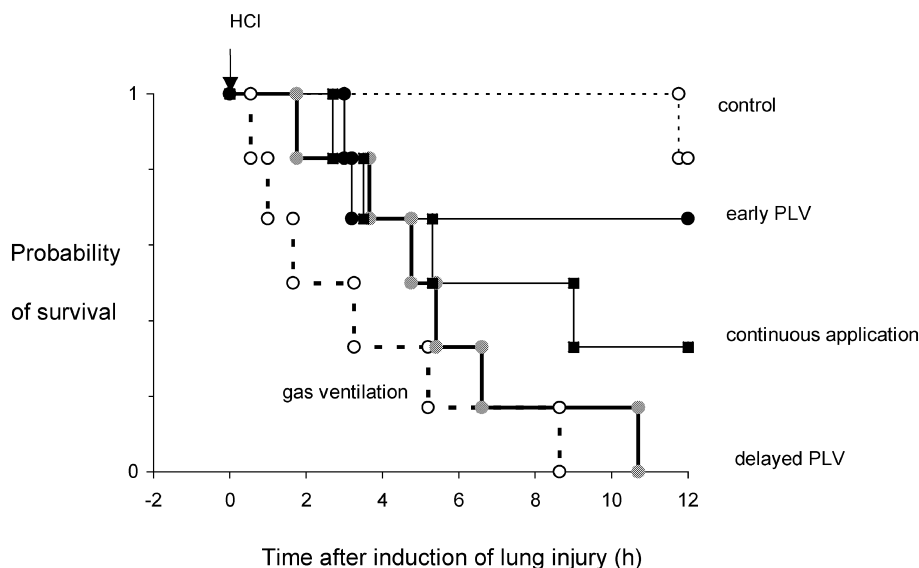
Fig. 5 Light photomicrographs of rat lungs after acid-induced injury (magnification ×400, ASD-chloroacetate-esterase staining). **a** Gas-ventilation. **b** Early partial liquid ventilation. **c** Delayed partial liquid ventilation. **d** Continued partial liquid ventilation. The times of mechanical ventilation were 195 min in the gas-ventilated lung (a), 315 min in the lung with a delayed partial liquid ventilation (c), and 12 h in the lungs with early (b) and continued partial liquid ventilation (d).
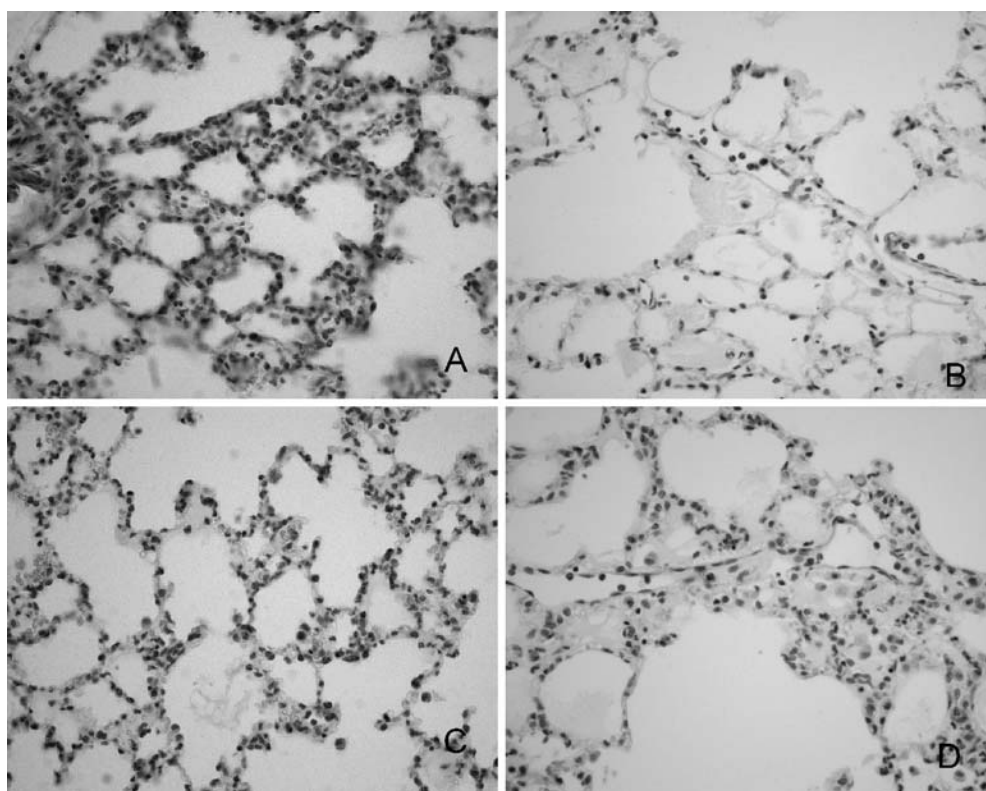

sure of 10 cmH$_2$O for a study period of 6 h. In our study, we applied tidal volumes of 6–8 ml/kg body weight and a positive end-expiratory of 5 cmH$_2$O resulting in normal blood gases over the entire study period in the control group.

Partial liquid ventilation

We studied the effects of early (after 5 min) and delayed (after 30 min) instillation of perfluorocarbon. This time interval was chosen under the assumption that after 30 min most of the physicochemical injury to the alveolocapillary membranes would have occurred. This as-

Fig. 6 Mean number of neutrophils per field in control lungs (*control*) and lungs with acid-induced lung injury (*GV*, *early PLV*, *delayed PLV*, and continued *PLV*). Data from 30 rats assigned randomly to the five groups, mean±SD, *n* = 6 in each group. Sections of lungs were studied with a light microscope (magnification ×400). *P*-values refer to differences between the partial liquid ventilation groups. We observed significantly less neutrophil accumulation with early partial liquid ventilation compared to the delayed partial liquid ventilation group.
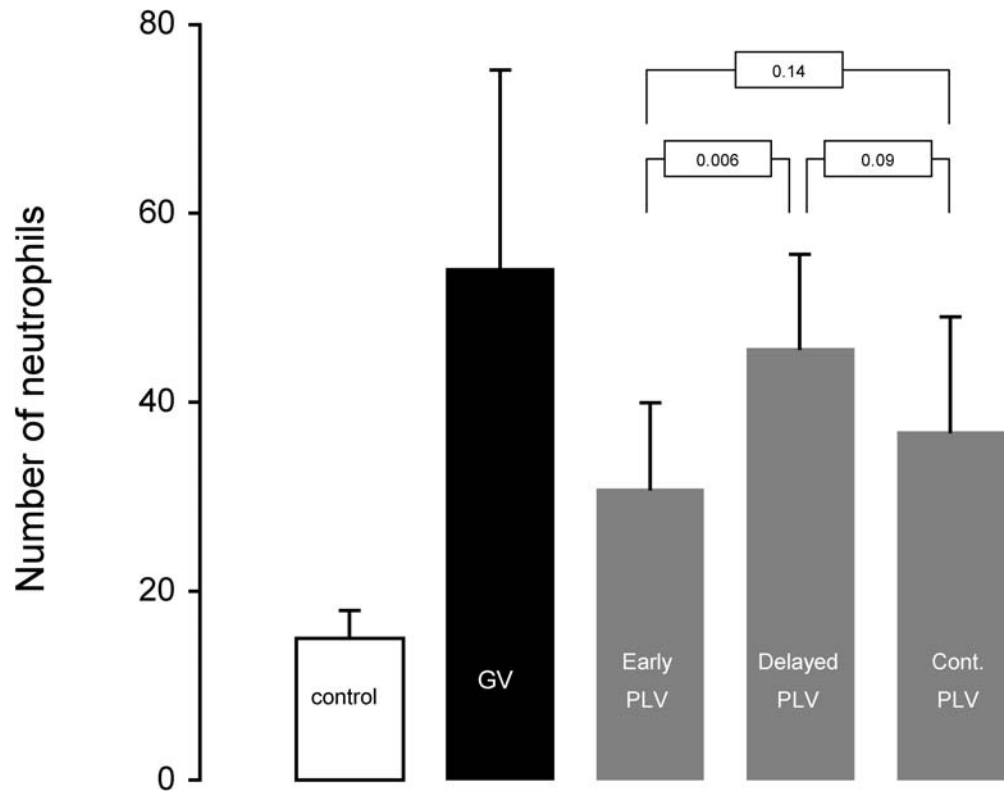
sumption is based on our own observations in isolated rabbit lungs in which filtration coefficients increased to a maximum 30 min after the acid injury [13]. Whereas in larger animals up to 30 ml/kg perfluorocarbon have been instilled after the acid-induced lung injury [9, 10], we administered 5 ml/kg perfluorocarbon. This volume was somewhat smaller than the volume chosen by Kawamae et al. in their rat acid aspiration model (about 7 ml/kg) [12] which resulted in a fluid meniscus in the tracheal cannula at end-expiration. In our study, no relevant pulmonary side effects due to the perfluorocarbon instillation, such as liquid or air in the pleural space, were detected in the autopsy at the end of the experiments. A further reason to use this volume was the observation in isolated acid-injured rabbit lungs that with additional perfluorocarbon volumes of 10 ml/kg or 15 ml/kg no beneficial effects on filtration coefficients could be achieved [13]. In previous studies with this particular perfluorocarbon (PF 5080) we observed an elimination half-time of a few hours [15, 16, 17]. Therefore, we assume that most of the liquid had been eliminated from the lungs within the study period with exception of the lungs of the group that received a continuous instillation of 5 ml/kg perfluorocarbon until the end of the experiments.

Blood gas monitoring

Because rapid changes in gas exchange following induction of lung injury and during the different treatment options may not have been detected with intermittent blood gas analysis, we introduced photochemical sensors via a carotid artery into the aorta of the rats. These sensors allowed us to record the effects of hydrochloric acid and gas- or partial liquid ventilation on arterial blood gases immediately and continuously and without the need to draw arterial blood samples. In previous experiments in rats we observed that these sensors measured arterial blood gases over a wide range of PO_2-, PCO_2-, and pH-values up to 12 h with acceptable accuracy and reproducibility [15]. The observed impairment in oxygenation following acid instillation in the present study was within the range observed before by other investigators [10, 11, 12]. In agreement with previous studies we found a marked improvement in oxygenation during partial liquid ventilation, irrespective of whether partial liquid was started early or delayed. However, in contrast to these studies, we also observed similar improvements in the gas-ventilated lungs, suggesting that the improvement in oxygenation cannot be attributed to partial liquid ventilation alone. The difference observed in the gas-ventilated control-group may be explained by the application of lung protective mechanical ventilation (positive end-expiratory pressures and low tidal volumes).

Interpretation of the results

Our results suggest that after extended acid-induced lung injury early administration of perfluorocarbons is superior to a delayed administration which did not increase survival rate compared to low-tidal volume ventilation with positive end-expiratory pressures. Most animals who did not survive the study period died within the first 6 h after induction of lung injury. Our findings can be explained by two different mechanisms. First, early partial liquid ventilation may affect the early ongoing physicochemical injury to the alveolocapillary membranes. Perfluorocarbons have a higher density than hydrochloric acid, they do not mix with them, and have a low surface tension. Therefore, it is possible that they remove the acid from the alveolar membrane, especially of dependent lung regions, so that the physicochemical injury is limited and the vicious circle including inflammatory reactions associated with ongoing lung injury is reduced. Such "lavage-like" effects of perfluorocarbons have been observed in acute pulmonary edema due to sucrose instillation or meconium aspiration [18, 19]. The second mechanism is related to the effects of partial liquid ventilation on intrapulmonary neutrophil accumulation. In this context it has been observed that perfluorocarbons reduce the recruitment of activated neutrophils from extrapulmonary sites into the lungs by modifying multiple inflammatory responses [20, 23]. In our study, we found less pulmonary neutrophil accumulation at the end of the experiments when the acid-injured lungs received either early partial liquid ventilation or a delayed partial liquid ventilation followed by a continuous application. Although the differences in the absolute number of neutrophils cannot be compared directly because of different ventilation times, our results suggest that the anti-inflammatory effects of the instilled perfluorocarbons may have contributed to the increase in survival rate observed in our experiments. Interestingly, in a study by Nader et al., intraperitoneal administration of perfluorocarbons (15 ml/kg) before or at the time of injury also attenuated neutrophilic infiltration in the lung after acid aspiration and decreased alveolar protein leakage [21, 22]. These findings strongly suggest that perfluorocarbons exert local as well as systemic effects. Therefore, it is likely that in our study systemic antiinflammatory effects have also occurred reducing the systemic inflammatory response to acid aspiration and by this mechanism increasing survival rate.

In conclusion, our results suggest that in the acute phase of acid-induced lung injury, early partial liquid ventilation increases survival rate and decreases neutrophil accumulation within the lungs.

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