Intensive Care Med (2007) 33:308–314
DOI 10.1007/s00134-006-0428-7

EXPERIMENTAL

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Effects of vaporized perfluorohexane and partial liquid ventilation on regional distribution of alveolar damage in experimental lung injury

Received: 15 May 2006
Accepted: 19 September 2006
Published online: 8 November 2006

Electronic supplementary material
Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00134-006-0428-7 and is accessible for authorized users.

This work was supported by grant nos. AB 135/1-1 and HU 818/3-1 from the Deutsche Forschungsgemeinschaft (DFG), Bonn, Germany

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Abstract *Objective:* To determine whether the patterns of distribution of histological effects of vaporized perfluorohexane (PFH) and partial liquid ventilation (PLV) differ significantly in acute lung injury. *Design and setting:* Experimental study in an animal research laboratory. *Subjects:* Eighteen pigs. *Interventions:* After induction of acute lung injury by means of infusion of oleic acid animals were randomly assigned to PFH, PLV, or gas ventilation (GV) groups. Six hours thereafter animals were killed, and lung tissue samples were taken for analysis. *Measurements and results:* Histopathological analysis revealed less damage with PFH than with GV or PLV in the nondependent and central regions. PFH and PLV showed less injury in the dependent regions than GV. GV and PFH were associated with less histological damage in the nondependent than the dependent regions, whereas PLV presented the opposite pattern. Morphometric analysis showed increased aeration in nondependent than dependent regions with PFH and GV. PLV led to more aeration in the periphery than in central areas. *Conclusions:* PFH was associated with a more homogeneous attenuation of alveolar damage across the lungs, although this therapy had more pronounced effects in nondependent zones. PLV showed the opposite pattern, with more important reduction in alveolar damage in dependent lung regions. Interestingly, reduction in alveolar damage with PFH was as effective as with PLV in dependent zones. Our findings suggest that vaporized perfluorocarbon could be advantageous as adjunctive therapy in the treatment of acute lung injury.

Keywords Liquid ventilation · Fluorocarbons · Animal · Acute lung injury · Histology · Oleic acid

Introduction

After initial promising results with partial liquid ventilation (PLV) [1], recent studies have shown that the use of liquid perfluorocarbons as adjunctive therapy to mechanical ventilation (gas ventilation, GV) does not result in better outcome of patients with acute lung injury or the acute respiratory distress syndrome [2, 3]. However, alternative application forms of perfluorocarbons, for example, aerosol and vapor, may lead to different results [4, 5, 6]. In a recently published work our group has shown that vaporized perfluorohexane (PFH) is associated with improved histological findings and permits stabilization of the lungs at lower PEEP levels than PLV and GV in oleic acid induced lung injury [7]. We hypothesized that such findings are related to distinct patterns of distribution of effects of each therapy. In view of its possible implications we expanded the analysis in our previous study to investigate this issue. The results of this study were presented in part at the Annual Meeting of the American Thoracic Society, San Diego, Calif., 19–25 May 2005 [8].

Materials and methods

Experimental protocol

Since in our previous study the most pronounced beneficial effects on diffuse alveolar damage (DAD) were observed at moderately high concentrations of PFH, the present work compared the animals of the GV, PLV, and 5% PFH groups. The detailed protocol of the animal experiments was described in our previous work [8] and is presented in the Electronic Supplementary Material (ESM) accompanying this article. Briefly, 18 piglets (30.9 ± 3.3 kg) were anesthetized and ventilated with an FIO_2 of 1.0, PEEP 5 cmH_2O, inspiratory/expiratory ratio 1:1.7, and tidal volume 9 ml/kg. Respiratory rates were adjusted to achieve a $PaCO_2$ of 35–45 mmHg at baseline and maintained unchanged thereafter. Following instrumentation lung injury was induced by central venous infusion of oleic acid until the PaO_2/FIO_2 ratio fell below 200 mmHg and did not improve spontaneously within 30 min. After lung injury animals were randomly assigned to one of the following groups ($n = 6$ each): (a) GV, (b) PLV with 30 ml/kg perfluoroctane, (c) administration of PFH. Two hours after randomization a decremental PEEP trial was performed, and PEEP was set according to the minimal lung elastance (open lung approach). Ventilator settings were then kept constant for a further 4 h, yielding a total observation period of 6 h.

PFH (C_6F_{14}; ABCR, Karlsruhe, Germany) was administered by means of two standard bypass vaporizers type 19n (Drägerwerke, Lübeck, Germany). PLV was performed after careful instillation of 30 ml/kg perfluorooctane (C_8F_{18}; ABCR) into the trachea (functional residual capacity dose). Gas exchange, lung mechanics, and functional residual capacity (only PFH and GV groups) were assessed at baseline, after induction of lung injury (t_0), 2 h thereafter (t_2) and 2 (t_4) and 4 h after adjustment of PEEP (t_4) using standard procedures which are described in detail in the ESM. Finally, animals were killed by means of intravenous boluses of thiopental (2 g) and KCl (50 mEq) and the lungs extracted at atmospheric pressure for further analysis.

Tissue processing

Tissue samples were taken from central and peripheral regions in the upper and lower lobes of the right lungs at atmospheric pressure according to a standardized protocol. Blocks of lung tissue (approx. 8 cm^3) were taken from the outermost apex of both right upper and lower lobes, representing peripheral regions and from central areas, using the proximal part of the lobar bronchus as anatomical landmark. In a simplified manner lung specimens taken from the upper lobes representing gravitational nondependent (ventral) regions, whereas specimens of the lower lobes stood for gravitational dependent (dorsal) lung regions. Samples of each region were fixed by immersion in a 4% buffered formaldehyde solution, embedded in paraffin, stained with hematoxylin-eosin, and cut in slices for morphometric and histological analysis according to routine histological procedures.

Digital image processing

Photomicrographs were obtained from four nonoverlapping fields of view per section using a light microscope (DM RB, Leica, Wetzlar, Germany). Images were digitized and processed by means of a computer-based system and image-analyzing software (AnalySIS, version 3.1, Soft Imaging System, Münster, Germany). For morphometric analysis digitized photomicrographs were binarized, with black portions representing parenchyma, edema, or infiltration (nonaerated) and white portions representing aerated areas. Raster electron-microscopy was performed in representative lung specimen using a scanning electron microscope (LEO S430, Carl Zeiss, Oberkochen, Germany).

Histological analysis

DAD was quantified by an expert in lung pathology blinded to the experimental protocol and the therapy groups using a weighted scoring system described in detail in the ESM. Structural effects on lung parenchyma

Table 1 Summary of most relevant gas exchange, lung mechanics and lung volume data [*GV* gas ventilation, *PLV* partial liquid ventilation, *PFH* 5% vaporized perfluorohexane, V_T actual tidal volume, *RR* respiratory rate, *PEEP* positive end-expiratory pressure, P_{aw} mean airway pressure, P_{pl} inspiratory plateau pressure, P_{peak} peak inspiratory pressure, E_L lung elastance, *FRC* functional residual capacity. n.c. unchanged; time effect pattern: *a* $p<0.05$ vs. baseline (paired *t* test), *b* $p<0.05$ vs. t_0 (post-hoc two-way analysis of variance), *c* $p<0.05$ vs. t_2 (post-hoc two-way analysis of variance)]

	Baseline	Injury	2 h	4 h	6 h
paO_2/FIO_2 (mmHg)					
GV	523.0 ± 44.1	148.3 ± 46.3	79.3 ± 34.3	359.5 ± 92.6	340.1 ± 188.4
PLV	557.6 ± 23.2	183.1 ± 13.0	145.4 ± 92.9	257.8 ± 139.0	139.6 ± 87.0
PFH	557.6 ± 23.1	139.6 ± 23.2	88.0 ± 16.1	244.9 ± 165.0	243.9 ± 196.2
Time pattern effect	–	a	b	b, c	b, c
$paCO_2$ (mmHg)					
GV	38.7 ± 2.8	56.1 ± 12.3	59.3 ± 18.2	62.9 ± 12.5	62.1 ± 23.9
PLV	38.1 ± 3.2	51.1 ± 5.1	68.9 ± 17.5	63.7 ± 16.2	66.4 ± 12.6
PFH	39.0 ± 5.0	51.3 ± 7.0	60.5 ± 9.3	58.5 ± 14.1	57.1 ± 11.4
Time pattern effect	–	a	b	b	b
V_T (ml)					
GV	366.3 ± 56.2	364.4 ± 46.4	369.7 ± 59.7	373.5 ± 63.5	372.1 ± 60.8
PLV	300.4 ± 24.7	314.7 ± 24.5	295.8 ± 25.1	301.0 ± 25.1	291.5 ± 30.8
PFH	369.1 ± 51.2	351.1 ± 45.2	328.4 ± 34.7	332.6 ± 37.8	331.3 ± 36.4
RR (min)					
GV	28.2 ± 2.1	n.c.	n.c.	n.c.	n.c.
PLV	26.0 ± 2.3	n.c.	n.c.	n.c.	n.c.
PFH	27.3 ± 1.2	n.c.	n.c.	n.c.	n.c.
PEEP (cmH_2O)					
GV	5	5	14.2 ± 2	n.c.	n.c.
PLV	5	5	16.7 ± 2.6	n.c.	n.c.
PFH	5	5	10.8 ± 2**,***	n.c.	n.c.
P_{aw} (cmH_2O)					
GV	9.4 ± 0.7	13.0 ± 1.7	13.8 ± 1.7	20.4 ± 2.4	20.7 ± 2.1
PLV	9.4 ± 0.9	11.8 ± 1.1	18.2 ± 1.5*	26.1 ± 4.0*	26.3 ± 3.6*
PFH	10.0 ± 1.0	12.6 ± 2.0	13.3 ± 3.2	19.3 ± 2.3	19.8 ± 2.8
Time pattern effect	–	a	b	b, c	b, c
P_{pl} (cmH_2O)					
GV	14.2 ± 1.1	23.6 ± 2.2	25.9 ± 4.7	30.9 ± 2.2	28.9 ± 5.2
PLV	13.4 ± 0.7	21.5 ± 4.5	26.8 ± 0.4	33.9 ± 3.2	36.3 ± 3.4*
PFH	14.9 ± 1.5	25.6 ± 4.2	25.7 ± 6.3	32.12 ± 4.4	32.5 ± 5.9
Time pattern effect	–	a	b	b, c	b, c
P_{peak} (cmH_2O)					
GV	19.5 ± 2.1	37.1 ± 6.3	40.1 ± 6.7	40.7 ± 4.7	41.1 ± 3.0
PLV	18.8 ± 1.6	33.4 ± 4.9	46.2 ± 4.8	48.9 ± 5.8*	50.7 ± 4.3*
PFH	20.8 ± 2.3	34.3 ± 6.5	35.5 ± 12.5	41.3 ± 5.4	43.3 ± 10.5
Time pattern effect	–	a	b	c	b, c
E_L ($cmH_2O.l^{-1}$)					
GV	23.9 ± 2.8	67.9 ± 13.0	77.6 ± 15.0	58.8 ± 16.0	53.1 ± 7.6
PLV	25.1 ± 7.7	72.0 ± 22.5	67.8 ± 12.8	51.7 ± 15.1	57.8 ± 17.0
PFH	25.6 ± 4.7	60.6 ± 13.1	56.4 ± 22.0	51.0 ± 11.0	49.8 ± 12.6
Time pattern effect	–	a	b	b, c	b, c
FRC (ml)					
GV	846 ± 199	544 ± 72	407 ± 91	883 ± 136	865 ± 109
PLV	–	–	–	–	–
PFH	915 ± 215	673 ± 107	602 ± 154	981 ± 241	869 ± 296
Time pattern effect	–	a	b	b, c	b, c

* $p<0.05$ vs. GV (within a given time point; paired *t* test), ** $p<0.05$ vs. GV (one-way, analysis of variance), *** $p<0.05$ vs. PLV (one-way analysis of variance)

were determined by systematic morphometric quantification of chord length and area in air in the binarized photomicrographs using standard tools of the image-analyzing system.

Statistical analysis

Statistical procedures used are shown in detail in the ESM. Values of PEEP, amount of oleic acid, and time

Table 2 Distribution of diffuse alveolar damage scores (*DAD* diffuse alveolar damage, *GV* gas ventilated control group, *PFH* 5% vaporized perfluorohexane, *PLV* partial liquid ventilation)

	GV	PLV	PFH
Nondependent			
Intra-alveolar edema	1.77 ± 2.04	1.81 ± 1.65	$0.35 \pm 0.64^{*,***,4*}$
Interstitial edema	$1.98 \pm 1.51^{*}$	2.71 ± 2.39	1.17 ± 1.34
Hemorrhage	$1.63 \pm 1.38^{*}$	1.48 ± 1.17	1.04 ± 1.22
Inflammatory infiltration	$3.81 \pm 3.21^{*}$	3.33 ± 2.51	$2.33 \pm 2.57^{*}$
Epithelial destruction	2.27 ± 2.90	3.10 ± 2.26	$0.81 \pm 1.25^{***,4*}$
Microatelectasis	$1.13 \pm 1.00^{*,4*}$	2.75 ± 1.91	$1.02 \pm 1.14^{*,4*}$
Overdistension	7.46 ± 3.54	8.48 ± 4.35	7.21 ± 3.24
Cumulated score	$20.04 \pm 7.53^{*}$	23.67 ± 7.26	$13.94 \pm 5.34^{*,***,4*}$
Dependent			
Intra-alveolar edema	2.33 ± 1.56	$1.15 \pm 0.92^{***}$	$1.23 \pm 1.48^{***}$
Interstitial edema	3.79 ± 2.37	$2.17 \pm 2.04^{***}$	$2.04 \pm 1.50^{***}$
Hemorrhage	3.23 ± 2.02	$0.67 \pm 1.00^{***,5*}$	$1.75 \pm 1.52^{***}$
Inflammatory infiltration	5.88 ± 3.17	$3.12 \pm 2.03^{***}$	$4.00 \pm 3.00^{***}$
Epithelial destruction	3.21 ± 2.30	2.06 ± 1.83	$1.90 \pm 2.16^{***}$
Microatelectasis	2.88 ± 1.78	2.75 ± 1.16	2.35 ± 1.66
Overdistension	$4.56 \pm 2.34^{*,4*}$	7.02 ± 1.94	$5.23 \pm 3.20^{***}$
Cumulated score	25.87 ± 8.30	$18.94 \pm 5.31^{*,***}$	$18.50 \pm 7.29^{***}$
Peripheral			
Intra-alveolar edema	1.87 ± 1.39	1.29 ± 1.58	$0.75 \pm 0.91^{***}$
Interstitial edema	2.44 ± 1.99	2.23 ± 1.89	1.38 ± 1.47
Hemorrhage	2.40 ± 2.14	$1.15 \pm 1.09^{***}$	$1.37 \pm 1.23^{***}$
Inflammatory infiltration	$3.79 \pm 2.88^{**}$	$2.06 \pm 1.95^{**,***}$	2.63 ± 2.65
Epithelial destruction	2.17 ± 1.83	2.23 ± 2.02	1.12 ± 1.65
Microatelectasis	1.88 ± 2.06	$2.08 \pm 1.57^{**}$	1.69 ± 1.72
Overdistension	6.15 ± 3.47	9.00 ± 3.44	7.10 ± 3.09
Cumulated score	$20.69 \pm 7.65^{**}$	20.04 ± 6.66	$16.04 \pm 6.42^{***}$
Central			
Intra-alveolar edema	2.23 ± 2.19	1.67 ± 1.10	$0.83 \pm 1.46^{***}$
Interstitial edema	3.33 ± 2.28	2.65 ± 2.51	$1.83 \pm 1.48^{***}$
Hemorrhage	2.46 ± 1.65	$1.00 \pm 1.22^{***}$	$1.42 \pm 1.60^{***}$
Inflammatory infiltration	5.90 ± 3.46	4.40 ± 1.97	$3.71 \pm 3.07^{***}$
Epithelial destruction	3.31 ± 3.18	2.94 ± 2.16	$1.58 \pm 2.00^{***,4*}$
Microatelectasis	2.13 ± 1.21	3.42 ± 1.27	1.69 ± 1.42
Overdistension	5.87 ± 3.19	$6.50 \pm 2.96^{**}$	5.33 ± 3.41
Cumulated score	25.23 ± 8.60	22.56 ± 6.69	$16.40 \pm 7.15^{***,4*}$

$^{*}p < 0.05$ vs. opposite dependent/nondependent region within group, $^{**}p < 0.05$ vs. opposite central/peripheral region within group, $^{***}p < 0.05$ vs. GV, $^{4*}p < 0.05$ vs. PLV, $^{5*}p < 0.05$ vs. PFH (mixed model, Tukey-Kramer post-hoc test)

to achieve injury were compared using one-way analysis of variance. Effects of injury on functional variables (baseline vs. t_0) were determined by paired t test, and their time courses were tested using analysis of variance with repeated measures followed by post-hoc analysis (Student-Newmann-Keuls test). The t test and analysis of variance used the software SPSS version 11.5 (SPSS, Chicago, Ill., USA). The regional distribution of DAD score characteristics and morphometric correlates were determined by means of mixed linear models with repeated measures (procedure mixed, SAS version 8, SAS Institute, Cary, N.C., USA). Differences between means were tested by the post-hoc Tukey-Kramer test. The global significance level was 0.05 in all performed tests.

Results

Functional parameters

The total amounts of oleic acid administered and the time of administration were 0.03–1.25 ml/kg and 1–2 h, respectively, and did not differ significantly between groups. Table 1 shows the most relevant gas exchange, lung mechanics, and lung volume data. Following the PEEP trial PEEP had to be increased in every animal to optimize lung elastance, but values needed to stabilize the lungs of animals treated with PFH were significant lower than those in PLV and GV animals. Arterial oxygenation, lung elastance, and lung volumes improved markedly after the recruitment maneuver (t_4, t_6) but did not differ

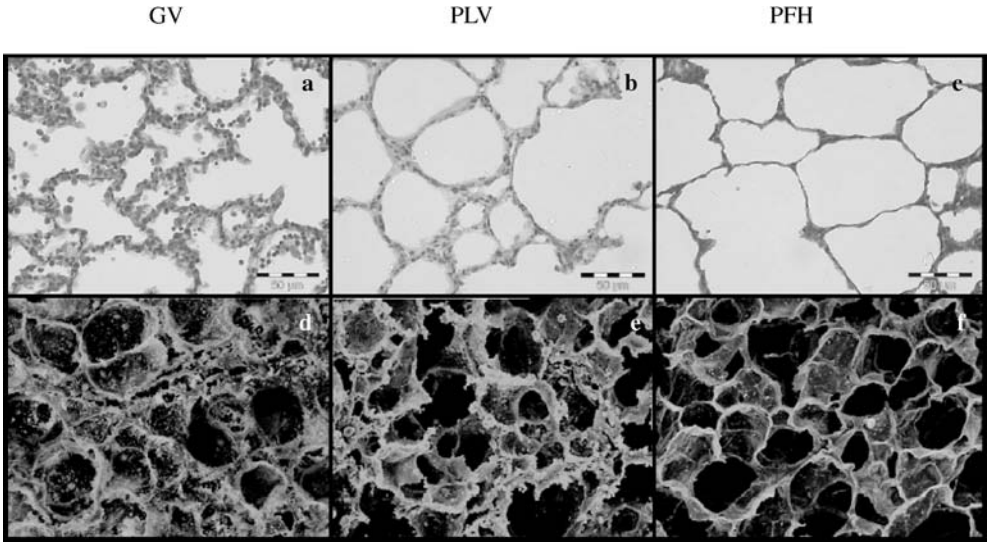

Fig. 1 Representative light and raster electron microscopic findings. Representative photomicrographs of light-microscopy (× 250; **a**, **b**, **c**) and raster electron microscopy (× 400; **d**, **e**, **f**) from lung samples of animals investigated. **a**, **d** Gas ventilation (*GV*). **b**, **e** Partial liquid ventilation (*PLV*). **c**, **f** Vaporized perfluorohexane 5% (*PFH*). Samples were taken from central parts of the right upper lobe. Photomicrographs reveal better lung preservation with PFH than with PLV or GV

Table 3 Distribution of morphometric features (*GV* gas ventilated control group, *PFH* 5% vaporized perfluorohexane, *PLV* partial liquid ventilation)

	GV	PLV	PFH
Chord length in air (μm)			
Nondependent	$38.54 \pm 12.66^{*}$	39.10 ± 17.30	$44.44 \pm 15.24^{*}$
Dependent	24.03 ± 9.15	$36.32 \pm 13.41^{***,4*}$	27.29 ± 12.12
Peripheral	33.96 ± 15.14	$44.86 \pm 14.49^{**,***}$	37.85 ± 16.96
Central	28.61 ± 10.38	30.56 ± 12.98	33.89 ± 15.29
Overall	31.28 ± 13.19	$37.71 \pm 15.46^{***}$	$35.87 \pm 16.18^{***}$
Area in air (mm^2)			
Nondependent	$2.91 \pm 0.55^{*}$	2.94 ± 0.59	$3.11 \pm 0.64^{*}$
Dependent	2.29 ± 0.51	$2.69 \pm 0.58^{***,4*}$	2.29 ± 0.69
Peripheral	2.67 ± 0.72	$3.12 \pm 0.54^{**,***,4*}$	2.77 ± 0.79
Central	2.52 ± 0.47	2.50 ± 0.49	2.63 ± 0.77
Overall	2.60 ± 0.61	$2.81 \pm 0.60^{***}$	2.70 ± 0.78

$^{*}p < 0.05$ vs. opposite dependent/nondependent region within group, $^{**}p < 0.05$ vs. opposite central/peripheral region within group, $^{***}p < 0.05$ vs. GV within region, $^{4*}p < 0.05$ vs. PFH within region (mixed model, Tukey-Kramer post-hoc test)

significantly among groups at any time point. Mean airway pressures as well as peak and inspiratory plateau pressures were significantly higher in the PLV than in the GV group.

Histological findings

Representative light and raster electron microscopic findings are shown in Fig. 1, which revealed less alveolar damage in the PFH group. The regional distribution of DAD scores is summarized in Table 2. PFH reduced DAD more importantly in nondependent zones while PLV showed the opposite pattern. In addition, a more homogeneous reduction in alveolar damage was observed in the PFH group. Detailed results of the morphometric analysis are shown in Table 3. PLV and PFH showed increased chord length than GV. PLV led to increased chord length in dependent and peripheral regions while PFH and GV were associated with increased chord lengths in nondependent areas. The area in air measured across all lung regions was increased in the PLV than the GV group. The analysis of regional distribution revealed increased area in air in dependent and peripheral regions in the PLV and in nondependent regions in the PFH and GV groups.

Discussion

Recently it has been suggested that the use of PLV in combination with mechanical ventilation strategies aimed at increasing aerated lung volume does not add further benefit to lung function [9] or mortality [4] but is able to attenuate the inflammatory response of lungs [10, 11]. The results of our study are in agreement with those reports. Despite the lack of beneficial effects on functional parameters our data suggest that perfluorocarbons would be useful for attenuat-

ing alveolar damage in acute lung injury. According to our results, PLV reduced DAD in dependent and peripheral regions whereas the effects of the vaporized perfluorocarbon were more pronounced in nondependent regions. We attribute this observation to the gravity-oriented spreading of the liquid perfluorocarbon towards dependent zones [12]. Despite this, PFH was able to reduce alveolar damage as efficiently as PLV in the dependent zones.

It is worth noting that the time course of lung mechanics and gas exchange did not mirror each other in our animals. This is most probably explained by the fact that lung injury caused an increase in stiffness that could not be compensated by any mechanism, whereas the shifting of blood flow to nondamaged lung areas contributed to a different dynamic of gas exchange. We observed that E_L deteriorated more rapidly than PaO_2/FIO_2 in almost every single animal during induction of lung injury (data not shown).

Perhaps the most interesting finding of this work was that PFH not only exerted more pronounced protective effects on most of the DAD features and regions investigated, but also that it was associated with a more homogeneous pattern of distribution of those effects, i.e., with less differences in injury findings across different lung zones. Accordingly, central and peripheral areas as well as dependent and nondependent lung zones benefited more from the therapy with PFH. The observation that the therapy with vaporized perflurocarbon was associated with a more homogeneous pattern of distribution of beneficial effects on lung tissue is most probably associated with the use of recruitment maneuvers and higher PEEP levels set to keep the lungs open in our work, which permitted the perfluorocarbon vapor to reach lung units in different zones, including the most dependent ones. Our findings partially agree with those reported by Kemming et al. [14] who suggested an inhomogeneous distribution of PLV effects on histological analysis and the ability of vaporized perfluorohexane to reach peripheral lung regions. Unfortunately, the use of lower PEEP levels and limitation of histological analysis to one single lung region in their study [14] precludes further comparison with our work.

Limitations

It should be kept in mind that the use of different perfluorocarbons may have influenced our results [15, 16]. The substances were chosen taking the appropriateness of physicochemical characteristics for the respective application form and the issue of comparability with previous studies into account. Another important aspect is that animals treated with PLV were ventilated with comparatively higher airway pressures than GV and PFH. Therefore the combination of full functional residual capacity dosing of liquid perfluorocarbon with higher PEEP levels may have contributed to increased alveolar overdistension in the PLV group, as suggested by increased airway pressure values. However, this bias can also be interpreted as a disadvantage inherent to PLV. Finally, we must acknowledge that the removal of the lungs without use of continuous positive airway pressure may have introduced atelectasis artifacts in our analysis. According to our experience, however, oleic acid injured lungs become extremely stiff and lung collapse after lung extraction does not present a major concern.

Conclusion

This study showed for the first time that PFH and PLV are associated with opposite distribution patterns of histological findings. Whereas PLV exerted most effects on dependent lung zones, reduction in lung injury with PFH was more pronounced in nondependent areas. Despite the gravity-oriented effects PFH showed a more homogeneous and pronounced attenuation in alveolar damage. Due to its behavior as vapor PFH has only minor mechanical impact on the lungs and can be used in combination with any given mechanical ventilation strategy. Such properties suggest PFH could prove a useful alternative to PLV in acute lung injury, but further studies are necessary to confirm this claim.

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