Intensive Care Med (1991) 17:293–298

Intensive Care Medicine

The consequences of continuous haemofiltration on lung mechanics and extravascular lung water in a porcine endotoxic shock model

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Received: 10 December 1990; accepted: 22 May 1991

Abstract. Endotoxinaemia (E. coli endotoxin, 0.111.B4) and pulmonary hypertension were evoked in 20 swine, randomly assigned to receive either zero-balanced veno-venous haemofiltration (HF) with an ultrafiltration and replacement rate of 600 ml/h (HF group, $n = 10$) or to undergo an uninfluenced spontaneous course (E group, $n = 10$) during a constant infusion of endotoxin until the end of the experiment. Endotoxin-induced pulmonary dysfunction was assessed on the basis of extravascular lung water (EVLW) using a thermo-dye technique via a fiberoptic intra-aortic probe, gas exchange and lung mechanics, the latter derived by a pressure-volume loop (P/V loop) of the respiratory system (super syringe, flow 30 ml/s, tidal volume 600 ml). A comparable increase in alveolo-arterial oxygen difference and a constant EVLW was observed in both groups. The progessive deterioration of hysteresis area and compliance parameters by endotoxinaemia was significantly blunted by HF. Independent of an impact on pulmonary oedema zero-balanced HF modifies endotoxin induced lung injury, probably by the convectice transport of mediator substances.

Key words: Septic shock – Haemofiltration – Lung mechanics

Sepsis and septic shock are a major cause of acute renal failure in intensive care medicine [1–4] usually appearing as multiple organ failure. The modern procedures of continuous blood purification improve the response of sepsis-induced acute renal failure to therapy [1, 2, 5, 6]. Clinical [7, 8] and experimental data [9–11] suggest that continuous haemofiltration may in addition exert a beneficial effect on pulmonary and haemodynamic dysfunction in septic shock [7–11] by its capacity to filter out medium-sized molecules by convective transport.

In order to elucidate this aspect we introduced a "zero-balanced" HF in a porcine model of endotoxic shock [9] and were able to show a slight modification of pulmonary circulation [9] and myocardial performance during continuous haemofiltration. These results are in accordance with data [11] showing a reversal of left ventricular dysfunction during sepsis in dogs and HF. As haemodynamic changes in an endotoxic shock model are accompanied by the early deterioration of lung mechanics, gas exchange and lung water [12–16] associated with the release of medium-sized molecules such as thromboxane [12] and leukotrienes [16] the question was raised whether this procedure may as well influence endotoxin-induced lung injury.

In the present investigation, as the second part of a study recently presented [9], the effect of early initiation of HF with a high ultrafiltration and replacement rate on parameters of pulmonary dysfunction in porcine endotoxic shock, i.e. lung mechanics, gas exchange and extravascular lung water was studied and compared to the spontaneous course.

Materials and methods

The experimental protocol described here was approved by the Administrative Government in Tübingen, FRG (reg. no. 339). Only animals with a baseline alveolo-arterial oxygen difference below 75 mmHg and a mean pulmonary artery pressure below 25 mmHg under mechanical ventilation ($FiO_2 = 0.4$) were included in the further investigation. Preparation and experimental protocol were described previously [9], but they are presented in detail for better understanding of this study.

Anaesthesia procedures and preparation

Domestic pigs (28–32 kg body weight, 16 weeks old) of either sex were premedicated with azaperone (3 mg/kg i.m. and atropine (0.08 mg/kg i.m.). After sedation with metomidate (5 mg/kg i.v.) and buprenorphine (0.6 mg i.v.) the trachea was intubated and the animals mechanically ventilated by continuous positive pressure ventilation (FiO_2: 0.4, PEEP +3 cmH_2O, breaths/min: 24–28, minute volume: 9–10 l/min). During preparation the inspired gas mixture consisted of N_2O and O_2 and during the observation period of air and O_2. Myorelaxation was performed by an initial administration of Alcuronium chloride

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(0.15 mg/kg i.v.) after intubation and 3 min later by Hexacarbacholine bromide (Imbretil®, 0.1 mg/kg i.v.).

Anaesthesia was maintained during the preparatory period by continuous administration of metomidate (2.5–5 mg/kg/h (i.v.), and during the observation period by a reduced dose of metomidate (0.2–0.7 mg/kg/h i.v.). At 5 min prior to each point of measurement, myorelaxation was repeated by Hexacarbacholine bromide (0.1 mg/kg i.v.). Depth of anaesthesia was controlled by EEG monitoring (Neurotrac, Interspec Inc., Cronskohocken, USA).

A 7-F catheter and a thermistor probe for monitoring cardiac output (CO) were inserted into the aortic arch, and a 5-F fiberoptic probe (PV 2024 FO-TD, Cold System, Pulsion, Munich, FRG) advanced to the level of the diaphragm (45 cm proximal to the femoral artery). A 5-F flow-directed catheter was placed in the pulmonary artery, and another 5-F catheter placed into the femoral artery. A silicone tube (i.d. 4.5 mm) served as an HF catheter for drawing blood from the right femoral vein; the blood was returned via a silicone cathether (i.d. 3.45 mm) to the external jugular vein. A suprapubic catheter was inserted to drain urine. ECG, rectal temperature, mean pulmonary artery pressure, mean arterial pressure and mean airways pressure (intratracheal tube) were monitored continuously in all animals.

Extravascular lung water (EVLW) was determined as a double assay by the thermo-dye double-indicator technique [16] with injection of the indicator indigocyanin green (Cardiogreen®, 0.25% in 10 ml water for injections at 1–1.5°) in the right atrium and signal perception at the tip of the fiberoptic probe in the aorta at diaphragm level, using a haemoreflectometer (IVH® 4, Schwarzer, FRG) and a computer system (Cold System, software Z O2®, Pulsion, Munich, FRG).

Experimental protocol

After baseline data were obtained, 20 animals received E. coli endotoxin (0.111 : B4, Difco Lab., Detroit, USA) by continuous central venous infusion. Starting at 2 µg/kg/h, the dosage was augmented at 10-min-intervals by steps of 2 µg/kg/h until the haemodynamic endpoint of doubling the mean pulmonary artery pressure was achieved (designated as time $1/PAP_{max}$). Thereafter the prevailing infusion rate was reduced by one-half, and this dosage maintained for 4 h until the end of the experiment.

At 15 min after doubling of the pulmonary artery pressure the animals were randomly assigned to either of 2 groups, 1 to observe the spontaneous course (defined as E group, $n = 10$), and the other to undergo continuous veno-venous haemofiltration (HF) until the end of the experiment (defined as HF group, $n = 10$).

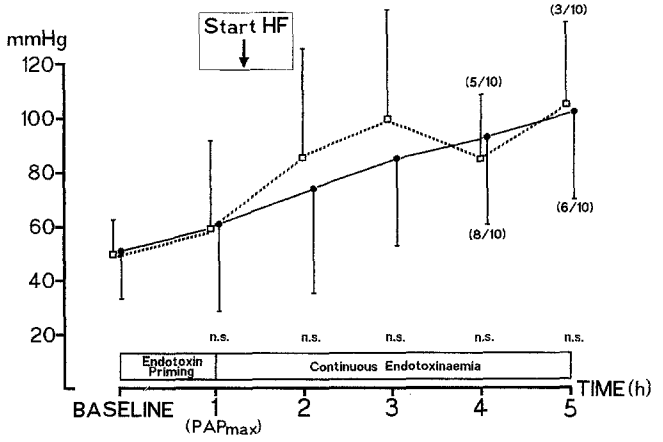

Fig. 1. Alveolo-arterial oxygen difference (A-a DO_2) during the stages of the experiment. Data points are expressed as mean ± SD. Time $1/PAP_{max}$ as the end of the priming period is approximated as 1 h of endotoxinaemia (51 ± 12 min). Time 2 until time 5 represent the following hourly points of measurement under continuous endotoxinaemia. *E Group*, endotoxin treated group, spontaneous course (*dotted line*); *HF Group*, haemofiltrated and endotoxin-treated group. *n.s.*, no statistical significance per point of measurement (E/HF)

"Zero-balanced" HF was performed by ultrafiltration of 600 ml/h and concurrent replacement of a Ringer's lactate solution (600 ml/h, SH 01, Schiwa, Glandorf, FRG) via 2 infusion pumps (Fig. 1), as described recently for the clinical use [18] and by means of an HF pump (NFG 05 SN, Dialysetechnik, Karlsruhe, FRG) and a polysulfone haemofilter (AV 400, Fresenius, Oberursel, FRG, inulin sieving coefficient: 0.99) at a blood flow rate of 50 ml/min.

Monitoring of haemodynamic parameters and sampling of arterial and mixed venous blood for analysis of blood gases, O_2 saturation, haemoglobin (IL 1302, IL 282, Instrumentation Laboratories, Lexington, USA) and plasma glucose (GOD-perid-method) were done first to obtain baseline data, at time $1/PAP_{max}$, and thereafter at hourly intervals (designated time 2 to 5) until the end of the experiment. The total amount of blood withdrawn averaged 120 ml in each animal.

All animals were given 7 ml/kg/h i.v. of Ringer's lactate solution for the duration of the experiment. No colloidal volume replacement was performed. Severe hypoglycaemia (< 3.0 mmol/l) occurred in 2 animals (1 E group, 1 HF group) and was treated with additional administration of glucose 40% solution (10–15 ml/h).

To assess the influence of anaesthesia, position and instrumentation on lung mechanics, three pigs of identical weight were subjected to the same experimental protocol, but without endotoxin infusion and haemofiltration (control group, $n = 3$).

Lung mechanics

The respiratory pressure-volume loop (P/V loop) was recorded at the end of a point of measurement after assuring patent airways and myorelaxation. Using a super syringe (content 1.5 l), a slow dynamic compliance (flow 30 ml/s, inflation and deflation 20 s each) with a constant tidal volume of 600 ml was determined, similar to the method described by Mankikian [19]. This procedure was repeated 3 min later to obtain a comparable "volume history" of the animals. Only the second P/V loop was regarded for further analysis. Recording was done using a lung function measurement unit (Pulmostar SM, Dr. Fenyves & Gut, Basel, Switzerland) and an x-y recorder (7041 A, Hewlett-Packard, USA).

Analysis of the original P/V loops included the slope of the P/V loop (V_0/P_{PEEP}; V_{600}/Px), representing the total compliance (lung and chest wall) at a tidal volume of 600 ml, and the hysteresis area (planimetry computer-aided after digitalization of the curve). In addition, the slope of the steep part of the inspiratory limb was determined. To standardize this calculation a volume segment between 0 and 400 ml, representing the mean tidal volume of the animals, and the corresponding pressure values were taken to assess the slope (V_0/P_{PEEP}, V_{400}/P_x). In addition, the "unrecovered volume" as the difference between inflation and deflation on the y axis, at atmospheric pressure [20, 21], was assessed.

Calculations and statistics

Alveolo-arterial oxgen difference (A-aDO_2) and oxygen consumption (VO_2) were calculated from standard equations. The SAS program (SAS® System, Carey, USA) was used for statistical analysis, performing two-way analysis of variance (time/group). When significant differences were found ($p < 0.05$), multivariate analysis of variance (MANOVA) was done to identify differences per point of measurement. Because of interindividual differences in hysteresis area, the values of each animal were referred to the baseline data (100%) and further expressed in percent of baseline data values. Because of the small number of survining animals in the E group at the end of the experiment (time 5, $n = 3$), only means and standard deviation were given.

Results

As the 3 control animals showed no significant changes (below 5% referred to baseline values) in haemodynamic parameters, A-a DO_2, EVLW and parameters of lung mechanics during the 6 h observation period their results

are not depicted except the demonstration of the P/V-loop in Fig. 6. The survival rate in the HF group was higher both at time 4 (8 of 10 animals in the HF group vs. 5 of 10 in the E group) and the end of the experiment, defined as time 5 (6 of 10 HF vs. 3 of 10 E). Statistical analysis showed no significant difference between both groups. Of 10 animals 9 within each group developed anuria before the end of the experiment.

Gas exchange and extravascular lung water

The course of alveolo-arterial oxygen difference (Fig. 1) shows a progressive and significant increment in both groups compared to baseline values. No differences were found between the two groups.

The course of EVLW is illustrated in Fig. 2. Although a trend to higher mean values towards the end of the experiment is evident, no significant differences were found in the analysis of variance.

VO_2 was constant during the stages of the experiment without differences between the groups (time 4: E Group 223±67 ml/min; HF Group 248±75 ml/min).

Lung mechanics

The haemofiltrated group (HF group) showed significant differences in the two-way analysis of variance (time/group) of hysteresis area (percent of baseline value, Fig. 3), compared to the spontaneous course (E group). Following nearly identical increases during endotoxin priming to 162% (E group) and 167% (HF group) referred to baseline values at time $1/PAP_{max}$, a progressive increase was evident in the E group, whereas the values of the haemofiltrated animals persisted at the same level. Statistical significance between the two groups per point of measurement (MANOVA) was found at times 3 and 4.

The total dynamic compliance is demonstrated in Fig. 4. Although a trend to higher mean values in the HF group is evident, the two-way analysis of variance failed to prove statistical significance ($p = 0.054$). Analysis of differences per point of measurement (MANOVA) was performed, however, and showed significance at time 4.

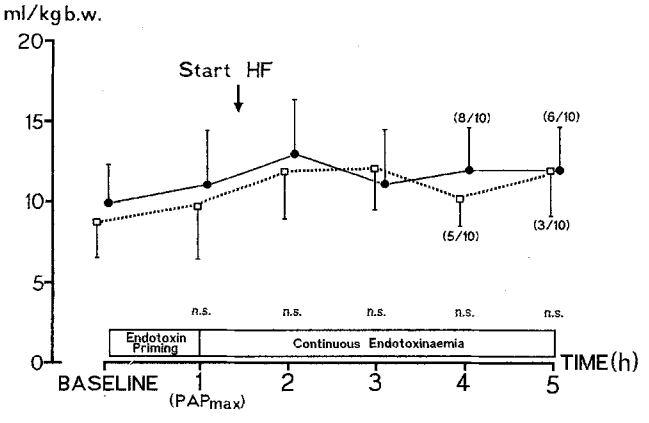

Fig. 2. Extravascular lung water (EVLW) during the stages of the experiment. Data points are expressed as mean±SD. *E Group*, endotoxin-treated group (*dotted line*); *HF Group*, Haemofiltrated and endotoxin-treated group. *n.s.*, no statistical significance per point of measurement (E/HF)

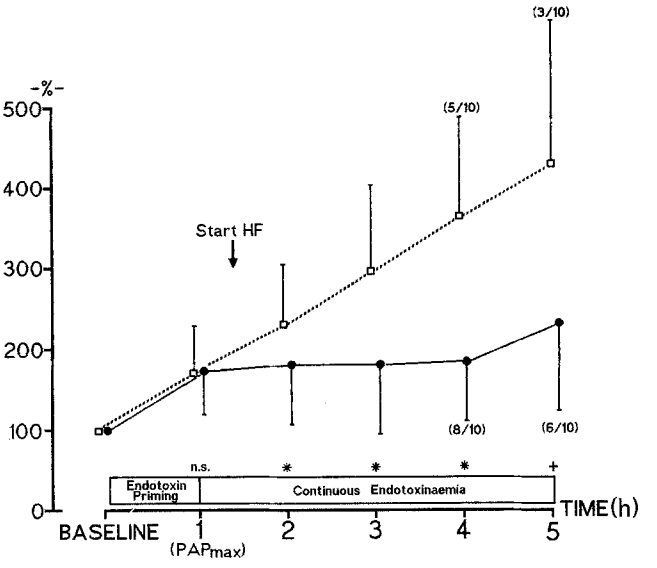

Fig. 3. Hysteresis area of the pressure-volume curve of the respiratory system during the stages of the experiment, given in percent referred to baseline value (100%). Data points are expressed as mean±SD. *E Group*, endotoxin-treated group (*dotted line*); *HF Group*, Haemofiltrated and endotoxin-treated group. *n.s.*, no statistical significance per point of measurement (E/HF). *: Statistical significance per point of measurement (MANOVA, E/HF), $p < 0.05$; +: because of the low number of surviving animals in the E Group, only descriptive statistics are given

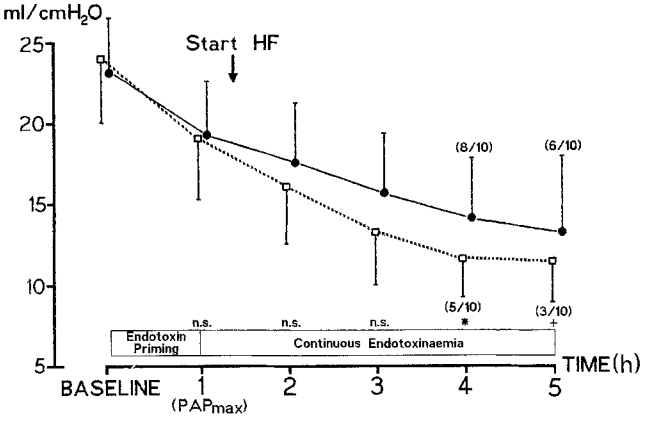

Fig. 4. Total compliance of the respiratory system during the stages of the experiment, given in means of ml/cm (H_2O). Data points are expressed as mean±SD. *E Group*, endotoxin-treated group (*dotted line*); *HF Group*, Haemofiltrated and endotoxin-treated group; *n.s.*, no statistical significance per point of measurement (E/HF). *: Statistical significance per point of measurement (MANOVA, E/HF), $p < 0.05$; +: because of the low number of surviving animals in the E Group, only descriptive statistics are given

Regarding the inspiratory compliance derived from the P/V curves in a volume segment of 0 to 400 ml and the corresponding pressure values (Fig. 5), analysis of variance showed significant differences ($p < 0.0001$) and different mean values at time 3 and 4 in the comparison between the two groups. Mean airway pressure (Baseline: E group 4.4±1.1 cmH_2O; HF group 4.3±0.8 cmH_2O) increased continuously in the E group during the stages of the experiment, with higher mean values compared to

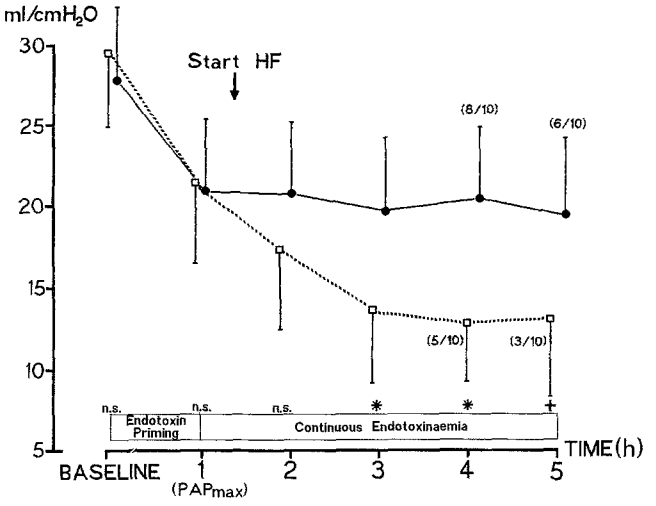

Fig. 5. Analysis of compliance of inflation as the slope of a volume segment of 0–400 ml and the corresponding pressure values during the stages of the experiment (expressed in means of ml/cm H_2O). Data points are expressed as mean±SD. *E Group*, endotoxin-treated group (*dotted line*); *HF Group*, Haemofiltrated and endotoxin-treated group. *n.s.*, no statistical significance per point of measurement (E/HF). *: Statistical significance per point of measurement (MANOVA, E/HF), $p<0.05$; +: because of the low number of surviving animals in the E Group, only descriptive statistics are given

the HF group from time 2 to time 5 and a significant difference at time 4 (E. 8.6±0.8 cmH_2O; HF: 6.9±2.0 cmH_2O).

Unrecovered volume showed no significant differences during the time course and between the two groups (Baseline: E 62.6±29 ml; HF 61.7±25 ml/time 4: E 65.3±25 ml HF 49.2±22 ml).

Figure 6 shows the time course of original P/V loops. Within each group the animals with values of hysteresis area and compliance closest to the mean value at time $1/PAP_{max}$ were selected.

Discussion

Acute renal failure in intensive care medicine often impresses as multiple organ failure syndrome [1–4, 6], mostly the consequence of sepsis and septic shock and the effect of bacterial endo- or exotoxins and mediator substances on different organ systems [11–16, 22, 23].

Continuous haemofiltration has proven its value in replacing excretory renal function [1, 2, 6] in this situation. Nevertheless, its interaction with the concurrent pulmonary dysfunction in sepsis is hardly investigated. The described improvement of gas exchange and survival rate during the course of septic ARDS [7, 8] as well as the modification of pulmonary circulation in a porcine model of endotoxic shock using a "zero-balanced" HF with a high ultrafiltration rate [9], suggested a beneficial effect of HF on endotoxin-induced lung dysfunction.

Mainly 2 mechanisms seem possible: firstly, a reduction of interstitial pulmonary oedema by negative balancing, especially when diuresis is impaired [25, 26]; and secondly, the convective transport of medium-sized mediator substances [7–9], such as prostaglandins [12] and leukotrienes [16], that are involved in the pathology of pulmonary hypertension, deterioration of lung mechanics and pulmonary oedema [12–16, 23, 27–30].

Whereas the first mechanism is undoubtedly a beneficial effect of HF [25, 26, 31, 32], we focused on the question whether the filtration process per se has an influence on lung injury in endotoxic shock. Consequently, the most important methodological aspect of this investigation was the avoidance of fluid resuscitation and the use of the "zero-balanced" technique [9] with simultaneous and identical rates of ultrafiltration and replacement fluid. This experimental approach was necessary to avoid any influence of the HF on the intravascular volume status with the implication that a hypodynamic state of endotoxic shock, with decreased cardiac filling was produced [9].

Recent data suggest that alterations of pulmonary compliance and airway resistance [12, 15, 16, 33, 34], in combination with pulmonary hypertension [12], are consistent expressions of early lung injury due to the complex effects of endotoxin and mediator substances.

This aspect and the lack of previous data makes the interference of HF with the deterioration of lung mechanics during endotoxinaemia to the most important aspect of this investigation.

Regarding respiratory pressure-volume curves (P/V curves) in paralyzed subjects by the syringe method,

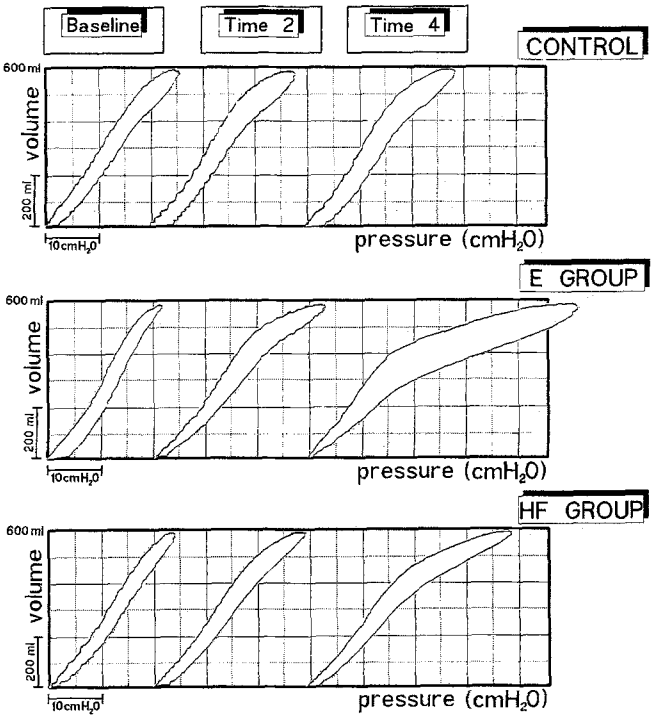

Fig. 6. Original pressure-volume curves of the respiratory system during the stages of the experiment (baseline, time 2/30′ after starting HF, time 4/150′ HF). Within each group the curve of one animal is shown, which represents at time $1/PAP_{max}$ values of hysteresis area and total compliance next to the mean value of this group. *Control*, control group, anesthesia and instrumentation without endotoxinaemia and haemofiltration ($n = 3$). *E Group*, endotoxin-treated group ($n = 10$); *HF Group*, haemofiltrated and endotoxin-treated group ($n = 10$)

methodological aspects as the influence of pulmonary gas exchange and O_2-consumption (VO_2), gas temperature and humidity on hysteresis area and the deflation compliance must be taken into account [20, 21]. In consequence, we concentrated upon the inspiratory P/V curves, being less influenced by these factors [20, 21].

Although we have to admit that we do not fully understand the mechanisms leading to hysteresis, the lack of differences in VO_2 and unrecovered volume between the two groups at any point of measurement makes it unlikely that a different gas exchange might be the main explanation for differences in hysteresis area between the 2 groups.

Also conflicting is the fact that the P/V-loop applied in this study represents a slow "dynamic compliance". We chose this procedure because a longer period of apnea would not be tolerated by the animals in endotoxic shock. Because of the lack of data about the time course of airway resistance we cannot differentiate the influence of different mechanisms on the shape of the P/V curve, i.e. changes in elastic properties, recruitment and derecruitment phenomena [35], changes of bronchial tone, airway resistance [12–16, 33, 34] and gas exchange [20, 21].

Even regarding these critical points, the most substantial result of this study is the description of a modified response of lung mechanics during zero-balanced, high volume veno-venous HF in a porcine endotoxic shock model.

Although a favorable influence of HF on pulmonary function and outcome in septic ARDS was described in previous clinical [7, 8] and experimental studies [31] the literatur contains no comparable data.

The design of this investigation as a zero-balanced HF and the results presented here support the contention that these alterations of pulmonary response to endotoxinaemia by HF are not identical to the well known effects on intravascular volume and on pulmonary oedema [7, 8, 25, 26, 31] by negative balancing. Although the time course of EVLW and A-aDO_2 are not changed by HF, compared to the spontaneous course, this procedure blunts the progressive deterioration of inflation compliance and hysteresis area and leads to significant lower mean airways pressures (Paw) under mechanical ventilation. Considering the difficult interpretation of data derived from respiratory pressure-volume curves [20, 21] this study is neither able to prove a definitive improvement of endotoxin-induced lung injury by HF nor to show a real clinical relevance [6]. Nevertheless, 2 aspects should be pointed out.

Firstly, these results represent another mosaic in the concept that the proven convective transport of endotoxin-induced mediator substances as eicosanoids [10] might be of pathophysiological relevance. They fit in well with recent results [12], showing that pulmonary hypertension and reduction of lung compliance are related to the release for Thromboxane A2. Pharmacological blocking of leukotrienes prevented pulmonary hypertension and an increase in airway resistance [16]. The size of leukotrienes (MW 600) make it likely that these mediators of importance in septic lung injury [5, 14–16, 27, 28] are eliminated by convective transport through the haemofilter as well as myocardial depressant substances [11, 31], interleukin 1 and α-TNF [19, 37]. The same mechanisms could be an explanation of the modification of mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), systemic and pulmonary vascular resistance [9] and reversal of left ventricular dysfunction during endotoxinaemia [11].

Secondly, the discrepancy of the beneficial influence of zero-balanced HF on lung mechanics and unaltered gas exchange and EVLW might be the expression that these parameters of endotoxic lung injury are impaired by different mechanisms and in a different sequence. Constancy of EVLW during the experiment might be the indicative of a delay of pulmonary edema with respect to alterations of gas exchange, lung mechanics and airway resistance during endotoxic shock, as supported by studies of McCaffree [33] and Esbenshade [34]. The interpretation that the combination of constant EVLW and lowered PCWP during HF are the expression of an increased capillary leak was first done by Sznajder in a canine acid aspiration model [38]. Methodological problems [17, 36] of the applied double-indicator technique [38] to assess EVLW as well as increasing mean airway pressures under controlled ventilation in our model, influencing markedly PCWP, make a similar interpretation rather hazardeous. Although deterioration of lung mechanics and gas exchange are the hallmarks of endotoxic lung injury [29, 33, 34], Kühl [12] could demonstrate during ovine endotoxinaemia a discrepancy between dynamic compliance, airway resistance and A-aDO_2, suggesting different underlying mechanisms.

Respecting the cautious interpretation of animal experimental findings, we conclude that there are additional effects of a zero-balanced HF in endotoxic induced pulmonary dysfunction, which are independent of an influence on the intravascular volume status and pulmonary oedema. Although the underlying mechanisms and the clinical relevance of our data remain hypothetical, the description of an impact of HF on hysteresis area, compliance and mean airway pressure during endotoxinaemia represents a new aspect with potential clinical implication and should stimulate further experimental and clinical investigations.

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