

Primary research

# Time-dependency of improvements in arterial oxygenation during partial liquid ventilation in experimental acute respiratory distress syndrome

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## Abstract

**Background:** The mechanisms by which partial liquid ventilation (PLV) can improve gas exchange in acute lung injury are still unclear. Therefore, we examined the time- and dose-dependency of the improvements in arterial oxygen tension ( $\text{PaO}_2$ ) due to PLV in eight pigs with experimental lung injury, in order to discriminate increases due to oxygen dissolved in perfluorocarbon before its intrapulmonary instillation from a persistent diffusion of the respiratory gas through the liquid column.

**Results:** Application of four sequential doses of perfluorocarbon resulted in a dose-dependent increase in  $\text{PaO}_2$ . Comparison of measurements 5 and 30 min after instillation of each dose revealed a time-dependent decrease in  $\text{PaO}_2$  for doses that approximated the functional residual capacity of the animals.

**Conclusion:** Although oxygen dissolved in perfluorocarbon at the onset of PLV can cause a short-term improvement in arterial oxygenation, diffusion of oxygen through the liquid may not be sufficient to maintain the initially observed increase in  $\text{PaO}_2$ .

**Keywords:** acute lung injury, partial liquid ventilation, perfluorocarbon

## Introduction

Partial liquid ventilation (PLV) is a novel technique to improve gas exchange in acute lung injury (ALI). It combines the intrapulmonary application of perfluorocarbons in volumes up to the functional residual capacity of the lungs with conventional gaseous ventilation [1], and has been shown to improve gas exchange and lung mechanics in a dose-dependent manner in experimental and clinical settings of severe respiratory failure [2–5]. Two different mechanisms are presently proposed to account for a persistent increase in arterial oxygenation during PLV. First, it is suggested that the low surface tension of perfluorocarbons

(10–15 dyn/cm) can facilitate the recruitment of atelectatic lung segments for ventilation, indicated by an increase in lung compliance [6]. Second, it is hypothesized that pooling of the dense compounds (1.75–1.92 g/ml) along the gravitational gradient causes a redistribution of pulmonary blood flow from dependent to nondependent, better ventilated lung areas, due to a compression of the pulmonary vasculature in the dorsal lung regions [7,8]. Additionally, the high solubility of oxygen and carbon dioxide in perfluorocarbons (40–60 and 160–210 ml/100 ml, respectively) suggests a potential role for these substances as transport media for the respiratory gases in nonventilated but perfluorocarbon-

filled, dependent lung segments, depending on the diffusion of oxygen and carbon dioxide through the liquid. A persistent effect on pulmonary gas exchange requires an efficient transfer of oxygen from the inspired gas to the perfluorocarbon and through the liquid column to the alveoli. Oxygen dissolved in perfluorocarbon before the intrapulmonary instillation of the compound, however, may cause only a short-lasting improvement in arterial oxygenation after the onset of PLV.

The aim of this study was to discriminate such diffusion-dependent short-term and long-term effects of PLV on arterial oxygenation by testing the time-dependency of increases in arterial oxygen tension ( $\text{PaO}_2$ ) during PLV with four different doses of perfluorocarbon in an experimental model of ALI in medium sized pigs. We found a time- and dose-dependent increase in  $\text{PaO}_2$  in this setting, suggesting a minor role of oxygen transfer through perfluorocarbon in the improvement of gas exchange observed during PLV.

## Materials and methods

### Animal preparation

The experimental protocol was approved by the appropriate governmental institution and the study was performed according to the Helsinki convention for the use and care of animals.

In eight female pigs ( $27 \pm 5$  kg body weight), anaesthesia was induced with metomidate (2 mg/kg) and maintained with the continuous infusion of methohexital (50–100 mg/kg per min) and sufentanil (25–50 ng/kg per min). Muscle relaxation was achieved with pancuronium bromide ( $3 \mu\text{g}/\text{kg}$  per min). All animals were positioned supine and a tracheotomy and subsequent intubation with a 8.0–9.0 mm inner diameter endotracheal tube were performed. Volume-controlled ventilation was instituted using a respirator (Servo 900 C; Siemens Elema, Lund, Sweden) with a fraction of inspired oxygen of 1.0, a respiratory rate of 20 breaths/min, a mean tidal volume of 10 ml/kg, a positive end-expiratory pressure (PEEP) of 5  $\text{cmH}_2\text{O}$  and an inspiration:expiration ratio of 1:2 without pause time. The ventilator setting remained unchanged during the study.

A 18 G arterial line (Vygon, Ecoen, France) and a 8.5 Fr venous sheath (Arrow Deutschland GmbH, Erding, Germany) for positioning of a right heart catheter (model 93A-431-7.5 F; Baxter Healthcare Corporation, Irvine, CA, USA) under transduced pressure guidance were percutaneously inserted into the femoral vessels.

The blood temperature, determined by means of the pulmonary artery catheter, was maintained at  $37.2 \pm 1.1^\circ\text{C}$  during the experiment using an infrared warming lamp and a warming pad. A continuous infusion of 4–5 ml/kg per min of a balanced electrolyte solution was administered for adequate hydration.

### Data acquisition

All haemodynamic measurements were taken in the supine position with zero reference level at the midchest. Central venous pressure, mean arterial pressure, mean pulmonary arterial pressure and pulmonary artery occlusion pressure of all animals were transduced (Baxter Deutschland GmbH, Unterschleißheim, Germany) and recorded (Hewlett-Packard Model 66 S monitor; Böblingen, Germany). Cardiac output was determined using standard thermodilution techniques (Baxter Deutschland GmbH) and expressed as the mean of three measurements at end-expiration of different respiratory cycles. Heart rate was taken from the blood pressure curve.

Arterial and mixed venous blood samples were collected anaerobically and immediately analyzed for partial oxygen tension, partial carbon dioxide tension and pH using standard blood gas electrodes (ABL 520; Radiometer, Copenhagen, Denmark). Species-specific spectrophotometry was performed to obtain arterial and mixed venous oxygen saturation and total haemoglobin concentration (OSM 3 Hemoximeter; Radiometer).

The oxygen contents (ml/dl) of arterial ( $\text{CaO}_2$ ), mixed venous ( $\text{CvO}_2$ ) and pulmonary capillary ( $\text{CcO}_2$ ) samples were calculated using the following formula: content of oxygen = (haemoglobin concentration  $\times$  1.34  $\times$  percentage oxygen saturation/100) + (partial oxygen tension  $\times$  0.0031). To calculate  $\text{CcO}_2$ , the pulmonary capillary oxygen tension was assumed to be equivalent to the alveolar partial oxygen tension, which was estimated as follows: barometric pressure – arterial carbon dioxide tension/respiratory quotient (assuming that the respiratory quotient is 0.8) – water vapour pressure (47 mmHg) – perfluorocarbon vapour pressure [61 mmHg for FC 3280 (3M Chemical Products, Neuss, Germany), only when PLV was performed] [9]. The venous admixture was derived from the standard shunt equation:  $(\text{CcO}_2 - \text{CaO}_2)/(\text{CcO}_2 - \text{CvO}_2)$ .

### Experimental protocol

ALI was induced in all animals according to the method of Lachmann *et al* [10] by surfactant depletion caused by repeated lung lavage with prewarmed saline (0.15 mol/l,  $37^\circ\text{C}$ , 30 ml/kg). Baseline values for ALI were collected after the  $\text{PaO}_2$  remained persistently below 100 mmHg for 1 h without further interventions. Subsequently, four incremental doses of 7.5 ml/kg FC 3280 (3M Chemical Products) were intratracheally administered via a swivel-connector (Portex, Kent, UK) without disconnecting the animals from the respirator or interrupting ventilation. Each dose was administered in volumes of 2–2.5 ml perfluorocarbon per inspiration, requiring approximately 4 min until the total volume of 7.5 ml/kg was applied. To compensate for losses due to evaporation, a volume of 4 ml/kg per h of FC 3280 was continuously administered endotracheally.

when PLV was performed [11]. FC 3280 ( $C_8F_{18}$ ) is a highly purified industrial perfluorocarbon with physical and chemical properties comparable to those of perflubron (LiquiVent; Alliance, San Diego, USA), which is at present the most commonly used perfluorocarbon in experimental and clinical settings of PLV, but which is not available in Europe. The density of FC 3280 is  $1.75 \text{ g/cm}^3$ , it has a viscosity of 0.7 centistokes, a vapour pressure of 61 torr and a surface tension of  $12 \text{ mN/m}$  at  $25^\circ\text{C}$ , and it can dissolve up to 40 ml oxygen/100 ml perfluorocarbon and 192 ml carbon dioxide/100 ml perfluorocarbon.

All haemodynamic and gas exchange parameters were determined 5 and 30 min after starting the instillation of each dose of perfluorocarbon. At the end of the study, all animals were killed with an intravenous application of potassium chloride.

### Statistical analyses

All data are expressed as means  $\pm$  standard deviation. Statistical analyses were performed using the NCSS 6.0.7 software package (NCSS, Kaysville, USA). The data were analyzed by analysis of variance for repeated measurements, followed by Bonferroni's multiple comparison test when analysis of variance revealed significant differences for all treatment periods.  $P < 0.05$  was considered statistically significant.

### Results

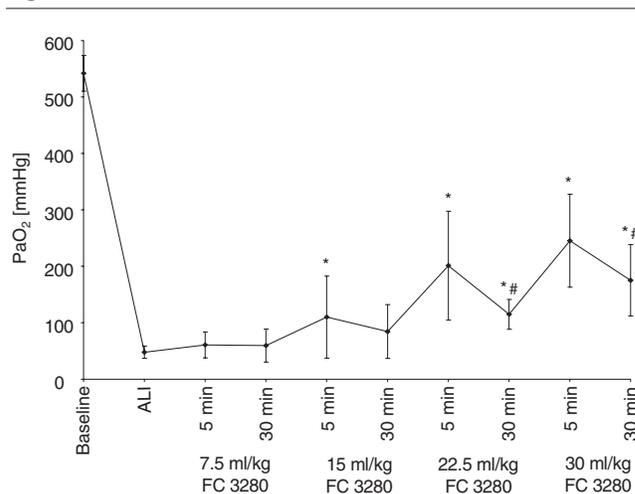
All animals survived the entire study period. Examination of all animals by a veterinary surgeon before the study confirmed the absence of any sign of infection or pulmonary disease. Total haemoglobin concentration and capillary oxygen content remained unchanged throughout the study.

A mean of  $8 \pm 2$  lavages had to be performed in order to obtain a stable ALI, with a persistent decrease in  $\text{PaO}_2$  from  $542 \pm 32$  to  $48 \pm 11 \text{ mmHg}$ .

### Gas exchange

Partial liquid ventilation resulted in a dose-dependent increase of arterial oxygenation, which reached statistical significance compared to ALI when  $\text{PaO}_2$  was measured 5 min after the onset of PLV with 15, 22.5 and 30 ml/kg perfluorocarbon, respectively ( $P < 0.001$ ). Determination of the  $\text{PaO}_2$  after 30 min revealed a persistent improvement in  $\text{PaO}_2$  compared with values after inducing lung injury, when PLV was performed with 22.5 and 30 ml/kg FC 3280 ( $P < 0.001$ ). A significant decrease in arterial oxygenation was observed with the latter doses when values after 5 min were compared with measurements obtained after 30 min, however ( $P < 0.001$ ; Fig. 1). The venous admixture decreased after the instillation of perfluorocarbon doses of 15 ml/kg or greater when compared with ALI, with no differences between measurements after 5 and 30 min for each dose (Table 1).  $\text{PaCO}_2$  increased

Figure 1



Time-dependency of arterial oxygen tension ( $\text{PaO}_2$ ) during partial liquid ventilation (PLV). Changes in  $\text{PaO}_2$  during PLV with four different doses of the perfluorocarbon FC 3280 (7.5, 15, 22.5 and 30 ml/kg). Baseline denotes measurements of  $\text{PaO}_2$  in the healthy, anaesthetized animals; acute lung injury (ALI) denotes values after the induction of lung injury; 5 and 30 min denote determination of  $\text{PaO}_2$  after 5 and 30 min PLV with each dose of perfluorocarbon. \* $P < 0.05$  versus ALI, # $P < 0.05$  versus values after 5 min with the same dose of perfluorocarbon.

from  $39 \pm 7$  to  $48 \pm 6 \text{ mmHg}$  ( $P < 0.001$ ) with a concomitant decrease in pH from  $7.48 \pm 0.08$  to  $7.37 \pm 0.06$  ( $P < 0.001$ ) after the induction of lung injury and remained stable thereafter throughout the study (Table 2).

### Haemodynamics

All haemodynamic data are summarized in Table 3. No changes for mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, heart rate and cardiac output were observed throughout the entire study period. Mean pulmonary arterial pressure increased from  $18 \pm 4$  to  $25 \pm 5 \text{ mmHg}$  ( $P < 0.001$ ) after the onset of ALI and remained unchanged thereafter.

### Discussion

The purpose of the present study was to determine the effect of time on the improvement in arterial oxygenation observed during PLV with four different doses of perfluorocarbon in an experimental model of ALI in pigs. The major finding was a time-dependent decrease in  $\text{PaO}_2$  during PLV with perfluorocarbon doses approximating the functional residual capacity of the animals [1]. This may indicate that, after initial deoxygenation of FC 3280, diffusion of the respiratory gases through the perfluorocarbon that pooled in the dependent unventilated or only poorly ventilated lung segments was not sufficient to maintain  $\text{PaO}_2$  values achieved immediately after instillation of the liquid. Additionally, the continuous administration of perfluorocarbon in order to substitute for evaporational losses

**Table 1**

**Gas exchange data**

	Baseline	PLV with 7.5 ml/kg FC 3280			PLV with 15 ml/kg FC 3280			PLV with 22.5 ml/kg FC 3280			PLV with 30 ml/kg FC 3280		
		ALI	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	
HbaO <sub>2</sub> (%)	99.1 ± 1.0	67.3 ± 14.1	78.0 ± 11.4	71.8 ± 23.1	89.9 ± 10.9	83.5 ± 13.7	94.6 ± 8.9*	92.5 ± 10.8*	98.7 ± 1.6*	94.5 ± 6.7*			
HbvO <sub>2</sub> (%)	80.1 ± 6.6	35.2 ± 16.5	44.5 ± 13.9	43.3 ± 23.3	57.2 ± 14.1	51.2 ± 16.1	64.8 ± 11.2*	62.6 ± 13.5*	67.2 ± 6.5*	63.4 ± 10.0*			
PvO <sub>2</sub> (mmHg)	51 ± 7	30 ± 8	34 ± 7	34 ± 11	42 ± 8*	40 ± 9*	47 ± 8*	44 ± 8*	48 ± 5*	45 ± 7*			
CaO <sub>2</sub> (ml/100 ml)	11.3 ± 1.8	6.1 ± 2.1	6.9 ± 1.5	6.7 ± 2.4	8.5 ± 1.5*	8.0 ± 2.2*	9.2 ± 1.5*	8.6 ± 1.9*	9.5 ± 1.8*	8.9 ± 1.9*			
CvO <sub>2</sub> (ml/100 ml)	8.0 ± 1.5	3.3 ± 1.9	4.0 ± 1.6	4.1 ± 2.6	5.4 ± 1.6*	5.0 ± 2.2	6.2 ± 1.8*	5.8 ± 1.7*	6.1 ± 1.5*	5.7 ± 1.4*			
Venous admixture (%)	12 ± 4	61 ± 7	55 ± 8	60 ± 13	43 ± 11*	49 ± 12*	36 ± 13*	43 ± 9*	28 ± 4*	37 ± 8*			

Values are expressed as mean ± standard deviation. \*P < 0.05 versus acute lung injury (ALI). CaO<sub>2</sub>, arterial oxygen content; CvO<sub>2</sub>, mixed venous oxygen content; HbaO<sub>2</sub>, arterial oxygen saturation; HbvO<sub>2</sub>, mixed venous oxygen saturation; PLV, partial liquid ventilation.

**Table 2**

**Gas exchange, peak airway pressure and metabolic data**

	Baseline	PLV with 7.5 ml/kg FC 3280			PLV with 15 ml/kg FC 3280			PLV with 22.5 ml/kg FC 3280			PLV with 30 ml/kg FC 3280		
		ALI	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	
AvDO <sub>2</sub> (ml/100 ml)	3.4 ± 0.9	2.8 ± 0.6	2.9 ± 0.4	2.6 ± 0.5	3.2 ± 0.4	3.1 ± 0.6	3.1 ± 0.5	2.9 ± 0.7	3.4 ± 0.6	3.1 ± 0.7			
VO <sub>2</sub> (ml/min)	158 ± 41	157 ± 44	163 ± 24	139 ± 31	159 ± 23	160 ± 37	146 ± 20	146 ± 36	164 ± 39	162 ± 48			
DO <sub>2</sub> (ml/min)	549 ± 189	345 ± 160	391 ± 111	351 ± 109	444 ± 138	420 ± 139	452 ± 135	441 ± 121	461 ± 104*	455 ± 122*			
PaCO <sub>2</sub> (mmHg)	39 ± 7	48 ± 6	48 ± 5	49 ± 4	49 ± 4	49 ± 8	47 ± 4	49 ± 5	49 ± 3	49 ± 3			
pH	7.48 ± 0.08	7.37 ± 0.06	7.38 ± 0.05	7.36 ± 0.04	7.36 ± 0.04	7.35 ± 0.04	7.37 ± 0.05	7.38 ± 0.04	7.37 ± 0.03	7.38 ± 0.05			
Peak airway pressure (cmH <sub>2</sub> O)	16 ± 3	31 ± 5	26 ± 2*	29 ± 6	27 ± 5*	29 ± 6	29 ± 7	29 ± 7	31 ± 6	31 ± 8			

Values are expressed as mean ± standard deviation. \*P < 0.05 versus acute lung injury (ALI). avDO<sub>2</sub>, arteriovenous oxygen content difference; DO<sub>2</sub>, oxygen delivery; VO<sub>2</sub>, oxygen consumption; PaCO<sub>2</sub>, arterial carbon dioxide tension; PLV, partial liquid ventilation.

**Table 3**

**Haemodynamic data**

	Baseline	PLV with 7.5 ml/kg FC 3280			PLV with 15 ml/kg FC 3280			PLV with 22.5 ml/kg FC 3280			PLV with 30 ml/kg FC 3280		
		ALI	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	5 min	30 min	
MAP (mmHg)	107 ± 13	98 ± 16	104 ± 18	104 ± 20	110 ± 15	106 ± 18	104 ± 14	92 ± 35	104 ± 14	99 ± 13	104 ± 6		
MPAP (mmHg)	18 ± 4	25 ± 5	23 ± 3	23 ± 5	24 ± 5	25 ± 5	26 ± 6	24 ± 6	26 ± 6	28 ± 5	28 ± 5		
CVP (mmHg)	7 ± 2	7 ± 3	7 ± 3	7 ± 3	8 ± 4	8 ± 3	8 ± 4	7 ± 4	8 ± 4	9 ± 3	8 ± 3		
PAOP (mmHg)	9 ± 3	9 ± 4	11 ± 4	9 ± 4	11 ± 3	10 ± 3	10 ± 4	10 ± 4	10 ± 4	11 ± 4	11 ± 5		
Carbon dioxide (l/min)	4.83 ± 1.26	5.53 ± 0.89	5.64 ± 0.99	5.39 ± 0.68	5.11 ± 0.95	5.26 ± 0.82	5.08 ± 0.80	4.82 ± 0.85	5.08 ± 0.80	4.87 ± 0.53	5.11 ± 0.60		
Heart rate (beats/min)	106 ± 24	103 ± 20	100 ± 16	110 ± 15	99 ± 15	106 ± 18	104 ± 16	98 ± 17	104 ± 16	95 ± 14	99 ± 13		

Values are expressed as mean ± standard deviation. ALI, acute lung injury; CVP, central venous pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary artery occlusion pressure; PLV, partial liquid ventilation.

can avoid a decrease in the total volume of perfluorocarbon in the lung, but there may be a significant difference in the distribution of the liquid when compared with the application of a bolus. Evaporation is likely to be increased in lung units reconducted to gaseous ventilation after recruitment due to the surfactant-like activity of perfluorocarbon. If the evaporational loss of perfluorocarbon in these units can not be substituted due to their localization, the alveoli may destabilize again and recurrent atelectasis may occur, resulting in a time-dependent decrease in arterial oxygenation.

The model we used in the present investigation was evaluated before [10] and has been shown to be stable, even over extended periods [12]. It has been extensively used in other experimental studies on the effect of PLV on pulmonary gas exchange and lung mechanics [6,12–14]. Although the early stage of the lung injury generated in this model resembles more the neonatal form of the respiratory distress syndrome, its late stage demonstrates all features of severe ARDS such as atelectasis, increased alveolar permeability and desquamation of airway epithelium [15]. The observation of the present study that PLV can improve gas exchange and peak airway pressure in the saline lung lavage model is in accordance with the results of other investigators. Also, physical or chemical differences between Perflubron (Liquivent; Alliance, San Diego, USA), recently under investigation in human trials, and FC 3280 used in the present study are unlikely to influence these effects, as previously shown by our group [11]. In contrast to these experimental findings, the first studies on humans with ARDS reported a more inhomogenous response to PLV. Hirschl *et al* [16] applied PLV to patients with acute respiratory distress on extracorporeal life support and found that some patients did not demonstrate improvements in pulmonary right-to-left shunt and arterial oxygenation after the endotracheal instillation of perfluorocarbon. Furthermore, a clinical study investigating the effect of PLV in premature infants with severe respiratory distress syndrome [3] also reported a wide range of individual responses. The reason for this lack of effect remains speculative, but it may be assumed that different degrees and causes of lung injury determining ventilation may account for this observation.

The transfer of oxygen from the inspired gas to the erythrocyte depends on several components such as the number of ventilated alveoli, the diameter of the airway, the thickness of the alveolar–capillary membrane and the capillary transit time as a function of cardiac output [17]. These variables are seriously affected in ARDS due to the increased weight of the infiltrated lung, which results in airway collapse and increased density preferentially in the dependent lung segments [18] and a severe reduction in the ventilated lung volume with a subsequent increase in pulmonary shunt

[19,20]. The application of a gaseous PEEP in patients with ARDS has been shown to recruit atelectatic lung segments, thereby increasing the volume of lung accessible for ventilation and improving gas exchange [20]. Consequently, the instillation of perfluorocarbon has been proposed to act like a liquid PEEP, exerting its vertically graded, beneficial effect of distending collapsed lung regions preferentially in the dependent lung areas due to the high density of the perfluorocarbons [21]. However, despite the recruitment of atelectatic alveoli, the pooling of perfluorocarbon in the dependent lung segments have been shown [7] to reduce or avoid gaseous ventilation in these areas, possibly impairing gas exchange unless a sufficient gas transfer over the liquid column can be achieved. Whether such a transfer through the perfluorocarbon actually occurs is still unclear [21]. Like during the instillation of the liquid, when the intense contact with the respiratory gas is assumed to result in complete oxygenation of the perfluorocarbon, it may depend on the existence of the postulated intrapulmonary *in vivo* bubble oxygenation and the contact surface between the inspiratory gas and the perfluorocarbon in comparison with the alveolar surface persistently covered by the liquid. Furthermore, the uptake of oxygen by the erythrocyte has to be equalled by its transfer from the gaseous tidal volume to the perfluorocarbon. Both determinants are still unknown. However, our observation that arterial oxygenation demonstrates a time-dependent decrease may indicate that this mechanism could be of inferior importance in maintaining gas exchange during PLV and that the redistribution of blood flow and the recruitment of alveoli that remain ventilated thereafter predominantly account for the improvement in PaO<sub>2</sub>. This conclusion is supported by data from Mates *et al* [9] who found a dose-dependent increase in pulmonary shunt during PLV in healthy piglets using the multiple inert gas elimination technique. They suggest that, apart from pure shunt, these results are due to a diffusion limitation of oxygen and carbon dioxide in lungs partly filled with perfluorocarbon.

These uncertainties need to be addressed in future studies investigating the ventilation:perfusion ratio and the diffusion of gases through the liquid perfluorocarbons, in order to understand better the mechanisms by which PLV can improve gas exchange and to elucidate the relevance of the compound as a transfer medium for oxygen and carbon dioxide during PLV.

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