Fluctuating CPAP (F-CPAP) versus Conventional CPAP (C-CPAP) in Dogs with Blood Aspiration

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Fluctuating CPAP(F-CPAP) is a combination of spontaneous ventilation and fluctuating PEEP, in which end-expiratory pressure (EEP) is periodically changed within a certain range. In a dog model with localized lung injury induced by the aspiration of non-heparinized blood (2 $ml \cdot kg^{-1}$ body weight), we carried out a comparative study of the effects of F-CPAP in which the EEP was cyclically changed from 4 to 12 cmH_2O with periods of 10 min and those of conventional CPAP with a fixed EEP of 8 cmH_2O (C-CPAP), on hemodynamics and pulmonary oxygenation. The blood aspiration produced significant increases in the intrapulmonary shunt ($\dot{Q}sp/\dot{Q}t$), the alveolar-arterial difference of partial pressure of oxygen (A-aDO_2), and the respiratory rate (RR). Although both F-CPAP and C-CPAP reduced $\dot{Q}sp/\dot{Q}t$ and A-aDO_2 and RR, 7 dogs treated with F-CPAP showed a significantly greater recovery of $\dot{Q}sp/\dot{Q}t$ and A-aDO_2 than 7 dogs treated with C-CPAP. There were no significant differences in hemodynamic variables between the two groups. These results suggest that F-CPAP is more useful in the treatment of some kinds of hypoxic respiratory failure due to uneven distribution of lung injury. (Key words: fluctuating positive end-expiratory pressure, fluctuating continuous positive airway pressure, alveolar-arterial difference of partial pressure of oxygen, intrapulmonary shunt, cardiac output)

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Fluctuating PEEP (F-PEEP) is a new type of PEEP, in which end-expiratory pressure (EEP) is periodically altered within a certain range so that a sine-curved change in EEP is obtained (fig. 1). We have performed comparative studies of F-PEEP and conventional PEEP with fixed EEPs (C-PEEP), and found, in combination with controlled ventilation, more beneficial effects of F-PEEP on pulmonary oxygenation in three kinds of canine models with acute hypoxic respiratory failure characterized by uneven distribution of lung injury[1–3]. In these unilaterally or relatively localized lung injuries, Pa_{O_2} was rapidly and more increased by F-PEEP (or fluctuating continuous positive pressure ventilation; F-CPPV). This enhanced Pa_{O_2} included periodical changes, which were reciprocally proportional to the EEP alteration. On the other hand, F-PEEP produced periodically altered hemodynamic depression, which was proportional to the EEP change. Thus, relatively high Pa_{O_2} and cardiac output were obtained at the low EEP phase of F-PEEP. Although C-PEEP (or conventional continuous positive pressure ventilation; C-CPPV) did gradu-

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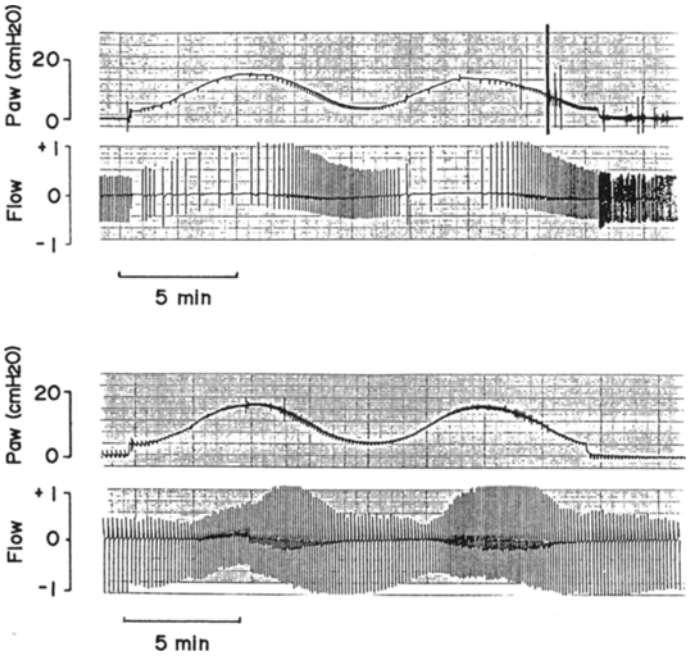

Fig. 1. Recording of airway pressure and respiratory flow during F-CPAP.

Respiratory rate was decreased in proportion to EEP. Extremely low respiratory rate or apnoea was observed during F-CPAP (upper panel). Cervical vagotomy abolished this alteration of respiratory rate (lower panel).

ally increase Pa_{O_2}, it failed to achieve better pulmonary oxygenation than F-PEEP. Furthermore, in one model of unilaterally dominant pulmonary edema[3], C-PEEP (C-CPPV) initially failed to improve pulmonary oxygenation.

PEEP therapy has been widely applied in conjunction not only with positive pressure ventilation (continuous positive pressure ventilation; CPPV) but also with spontaneous ventilation (continuous positive airway pressure CPAP). CPAP is favorable to CPPV for the management of some kinds of respiratory failure, since it keeps airway pressure lower than CPPV[4,5]. Therefore, it is of interest to compare F-PEEP (F-CPAP) and C-PEEP (C-CPAP) in conjunction with spontaneous breathing. In the present study, we compared the effects of F-CPAP with those of C-CPAP in dogs with aspiration of autologous blood.

Materials and Methods

In preliminary study, we found that respiratory rate was decreased with increasing the value of PEEP in dogs anesthetized with pentobarbital. PEEP as high as 15 cmH_2O produced an apnoea or extremely low respiratory rate, which was restored by either cervical vagotomy or discontinuation of PEEP (fig. 1). Thus, the range of F-CPAP in the following experiments was set between 4 and 12 cmH_2O. To make an appropriate comparison we adjusted C-CPAP to 8 cmH_2O.

Fourteen healthy mongrel dogs weighing from 9 kg to 15 kg (mean weight 12 kg) were anesthetized with 30 $mg \cdot kg^{-1}$ body weight of pentobarbital, and their tracheas were intubated with a cuffed endotracheal tube. They were placed in a supine position, and allowed to breathe a constant flow of gas mixture of 40% oxygen and 60% nitrogen spontaneously through a non-rebreathing circuit composed of two one-way valve and a wide reservoir bag.

Airway pressure was monitored at the proximal site of the tracheal tube. A catheter was introduced via the right femoral artery for the measurement of mean arterial pressure (MAP) and arterial blood sampling. A 7 Fr. Swan-Ganz catheter was introduced through the right femoral vein into the pulmonary artery, and the mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac

Table 1. Sequential measurement of Pa_{O_2} (mmHg)

	base-line	before CPAP	minutes after CPAP 20	25	40	45	60	65	90	95	120	125	180	185
Group I (F-CPAP)	178± 17#	68± 16	115± 20#	99± 29#	119± 27#	117± 32#	129± 22#	125± 28#	145± 23#*	128± 21#	154± 23#*	143± 16#+	165± 9#*	148± 18+
Group II (C-CPAP)	174± 14#	74± 9	93± 15#		99± 21#		102± 22#		110± 27#*		115± 27#*+		128± 27#*+	

During F-CPAP measurements were done at EEP = 4 (20, 40, 60, 90, 120 and 180 min) and at EEP = 12 cmH_2O (25, 45, 65, 95, 125 and 185 min).

#significant changes from the values before CPAP. *F-CPAP at EEP = 4 cmH_2O is significantly different from C-CPAP. +F-CPAP at EEP = 12 cmH_2O is significantly different from C-CPAP.

output were determined. A proximal lumen of the catheter was applied to the route of the infusion. We introduced another Swan-Ganz catheter via the right jugular vein into the right atrium to measure right atrial pressure (RAP) and to inject cold (approximately 0°C) 5% glucose solution for the determination of cardiac output by the thermodilution method (NTC-6200, Nihon Koden, Japan). The measurement of cardiac output was repeated twice, and the mean values were obtained. Lactate Ringer solution was continuously infused at the rate of 2 $ml \cdot kg^{-1}$ body $weight \cdot hr^{-1}$. Anesthesia was maintained with continuous intravenous administration of pentobarbital at 2 $ml \cdot kg^{-1}$ body $weight \cdot hr^{-1}$. All hemodynamic measurements were made at the end-expiratory phase. Body temperature was kept in the range of 36.0 to 38.0°C using heat lamps.

After the respiratory and cardiovascular status became stable, the baseline measurements were performed. Then, 2 $ml \cdot kg^{-1}$ body weight of autologous non-heparinized blood was slowly injected into the traches to produce atelectasis. The animals breathed without PEEP for 30 min, and then were treated in the following manner. Seven dogs (Group I) received F-CPAP in which EEP was periodically changed from 4 to 12 cmH_2O at intervals of 10 min. The other 7 dogs (Group II) were treated with C-CPAP in which EEP was fixed at 8 cmH_2O. Both kinds of CPAP were produced by placing an electrically controlled PEEP valve at the end of expiratory portion of respiratory circuit.

The hemodynamic measurements and samplings of both arterial and venous blood were performed immediately before the application of CPAP, and were repeated at 20, 40, 60, 90, 120 and 180 min after the application. In dogs treated with F-CPAP the measurements and samplings were done both at EEP = 4 cmH_2O (20, 40, 60, 90, 120 and 180 min) and at EEP = 12 cmH_2O (25, 45, 65, 95, 125 and 185 min).

Heparinized arterial and mixed-venous blood samples were analyzed for pH and blood gases (IL 1302, Instrumentation Laboratory, U.S.A.) and hemoglobin concentration (Compur M-1000, Compur-Electronic GmbH, West Germany). Alveolar-arterial difference of partial pressure of oxygen ($AaDo_2$) and intrapulmonary shunt ($\dot{Q}sp/\dot{Q}t$) were computed using the algorithms of Ruiz et al.[6]

The change in variables in each animal group were analyzed by one-way analysis of variance followed by the determination of least significant difference. Comparisons of C-CPAP with F-CPAP were made using one-way analysis of variance and the Dunnett's test. Both difference and change were considered to be significant when probability values were less than 0.05 ($P < 0.05$). All values in the table and figures were expressed as mean ± SD.

Results

The blood aspiration produced no significant changes in MPAP, PCWP and RAP (fig. 2). The application of C-CPAP or F-

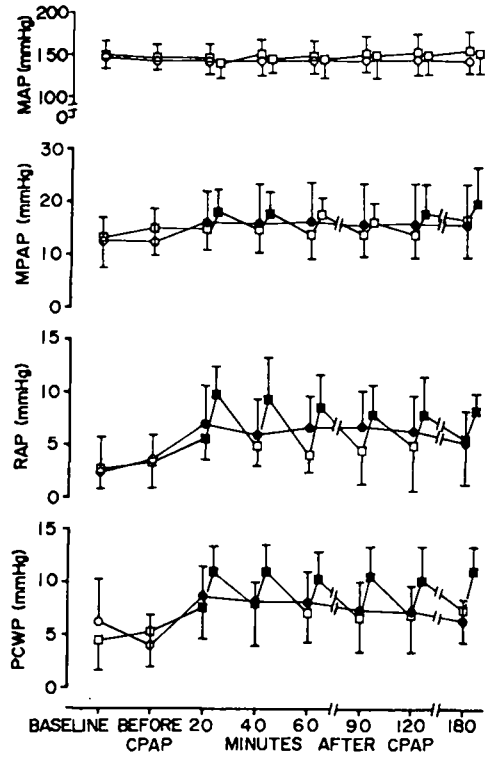

Fig. 2. Changes in MPAP, RAP and PCWP. Boxes denote Group I animals treated with F-CPAP, and circles represent Group II animals treated with C-CPAP. During F-CPAP measurements were performed at EEP = 4 (20, 40, 60, 90, 120 and 180 min) and at EEP = 12 cmH_2O (25, 45, 65, 95, 125 and 185 min). Closed symbols represent significant changes from the measurement before CPAP. All values are expressed as mean ± SD. Symbols are the same in figure 3 and 4.

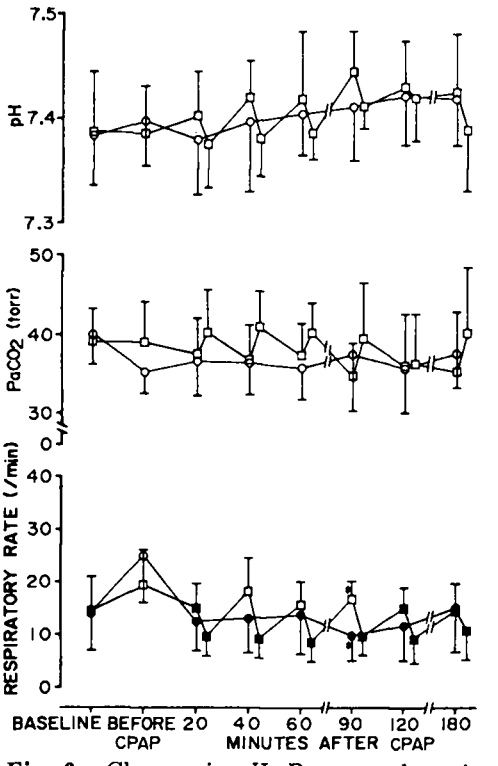

Fig. 3. Changes in pH, Pa_{CO_2} and respiratory rate.
*F-CPAP at EEP = 4 cmH_2O is significantly different from C-CPAP.

CPAP increased these values. The degree of the increases appeared to be correlated to the EEP, and in Group I animals treated with F-CPAP the values altered in proportion to the EEP change. There was no significant alterations of MAP either in Group I or Group II animals.

Figure 3 demonstrates the changes in arterial pH, Pa_{CO_2} and respiratory rate. In the both groups of dogs, respiratory rate was significantly incremented after the blood aspiration, and was decreased in reciprocal proportion to the EEP after the application of C-CPAP or F-CPAP. The periodic alteration of respiratory rate was produced by F-CPAP. Despite the significant change in respiratory rate, Pa_{CO_2} and pH were not significantly altered during the experimental course.

The changes in A-aDo_2, $\dot{Q}sp/\dot{Q}t$ and cardiac output are shown in figure 4. The sequential determinations of Pa_{O_2} were demonstrated in table 1. The blood aspiration produced a similar degree of increases in A-aDo_2 and $\dot{Q}sp/\dot{Q}t$ and decrease in Pa_{O_2} in the two groups. Both F-CPAP and C-CPAP improved A-aDo_2, $\dot{Q}sp/\dot{Q}t$ and Pa_{O_2}. However, significant differences in A-aDo_2, $\dot{Q}sp/\dot{Q}t$ and Pa_{O_2} between F-CPAP and C-CPAP became detectable from 120, 60 and 90 min, respectively. Cardiac output was not significantly altered by the aspiration of blood, but was significantly decreased from 45 min of the application of F-CPAP and immediately after C-CPAP. There was no significant difference in cardiac output between the two

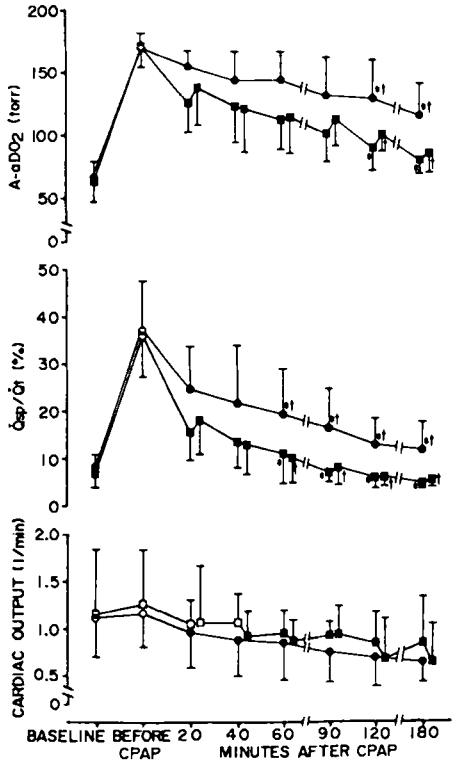

Fig. 4. Changes in A-aDo$_2$, Q̇sp/Q̇t and cardiac output.

*F-CPAP at EEP = 4 cmH_2O is significantly different from C-CPAP. $^+$F-CPAP at EEP = 12 cmH_2O is significantly different from C-CPAP.

groups. On the contrary to our previous reports on F-CPPV, periodical alterations of A-aDo$_2$, Pa_{O_2} and cardiac output were not prominent in Group I animals treated with F-CPAP.

Discussion

In the present study, acute lung injury was produced by the slow intratracheal injection of autologous non-heparinized blood, as reported by Halmagyi et al.[7] and Perel[8]. Our previous report revealed that the impaired gas exchange produced by this procedure was mainly due to the atelectatic change existing in the bilateral dependent portions of the lung[1].

In this type of lung injury, F-CPAP resulted in a greater improvement of pulmonary oxygenation than C-CPAP with a similar degree of cardiovascular depression, suggesting that F-CPAP is useful for the treatment of acute hypoxic respiratory failure due to increased ventilation-perfusion mismatching. This finding is in accord with that of our previous studies, which illustrated the beneficial effects of the combination of F-PEEP and continuous positive pressure ventilation (F-CPPV) in acute hypoxic respiratory failure due to uneven distribution of lung injury[1-3]. Therefore, it is suggested that F-PEEP is more useful in combination not only with CPPV but also with CPAP.

However, several findings in this study were different from those of our previous reports. First, in our previous study we mechanically ventilated animals with constant tidal volume and respiratory rate. In this study, we allowed the animals to breathe spontaneously. In the preliminary studies (fig. 1), we found that the respiratory rate was decreased by CPAP and periodically changed in reciprocal proportion to the EEP alteration during F-CPAP. Furthermore, apnoea produced by EEP exceeding 15 cmH_2O forced us to set the EEP range 4 to 12 cmH_2O in F-CPAP.

In anesthetized animals, it is well known that the inflation of the lung inhibited the spontaneous contraction of the diaphragm via pulmonary stretch receptors[9]. This Hering-Breuer reflex seems to be responsible not only for the periodical alteration of the respiratory rate during F-CPAP but also for the reduced respiratory rate after the application of F-CPAP or C-CPAP, because bilateral cervical vagotomy restored the reduced respiratory rate after F-CPAP or C-CPAP. The improvement of Pa_{O_2} and concomitant abolishment of hypoxic respiratory drive may also contribute to the decreased respiratory rate. However, the respiratory rate was decreased immediately after the application of F-CPAP or C-CPAP. Furthermore, the respiratory rate was periodically altered during F-CPAP, even after Pa_{O_2} was increased to the level at which hypoxic respiratory drive was absent. Thus, the improved arterial oxygenetion may not be responsible for the decreased respiratory rate.

Although the presence of potent Hering-Breuer reflex in anesthetized dogs limited the range of EEP in this experiment, we believe that higher EEP can be applied in clinical practice. It has been shown that the reflex is not so dominant in man[10] and high CPAP has been safely employed in patients with respiratory failure[11].

The second finding which is different from our previous observation is that the alteration of A-aDo_2, Pa_{O_2} and cardiac output is not prominent in F-CPAP. When F-PEEP was combined with mechanical ventilation (F-CPPV), periodical changes in Pa_{O_2} and/or A-aDo_2 reciproacally proportional to the EEP occurred immediately after the application of F-PEEP (F-CPPV), and the range of periodical changes became smaller with increasing number of cycles. Cardiac output changed periodically but in proportion to the EEP. Thus, better arterial oxygenation with less cardiac depression was obtained at the lowest EEP during F-PEEP (F-CPPV). On the other hand, as a whole, such periodical alterations of A-aDo_2, Pa_{O_2} and cardiac output were not evident in the present experiment. One possible explanation for the absence of periodical changes is the difference in the range of EEP alteration between the present experiment and previous experiments. However, even when the range of EEP change is same in F-CPAP and F-CPPV, the practical range of airway pressure change is more enlarged in F-CPPV not only due to the positive airway pressure but also the periodic alteration of dynamic compliance[1-3]. Because dynamic compliance is periodically altered in reciprocal proportion to the EEP in F-CPPV, the range of peak airway pressure change is more widened than the range of EEP change. Thus, the periodical changes in A-aDo_2, Pa_{O_2} and cardiac output may appear more distictly in F-CPPV. It should also be considered that the periodical changes in respiratory rate might exert some influence on the alteration of A-aDo_2 and Pa_{O_2}.

Similar explanations as those given for the beneficial effects of F-CPPV can also apply to F-CPAP. The periodical changes in EEP, the major difference between C-CPAP and F-CPAP, may prevent a sustained overinflation of some alveoli with high compliance, and an desirable shift of blood flow to poorly ventilated alveoli. Although relatively high EEP is required to open the closed alveli, it may be accompanied by an overinflation of uninjured alveoli in hypoxic respiratory failure due to localized lung injury. Thus, if EEP is kept constant, improvement of arterial oxygenation will be limited because of the undesirable distribution of ventilation and perfusion. On the other hand, in F-CPAP the distribution of ventilation and perfusion is always altered. High EEP given periodically during F-CPAP may be sufficient to open some closed alveoli. Once the closed alveoli are opened, the opening may be maintained during the decreasing phase of EEP because of the difference between the EEP values required to open the collapsed alveoli and to re-close them. Furthermore, the sustained overinflation of uninjured alveoli can be prevented during the decreasing phase of EEP, because the degree of inflation of these alveoli is fundamentally proportional to EEP. Therefore, favorable distribution of ventilation and perfusion can become obtainable in F-CPAP as the number of cycles of EEP changes increases.

Although we set the periods of cyclic EEP alteration at 10 min in this experiment, it is possible to reduce the periods to less than 1 min. This reduction seems to produce an similar ventilatory pattern as airway pressure release ventilation in which more rapid falls and rises in EEP occur[12]. Further investigations are necessary to determine an optimal pattern of EEP alteration in F-CPAP, including the length and range of cyclic alterations and the ratio of increasing period of EEP to decreasing period of EEP.

In summary, in a dog model with localized lung injury produced by blood aspiration, F-CPAP in which EEP is periodically changed from 4 to 12 cmH_2O produces a significantly accelerated improvement of pulmonary oxygenation than C-CPAP with a constant EEP of 8 cmH_2O. Although the entire mechanism for this enhanced improvement remains

to be clarified, we believe that F-CPAP, a combination of F-PEEP and spontaneous respiration, is a simply applicable and useful therapeutic maneuver in the management of acute hypoxic respiratory failure with an uneven distribution of lung injury.

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