Intensive Care Med (1986) 12:26 – 32

Intensive Care Medicine

Suppression of spontaneous breathing during high-frequency jet ventilation

Influence of dynamic changes and static levels of lung stretch

A. J. van Vught[1,2], A. Versprille[1] and J. R. C. Jansen[1]

[1]Pathophysiological Laboratory, Department of Pulmonary Diseases, Erasmus University, Rotterdam and [2]Pediatric Intensive Care Unit, University Children's Hospital "Het Wilhelmina Kinderziekenhuis", Utrecht, The Netherlands

Accepted: 8 July 1985

Abstract. Conditions which suppress spontaneous breathing activity during high-frequency jet ventilation (HFJV) were analysed in Yorkshire piglets under pentobarbital anesthesia. The highest P_aCO_2 at which the animals did not breathe against the ventilator (apnea point) was established during different patterns of ventilation, either by changing the minute volume or by adding CO_2 to the inspiratory gas. Arterial oxygen tension was maintained throughout the study above 80 mm Hg. An elevation of ventilatory rate increased the apnea point, suggesting a progressive suppression of spontaneous breathing. This suppression did not depend on the amount of lung stretch during insufflation, because at higher rates lower tidal volumes were used. Suppression also appeared to be independent of insufflatory flow, i.e. the velocity of lung stretch. At higher frequencies end-expiratory airway pressure (P_{EE}) increased and there appeared to be a positive relationship between the apnea point and P_{EE}. In a separate series this positive relationship between the apnea point and P_{EE} was confirmed. A hysteresis effect in this relationship, however, suggests that other than jet frequency, lung volume rather than positive end-expiratory pressure (PEEP) is a major determinant of suppression of spontaneous breathing activity during HFJV.

Key words: Ventilatory pattern – PEEP – Lung volume – Respiratory drive – EMG diaphragm – Piglets

Suppression of spontaneous breathing is a feature of high-frequency ventilation which was observed in the very first experiments with this type of ventilation by Sjöstrand and coworkers [10, 11, 18, 19]. It has been reported repeatedly in animal experiments [2, 4, 5, 20] as well as in humans [3] both in high-frequency jet ventilation (HFJV) and in high-frequency oscillation (HFO). The phenomenon has been attributed to the stimulation of both vagal afferents from pulmonary receptors [2, 5, 10, 20] and nonvagal afferents from thoracic wall mechanoreceptors [5, 20].

The aim of our study was to analyze the mechanical stimuli leading to apnea during high-frequency jet ventilation by measuring the inhibiting effect of the different variables of the ventilating pattern on the central respiratory drive of CO_2. During mechanical ventilation, if a normal or increased arterial carbon dioxide tension (P_aCO_2) exists without any spontaneous breathing, some inhibition of the respiratory drive of CO_2 may be assumed to be present. The highest P_aCO_2 tolerated without spontaneous breathing may be called the apnea carbon dioxide value or 'the apnea point' (P_aCO_2-apnea). The higher the P_aCO_2-apnea is found to be, the greater the inhibitory effect upon the respiratory centre. Two types of mechanical stimuli are present during HFJV. Firstly, there is the dynamic or phasic effect on stretch receptors during each jet inflation and spontaneous expiration. Secondly, a static component will be present which is the level of lung stretch, i.e. lung volume, at the end of expiration, on which the insufflation is superimposed.

As phasic stimuli we studied the frequency of stretch application, the amount of stretch and the velocity of stretch by changing the frequency of jet ventilation, the tidal volume and the flow during insufflation respectively. The static component of end-expiratory stretch was studied by changing the end-expiratory pressure.

Methods

Preparation and measurements

Yorkshire piglets (5 – 7 weeks old, weighing 7 – 11 kg) were anesthetized with pentobarbital sodium

(30 mg · kg^{-1} i.p. as an initial dose) and placed in supine position on a thermocontrolled operating table, maintaining the rectal temperature at about 39 °C. Anesthesia was maintained by a continuous infusion of pentobarbital (7.5 – 10 mg · kg^{-1} i.v.), sufficient to eliminate pain reflexes but allowing the animals to breathe spontaneously. In 5 animals pentobarbital serum levels were estimated at the end of the experiment by means of gas chromatography analysis.

After tracheostomy the animals were connected to a Y-cannula allowing spontaneous inspiration via an inlet valve and expiration through a mixing box. Ventilatory (tidal) volume was calculated from mean airway flow by integration. Mean airway flow was recorded by a Fleisch pneumotachograph (type 0 Godart), placed behind the mixing box. Airway flow during insufflation was calculated from mean airway flow and insufflation time. Positive end-expiratory pressure could be established with a water seal in the expiratory tube.

A catheter was inserted into the right common carotid artery for pressure monitoring and blood sampling. Similarly, a 5F Swan-Ganz catheter was introduced into the pulmonary artery via the right external jugular vein. Through the same vein a 4-lumen catheter was inserted into the superior vena cava. One lumen was used for central venous pressure measurements and the others for infusions. Tracheal pressure was measured with a fluid filled catheter placed deep into the trachea. Heparin (250 IU · kg^{-1}) was administered intermittently each hour. Systemic arterial (P_{ao}), pulmonary artery (P_p), central venous (P_{cv}) and intratracheal pressure (P_T) were measured with Statham transducers (P23De). The frequency response of the fluid filled intratracheal catheter and transducer was checked with a microtip transducer (Honeywell) and was satisfactory up to 5 Hz. CO_2 and O_2 concentration in air were measured with a mass spectrometer (Perkin-Elmer, type MGA 1100). PO_2, PCO_2 and pH and metabolic acid-base variables were measured in arterial and mixed venous blood samples of 1.5 ml, by means of a blood gas analyzer (Radiometer ABL 3). Oxygen saturation and haemoglobin values were measured with an oximeter (Radiometer OSM 2). The compound action potentials of the diaphragm were measured by two electrodes placed in the diaphragm, and amplified and integrated with an EMG processor (Central electronics division, Department of Developmental Neurology, University of Groningen). Electrocardiogram (ECG), P_{ao}, P_{pa}, P_{cv}, P_T, mixed expiratory CO_2 fraction ($F_{\bar{E}CO_2}$), expired volume (V) and the electromyogram (EMG) of the diaphragm were simultaneously recorded on a Hewlett Packard 7758 A chart recorder.

Experimental procedures

The experimental set-up is shown in Figure 1. HFJV was applied with a ventilator developed in our laboratory. It consisted of an adjustable reduction valve and an electronically controlled solenoid valve to control the insufflatory flow (V_I'), jet frequency, thus cycle time, and inspiratory fraction, thus inspiratory time. The tidal volume was equal to the product of insufflation time and flow (Fig. 2).

In order to keep the arterial oxygen tension over 80 mm Hg and blood fully oxygenated under all circumstances the inspiratory gas contained 40% oxygen. The amount of carbon dioxide could be varied without changing the oxygen concentration (Ohio gas mixer), as indicated in Figure 1. Spontaneous ventilation was performed via the inspiratory valve. During HFJV this valve was clamped off in order to prevent entrainment of air. Spontaneous inspiratory activity during ventilation was detected by the concomitant decrease in the intratracheal, central venous and pulmonary artery pressure. In three animals electrical activity of the diaphragm was also monitored (Fig. 3), to check the validity of the former three pressures as selective indicators of spontaneous ventilation during HFJV. Neither in these animals nor in subsequent experiments on HFJV in our laboratory was a com-

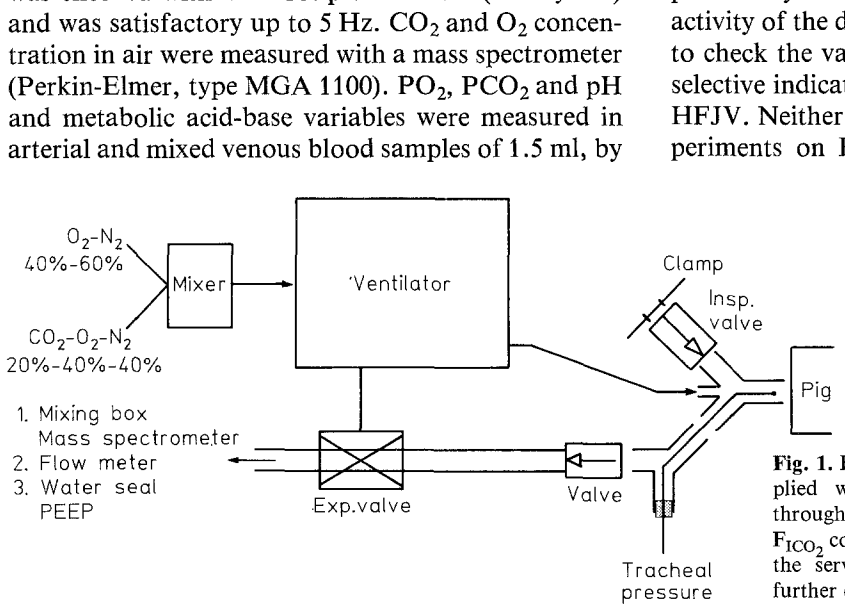

Fig. 1. Experimental set-up. The jet ventilator was supplied with respiratory gases from two containers through a mixer for maintaining F_{IO_2} at 0.40 while F_{ICO_2} could be varied from 0 – 0.20. During insufflation the servo-expiration valve was closed. See text for further details

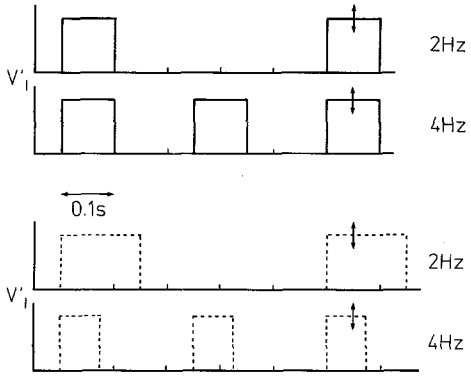

Fig. 2. The two types of ventilatory patterns. In the upper part the inspiratory time was kept constant at 0.1 s, for two frequencies as an example, by adapting the inspiratory fraction (closed lines). In the lower part the inspiratory fraction was kept constant at 0.3 (dashed lines). By varying insufflatory flow (V_I') tidal volume and so minute volume could be changed

pound action potential recorded without a decrease in the pressure recordings.

Ten piglets were ventilated with frequencies from 1 up to 5 Hz. Two types of ventilatory patterns were applied (Fig. 2). Firstly, in all animals inspiratory time was maintained at 0.1 s for all frequencies, and secondly in five of these animals ventilation was performed with a constant inspiratory fraction of 0.3 for all frequencies, varying inspiratory time proportionally with cycle time. These two modes of HFJV imposed two different types of dynamic activation of the stretch receptors. The flow of insufflation determined the velocity of stretch and the duration of this flow over the insufflation time determined the total increase of stretch. In order to detect P_aCO_2-apnea at the different ventilatory rates inspiratory flow was changed until apnea occurred. The value of inspiratory flow at the apnea point was noted. In eight piglets airway pressure was also measured. Three of these animals also belonged to the group of five in the series with constant inspiratory fraction.

In a separate group for four animals at a constant jet frequency of 3 Hz, an inspiratory time of 0.1 second and constant tidal volume, PEEP was applied in steps of 2.5 and 5.0 cm H_2O up to 25 cm H_2O. After each step the apnea point was searched for by changing the inspiratory CO_2 fraction (F_ICO_2). According to preliminary observations PEEP increased P_aCO_2. Therefore, the tidal volume, just giving apnea without extra PEEP, was increased to such an extent that a rise in P_aCO_2 at higher levels of PEEP would not surpass the corresponding apnea points.

Statistical analysis

Differences were tested by the t-test for paired and unpaired small samples [1].

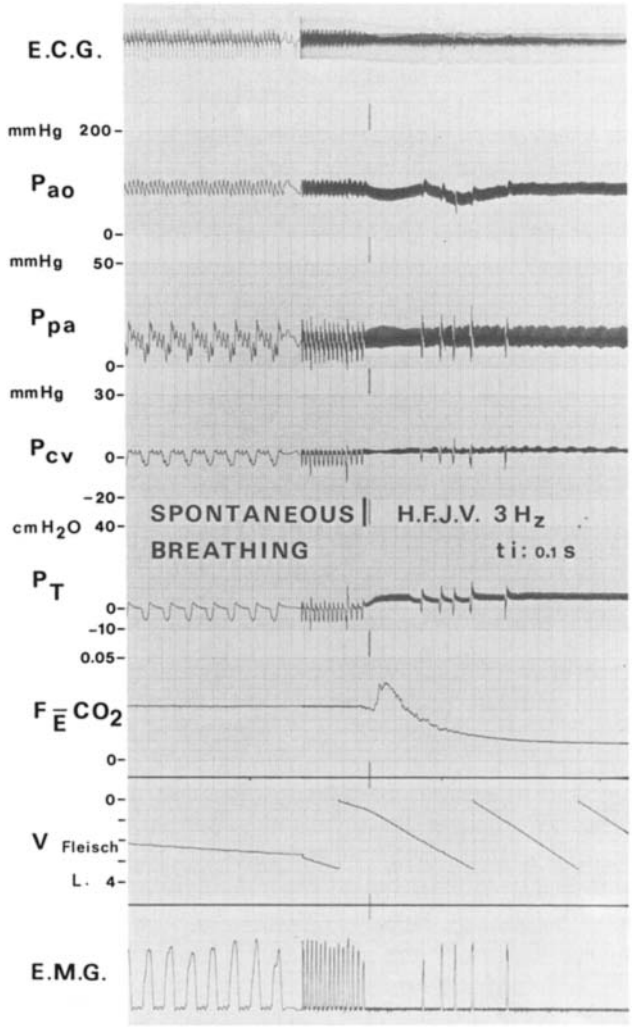

Fig. 3. A recording during spontaneous breathing and ventilation at a rate of 3 Hz and inspiratory time (t_I) 0.1 s P_{ao}: aortic pressure. P_{pa}: pulmonary artery pressure. P_{cv}: central venous pressure. P_T: intratracheal pressure. $F_{\bar{E}CO_2}$: mixed expiration fraction of CO_2. $V_{Fleisch}$: integral of mean airway flow as recorded by the Fleisch pneumotachograph. EMG: amplified and integrated compound action potentials of the diaphragm. Breathing against the ventilator is detected by electrical activity of the diaphragm as well as by changes in the intratracheal, central venous, pulmonary artery and to a lesser degree in the aortic pressures

Results

Frequency of HFJV and P_aCO_2-apnea

For comparison of all individual data P_aCO_2-apnea was expressed as a fraction of P_aCO_2 during spontaneous breathing, this value being taken as a reference for normal drive of ventilation.

The dependence of P_aCO_2-apnea on the frequency of HFJV is shown in Figure 4a for both modes of ventilation, the one with an inspiratory time of 0.1 s, the other with an inspiratory fraction of 0.3.

During both ventilatory patterns P_aCO_2-apnea increased when jet frequency was increased in all indi-

viduals. Below the jet frequency of 3 Hz this suppression seems to be relatively small because P_aCO_2-apnea was below the normal drive. Above 3 Hz a progressive increase in P_aCo_2-apnea occurred, especially in the series with constant inspiratory time of 0.1 s, (that is with an increasing inspiratory fraction for higher frequencies). The suppression in the series with constant inspiratory time of 0.1 s was significantly higher at 5 Hz ($p<0.02$) than that in the series with the constant inspiratory fraction of 0.3. In the first series of both the apnea occurred at P_aCO_2 values far above the value during spontaneous breathing.

Effect of tidal volume and flow of insufflation

For both HFJV-patterns, tidal volume and flow of insufflation were expressed as fractions of the values at 1 Hz to permit comparison within each population of experiments, and plotted against jet frequency (Fig. 4b and 4c).

Apnea occurred with lower tidal volumes at all higher jet frequencies (Fig. 4b). Apparently, suppression of spontaneous breathing does not depend on the amount of dynamic lung stretch during insufflation because during HFJV with large tidal volumes at lower rates less suppression was observed than during HFJV with smaller tidal volumes at higher rates. When inspiratory time was kept constant at 0.1 s, flow of insufflation at the apnea point decreased with higher jet frequencies whereas flow increased considerably when the inspiratory fraction was constant (Fig. 4c). Therefore, the velocity of stretch does not seem to be a determining factor for the amount of suppression of spontaneous breathing.

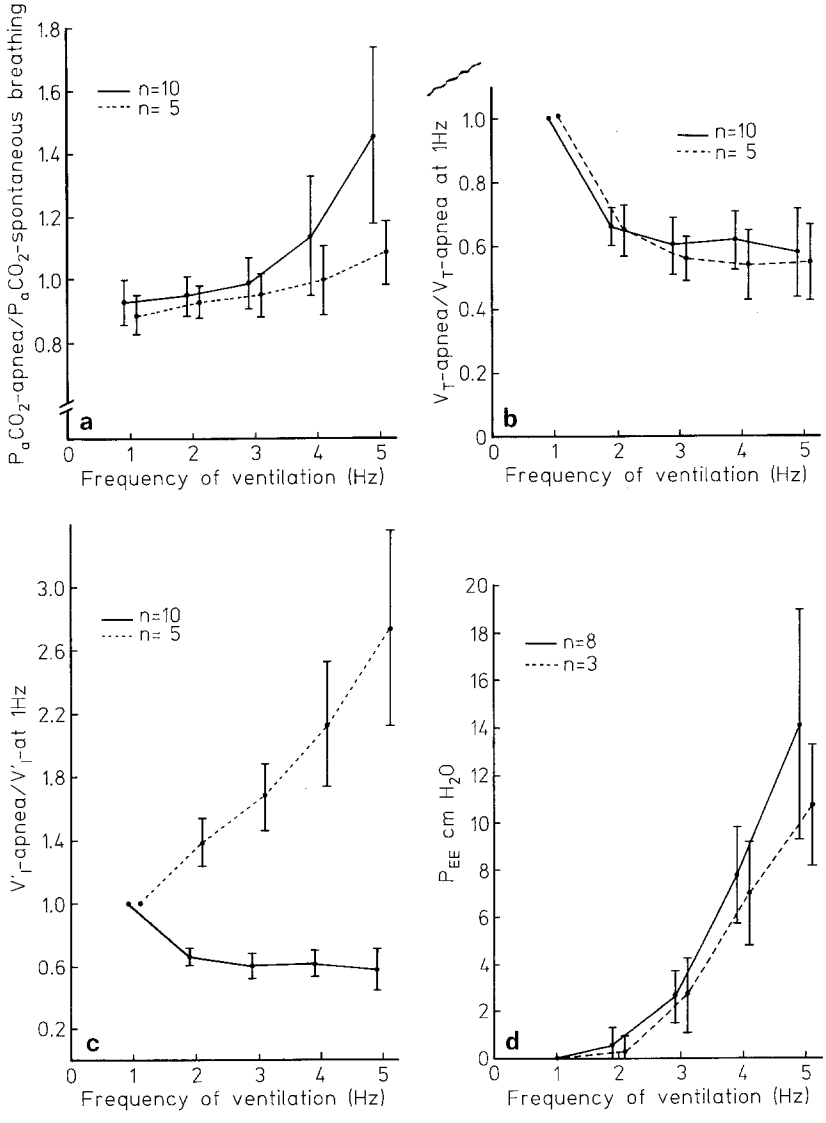

Fig. 4a–d. Relationship between a number of ventilatory variables and jet frequency in two series of observations. Continuous lines: ventilatory patterns were applied with a constant inspiratory time of 0.1 s. Dashed lines: ventilatory patterns with a constant inspiratory fraction of 0.3. Vertical bars represent ±1 SD. Ventilatory variables: **a** P_aCO_2 at the apnea point as a fraction of P_aCO_2 during spontaneous breathing previous to jet ventilation. **b** Tidal volume (V_T) at the apnea point as a fraction of V_T at the apnea point at 1 Hz. **c** Flow during insufflation (V'_I) at the apnea point as a fraction of V'_I at the apnea point at 1 Hz. **d** End-expiratory intratracheal pressure (P_{EE}) in absolute pressure. NB. For reasons of readability the mean values of both series at the same jet frequencies are plotted slightly separately

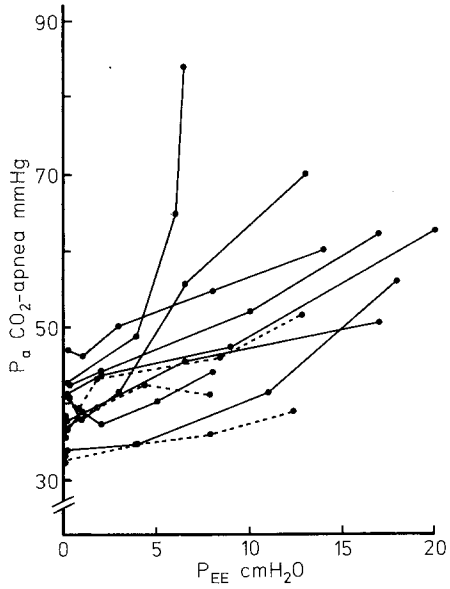

Fig. 5. The apnea point as a function of end-expiratory intratracheal pressure (P_{EE}). Results of individual experiments. Continuous and dashed lines represent the same ventilatory patterns as in Figure 4

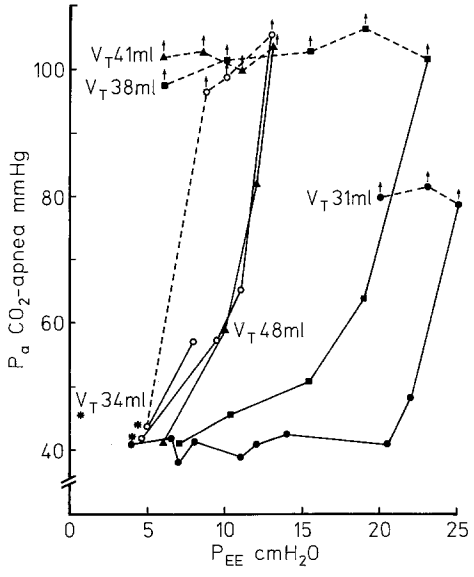

Fig. 6. Hysteresis effect in the relation between the apnea point and end expiratory intratracheal pressure (P_{EE}) in four piglets ventilated with a jet frequency of 3 Hz, and an inspiratory fraction of 0.3, thus an inspiratory time of 0.1 s and a constant tidal volume (V_T). The continuous lines connect the values measured during increase of P_{EE}, dashed lines during decrease. Arrows indicate an apnea point higher than the measured value. N.B. In the looped curve with open dots the starting V_T was 34 ml. This was increased to 48 ml and subsequently extra PEEP was applied (see text). At the end of the series (last two points in the curve) the V_T was again increased from 34 ml to 48 ml and the apnea point established without extra PEEP

The frequency of HFJV and PEEP

The relation between end-expiratory pressure and jet frequency at the apnea point is shown in Figure 4d for both conditions of ventilation. At 1 and 2 Hz no positive end-expiratory pressure (PEEP) was observed. At 3 Hz a PEEP of about 2.5 cm H_2O occurred, and at higher frequencies PEEP increased sharply. Comparing the total values for both conditions no significant differences could be demonstrated ($p > 0.1$ at 5 Hz). But in the three animals in which both series were performed, the increase in PEEP was markedly higher in the ventilatory pattern of constant inspiratory time compared to the series with constant inspiratory fraction. In all individual experiments a positive relation was found between P_aCO_2-apnea and PEEP (Fig. 5).

The effect of PEEP on the apnea point

The dependence of P_aCO_2-apnea on PEEP at a jet frequency of 3 Hz, inspiratory time of 0.1 s and a constant tidal volume is shown for four animals in Figure 6. Again a positive relation between the apnea point and PEEP was observed with a very progressive increase of P_aCO_2-apnea above certain levels of PEEP, which were rather different for the different animals. Suppression of spontaneous breathing appeared to be so complete that an increase of F_ICO_2 causing a P_aCO_2 above 80 mm Hg was insufficient to elicit spontaneous breathing. Therefore, we assume that these high values of measured P_aCO_2 were below the apnea point. When subsequently PEEP was diminished gradually and F_ICO_2 was maintained at a high level the animals did not resume spontaneous breathing. However, when the ventilator was stopped the animals started to breathe immediately, which suggests that it was not the high level of P_aCO_2 that suppressed breathing activity.

Stability of the animal model

In the five animals of the first series of 10, in which serum levels of pentobarbital were estimated, these levels were in the range $31.8 - 45.8\ mg \cdot l^{-1}$. In 9 of the series of 10 animal the apnea point at 1 Hz was checked at the end of the experiment and found to be unchanged in comparison with the value at the beginning of the experiment. In the animal in which this control was not available pentobarbital plasma concentration was $35.4\ mg \cdot l^{-1}$.

All 10 animals breathed spontaneously at the end of the series. Besides the overall results, the findings concerning P_aCO_2-apnea, jet frequency, tidal volume and flow of insufflation were similar for all individual animals, irrespective of pentobarbital level and P_aCO_2 at the end of the experiment.

Discussion

High-frequency ventilation may suppress central respiratory activity [2 – 5, 10, 11, 20]. The objectives of this study were to analyse the contribution of the mechanical effects of HFJV to the suppression of spontaneous breathing.

During HFJV four different kinds of mechanical receptor activation in the respiratory system can be postulated: (a) the repetitive activation of stretch receptors depending on jet frequency, (b) the intensity of the stretch stimulus depending on the tidal volume, (c) the velocity of stretch depending on the flow of inspiration, and (d) the basic level of tissue stretch at end expiration depending on PEEP.

In this study at higher jet frequencies a higher CO_2 drive was required to elicit breathing activity, indicating that more suppression of spontaneous breathing activity was achieved at higher frequencies. The increased suppression could not be attributed to a higher intensity of the stretch stimulus because this increased suppression was achieved at smaller tidal volumes. The degree of suppression was also found to be independent of the flow of inflation and thus of the velocity of stretch of the receptors.

End-expiratory pressure increased at higher frequencies. Thus, suppression of breathing activity was not only positively related to frequency but also to PEEP. Up to 3 Hz only a moderate increase in suppression of breathing activity was observed. At 4 and 5 Hz the suppressive effect of HFJV on central respiratory activity increased considerably, especially in the series with shorter expiratory times. The concomitant rise in PEEP suggests that besides ventilatory frequency PEEP could be a major factor in this effect.

The positive correlation between PEEP and P_aCO_2-apnea was confirmed during ventilation at a constant rate, pattern and volume, when extra PEEP was imposed. However, when PEEP was diminished gradually breathing did not resume and a hysteresis loop appeared.

Volume-pressure hysteresis is well known in lung physiology and is believed to be caused by either increased surfactant activity when the lungs are inflated, recruitment of collapsed alveoli or air trapping by meniscus formation over the terminal airways [7, 13], all causing increased lung volume during decrease of PEEP.

It may be that the hysteresis loop in the relation between PEEP and P_aCO_2 is linked to the volume-pressure curve of the lung. As a consequence of this hysteresis effect, a different amount of suppression can be detected at the same level of PEEP when going up compared to when going down. Therefore, we do not believe that PEEP on its own is the major factor in suppression of spontaneous breathing, as Chakrabarti et al. [4] concluded, but we suggest that lung volume is the main factor. Intrapulmonary [15] and extrapulmonary [8, 9, 12] stretch receptors were reported to inhibit spontaneous breathing when activated. The pulmonary stretch receptors are believed to respond to the overall degree of inflation but also to the rate of inflation. The response of the rapidly adapting pulmonary receptors is markedly dependent on the velocity of stretch and so on the rate of inflation [14]. In this light, our finding that suppression of spontaneous breathing is independent of insufflation flow negates Jonzon's hypothesis [10] that rapidly adapting receptors, giving rise to the basal discharge in the vagal nerve, could be responsible for suppression of spontaneous breathing.

Thompson et al. [20] produced apnea in dogs by applying high-frequency oscillations with a frequency of 15 Hz without changing mean airway pressure. After vagotomy spontaneous breathing activity could not be suppressed anymore with the same P_aCO_2. They suggested that the rapid phasic stimulation of pulmonary stretch receptors inhibits central respiratory activity by vagal pathways, although extravagal inhibitory afferents, c.q. from the chest wall, should also be considered. This is in contrast with Chakrabarti et al. [4], who concluded, using a jet ventilator, that frequency per se, without a PEEP-effect, had no effect on breathing.

Subsequently, England et al. [5] demonstrated enhancement of phrenic nerve activity after neuromuscular blockade during high-frequency oscillation, indicating an involvement of thoracic wall receptors in suppression of spontaneous respiratory activity. According to these authors [5, 20] lung volume changes could not be involved bacause mean airway pressures remained unchanged. However, Fletcher [6] demonstrated substantially higher end-expiratory alveolar pressures and therefore higher alveolar volumes during high-frequency jet ventilation even without PEEP in the main airways. Recently, Simon et al. [17], by studying the relationship between mean airway pressure and mean alveolar pressure, concluded that during high-frequency oscillation in which inflated air is actively evacuated, mean airway pressure could significantly underestimate mean alveolar pressure. This was more pronounced at low mean airway pressures, at larger tidal volumes and at higher frequencies. Whe therefore speculate that lung volume might have changed in the experiments of Thompson et al. [20] and England et al. [5].

Banzett et al. [2] found a lengthening of expiration up to apnea during high-frequency oscillation with 15 Hz even when lung volume was carefully kept constant. Increase in lung volume accentuated this effect, due to an Hering-Breuer inflation reflex.

Therefore, there is strong evidence that at least during high-frequency oscillation at 15 Hz both repetitive activation and static activation of stretch receptors suppresses spontaneous breathing activity. However, no conclusions can be drawn from these studies with regard to other methods of mechanical receptor activation.

The possible influence of pentobarbital has been a major concern in interpreting our results. So far all experimental studies in animals on suppression of breathing activity during high-frequency ventilation have been performed under barbiturate anesthesia. Only Banzett et al. [2] discussed the possible role of anesthetic depth and "arousal" on breathing activity. Butler et al. [3] could not induce apnea in awake healthy volunteers. Thiopental induced a period of apnea that persisted until the subjects awakened. Only 2 of their 12 patients, the oldest one, a 74-year-old man and the youngest one, a 2.5-kg neonate, were apneic, although fully conscious.

Respiratory activity is the result of a multi-input system. To study the effects of stimuli from lungs and thoracic wall other inputs should be kept constant. Apparently, one of these inputs is stimulation from higher cerebral regions and pentobarbital acts upon this system. Our studies have been performed under light pentobarbital anesthesia. This light anesthesia, sufficient to eliminate pain reflexes but alowing the animals to breathe spontaneously could be maintained for more than 8 h by a continuous infusion of pentobarbital of $7.5-10.0\,mg \cdot kg^{-1} \cdot h^{-1}$. In a previously published study [16] we found stable pentobarbital plasma concentrations with an infusion of $7.5\,mg \cdot kg^{-1} \cdot u^{-1}$ over 3 h. With these plasma levels piglets were able to breathe spontaneously with normal P_aCO_2. The constancy of the influence of pentobarbital on the central respiratory activity during the experiment was proven by a stable P_aCO_2 during spontaneous breathing or an unchanged P_aCO_2-apnea at 1 Hz at the end of the experiment. Thus, we do not believe that the character of our results and therefore our conclusions depend on the anesthesia.

From our experiments we concluded that neither the change of stretch nor the velocity of stretch of pulmonary or thoracic mechanoreceptors are involved in the suppression of spontaneous breathing during high-frequency jet ventilation. However, other than jet frequency, lung volume is a major factor in apnea.

Acknowledgements. Our thanks to A. Drop for technical assistance, to Professor V. J. Huber, University of Utrecht, for his help in preparing the manuscript and Dr. J. O'Brien, University of Groningen, for his comments on the manuscript and for putting EMG monitoring equipment at our disposal.

References

1. Bancroft H (1966) Introduction to biostatistics. Harper and Row, New York
2. Banzett R, Lehr J, Geffroy B (1983) High-frequency ventilation lengthens expiration in the anesthetized dog. J Appl Physiol 55:329
3. Butler WJ, Bohn DJ, Bryan AC, Froese AB (1980) Ventilation by high-frequency oscillation in humans. Anesth Analg 59:577
4. Chakrabarti MK, Whitwam JG (1983) Evaluation of a new valveless all purpose ventilator: effect of ventilating frequency, PEEP, P_aCO_2 and P_aO_2 on phrenic nerve activity. In: Scheck PA, Sjöstrand UH, Smith RB (eds) Perspectives in high frequency ventilation. Martinus Nijhoff, The Hague, p 140
5. England SJ, Onayemi A, Bryan AC (1984) Neuromuscular blockade enhances phrenic nerve activity during high-frequency ventilation. J Appl Physiol 56:31
6. Fletcher PR (1983) Alveolar pressures during high frequency ventilation. In: Scheck PA, Sjöstrand UH, Smith RB (eds) Perspectives in high frequency ventilation. Martinus Nijhoff, The Hague, p 92
7. Frazer DG, Franz GN (1981) Trapped gas and lung hysteresis. Respir Physiol 46:237
8. Hagan R, Bryan AC, Bryan MH, Gulston G (1977) Neonatal chest wall afferents and regulation of respiration. J Appl Physiol 42:362
9. Homma I (1980) Inspiratory inhibitory reflex caused by the chest wall vibration in man. Respir Physiol 39:345
10. Jonzon A (1977) Phrenic and vagal nerve activities during spontaneous respiration and positive-pressure ventilation. Acta Anaesth Scand Suppl 64:29
11. Jonzon A, Oberg PA, Sedin G, Sjöstrand U (1971) High-frequency positive-pressure ventilation by endotracheal insufflation. Acta Anaesth Scand Suppl 43:5
12. Knill R, Bryan AC (1976) An intercostal-phrenic inhibitory reflex in human newborn infants. J Appl Physiol 40:352
13. Macklem PT (1978) Respiratory mechanics. Ann Rev Physiol 40:157
14. Pack AI (1981) Sensory inputs to the medulla. Ann Rev Physiol 43:73
15. Patberg WR (1983) Effect of graded vagal blockade and pulmonary volume on tonic inspiratory activity in rabbits. Pflügers Arch 398:88
16. Schreuder JJ, Jansen JRC, Bogaard JM, Versprille A (1982) Hemodynamic effects of positive end-expiratory pressure applied as a ramp. J Appl Physiol 53:1239
17. Simon BA, Weinmann GG, Mitzner W (1984) Mean airway pressure and alveolar pressure during high-frequency ventilation. J Appl Physiol 57:1069
18. Sjöstrand U (1977) Summary of experimental and clinical features of high-frequency positive-pressure ventilation HFPPV. Acta Anaesth Scand Suppl 64:165
19. Sjöstrand U (1980) High-frequency positive-pressure ventilation (HFPPV): a review. Crit Care Med 8:345
20. Thompson WK, Marchak BE, Bryan AC, Froes AB (1981) Vagotomy reverses apnea induced by high-frequency oscillatory ventilation. J Appl Physiol 51:1484

A. T. van Vught, M.D.
Pathophysiological Laboratory
Department of Pulmonary Diseases
Erasmus University
P.O. Box 1738
NL-3000 DR Rotterdam
The Netherlands