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Effect of external high-frequency oscillation on severe cardiogenic pulmonary edema

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Abstract: Effective gas exchange can be maintained in animals without endotracheal intubation using external high-frequency oscillation (EHFO). The aim of this study was to evaluate the effect of EHFO in patients with respiratory failure due to severe cardiogenic pulmonary edema. Seven patients were ventilated with EHFO for 2 h at 60 oscillations·min^{-1}, with a cuirass pressure of 36 cmH_2O (−26 to +10) and an inspiratory to expiratory ratio of 1:1, with EHFO. Blood gas values and hemodynamic parameters were measured. Significant increases were noted in cardiac index (2.3 ± 0.5 to 2.5 ± 0.5 l·m^{-2}; $P < 0.05$), stroke volume index (24 ± 7 to 28 ± 8 ml·m^{-2}; $P < 0.05$), and arterial O_2 pressure (Pao_2) (70 ± 4 to 95 ± 23 mmHg; $P < 0.01$) without a change in pulmonary artery wedge pressure at 1 h after EHFO. The respiratory rate decreased from 28 ± 3 to 22 ± 3 breaths·min^{-1} at 5 min after the termination of EHFO ($P < 0.01$). Arterial CO_2 pressure ($Paco_2$) did not, however, decrease. Increased stroke volume without a change in pulmonary artery wedge pressure (preload) suggests either improved inotropic function of the left ventricle or reduced left ventricular afterload with EHFO. The use of EHFO may be effective not only for gas exchange but also for left ventricular function in patients with severe cardiogenic pulmonary edema.

Key words: External high-frequency oscillation, Heart failure, Hypoxemia, Pulmonary edema, Respiratory failure

Introduction

Severe cardiogenic pulmonary edema is a frequent cause of respiratory failure, and many patients with this condition require endotracheal intubation and mechanical ventilation. The possible benefits of continuous positive airway pressure (CPAP) include an improvement in oxygenation, a decrease in respiratory work, and a decrease in left ventricular afterload [1–3]. CPAP delivered via a mask can reduce the requirement for mechanical ventilation with intubation, and accelerate improvements in oxygenation and respiratory rate in cardiogenic pulmonary edema [4]. However, for some patients, this technique produces claustrophobia and they find it difficult to tolerate either because of leakage from the mouth when using a nasal mask [5], or because of excessive pressure and difficulty in managing secretions when using a face mask [6].

Effective gas exchange can be maintained without resorting to endotracheal intubation by using external high-frequency oscillation (EHFO) [7–9]. A recently developed approach to EHFO employs a cuirass system to oscillate the anterolateral area of the chest and abdomen with negative and positive pressures in combination with a continuous negative baseline pressure [7]. Oscillatory tidal volume as well as mean lung volume can be controlled, a mouthpiece is unnecessary, and inspired air is warmed and humidified naturally.

The aim of this study was to investigate whether EHFO improves oxygenation and produces beneficial effects on hemodynamic status in patients with respiratory failure due to severe cardiogenic pulmonary edema.

Patients and methods

This study was approved by our institutional Committee on Human Subjects. Because of the severity of cardiogenic pulmonary edema, no patient was able to give valid informed consent at the time of entry into the study. Therefore, information was given to the patient and his or her next of kin and consent was obtained from the patient's next of kin prior to study entry. The

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patients consisted of seven adults with respiratory failure due to severe cardiogenic pulmonary edema. Cardiogenic pulmonary edema was diagnosed when the patient had dyspnea of sudden onset, typical findings on chest radiography, widespread rales without a history suggestive of pulmonary aspiration or infection, and a pulmonary artery wedge pressure greater than 18 mmHg.

All patients with cardiogenic pulmonary edema who had respiratory distress, an arterial oxygen pressure (Pao_2) below 80 mmHg while receiving oxygen at a rate of 12 $l \cdot min^{-1}$ through a semirigid face mask, and Pao_2 below 60 mmHg on room air, were enrolled. All of the patients also received oxygen through a semirigid face mask at a flow rate of 12 $l \cdot min^{-1}$ during this study. The study was performed at a time when the patients were clinically stable and had no evidence of cardiac arrhythmias or myocardial ischemia. At study entry, a catheter was placed in the radial artery of all patients to measure arterial blood pressure, and to obtain samples for blood gases. A flow-directed pulmonary artery catheter was inserted to measure hemodynamics and thermal-dilution cardiac output. Correct positioning of the pulmonary artery catheter in a branch of the pulmonary artery was confirmed by chest radiography. Hemodynamic parameters were measured at the phase of the EHFO expiratory cycle. Blood gas analysis was measured with standard blood gas electrodes (ABL 300, Radiometer, Copenhagen, Denmark). Additional monitoring in all patients included an electrocardiogram (DS-1060, Fukuda Denshi, Tokyo, Japan) and pulse oximetry (N 180 pulse oximeter, Nellcor, Tokyo, Japan). The study was initiated at least 4 h after the last diuretic dose and when the dose of vasocative medications had been stable for at least 4 h. Each patient was ventilated with EHFO using a Hayek Oscillator (Breasy Medical Equipment, London, UK).

The oscillator consists of a chest cuirass, a power unit, and a control unit. The cuirass is made of clear, flexible, lightweight plastic and is bordered by soft foam rubber. It is designed to fit snugly over the chest and upper abdomen. The cuirass is connected to the power unit with wide-bore tubing. Within the power unit is a diaphragmatic pump with a maximum stroke of 3.5 l, which can operate over a wide range of frequencies, 8–999 oscillations $\cdot min^{-1}$, to generate an oscillating pressure. An additional pump enables this oscillation to be superimposed on a negative baseline, permitting control over end-expiratory chamber pressure and hence lung volume. The frequency, inspiratory pressure, expiratory pressure, and inspiratory to expiratory (I/E) ratio can be set on the automatic control unit which then adjusts the performance of the power unit by negative feedback from a pressure transducer connected to the inside of the cuirass. Since both the inspiratory and expiratory phases are controlled, high frequencies can be achieved. Each patient was ventilated at 60 oscillations $\cdot min^{-1}$ as high frequency for 2 h. Cuirass pressures were −26 cm H_2O inspiratory and +10 cm H_2O expiratory in all patients. The I/E ratio was maintained at 1:1.

Blood gas values and hemodynamics were assessed prior to EHFO (baseline), and at 10 min, 30 min, 1 h, and 2 h after EHFO, as well as at 5 min and 1 h after the termination of EHFO. Respiratory rate was measured prior to EHFO (baseline), and at 5 min and 1 h after the termination of EHFO.

Statistical analysis

The results were expressed as mean ± SD. All results were analyzed using analysis of variance followed by the Dunnett multiple comparisons procedure. All P values less than 0.05 were considered statistically significant.

Results

Patient characteristics (Table 1)

Four patients underwent treatment with inotropic agents, specifically dopamine and/or dobutamine. Two patients who had acute myocardial infarction had undergone reperfusion therapy with tissue plasminogen activator.

Hemodynamic status (Table 2)

Cardiac and stroke volume indices were significantly higher at 1 h after EHFO than at baseline. These significant changes continued until 1 h after the termination of EHFO. Other hemodynamic parameters did not, however, change significantly during the study period. Arterial blood pressure and heart rate showed no adverse effects.

Table 1. Patient characteristics at study entry

Age (years)	68 ± 8
Sex (male/female)	5 / 2
Etiology of CHF (no. of patients)	
Hypertensive heart disease	2
Acute myocardial infarction	2
Prior myocardial infarction	2
Mitral valve regurgitation	1
Drug treatment (no. of patients/dose)	
Nitroglycerin ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	7 / 0.4 ± 0.3
Furosemide ($mg \cdot day^{-1}$)	6 / 43 ± 20
Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	4 / 3.3 ± 1.3
Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	3 / 3.0 ± 1.0

CHF, congestive heart failure.
Each value represents the mean ± SD.

Table 2. Changes in hemodynamic status

	Baseline	After initiation of EHFO				After termination of EHFO	
		10 min	30 min	1 h	2 h	5 min	1 h
MAP (mmHg)	70 ± 8	76 ± 10	77 ± 14	78 ± 12	76 ± 12	75 ± 8	73 ± 10
HR (beats·min^{-1})	98 ± 24	97 ± 19	97 ± 17	95 ± 17	99 ± 16	95 ± 16	95 ± 19
CVP (mmHg)	16 ± 6	16 ± 5	16 ± 5	15 ± 5	14 ± 4	14 ± 3	13 ± 2
MPAP (mmHg)	31 ± 10	33 ± 13	33 ± 14	32 ± 12	30 ± 10	30 ± 10	28 ± 9
PAWP (mmHg)	22 ± 3	22 ± 4	22 ± 5	20 ± 4	20 ± 3	20 ± 3	19 ± 2
CI (l·min^{-1}·m^{-2})	2.3 ± 0.5	2.3 ± 0.4	2.5 ± 0.4	2.5 ± 0.5*	2.6 ± 0.4**	2.6 ± 0.4**	2.7 ± 0.3**
SVI (ml·m^{-2})	24 ± 7	25 ± 5	26 ± 5	28 ± 8*	28 ± 7*	28 ± 6**	30 ± 9**
SVRI (dynes·s·cm^{-5}·m^{-2})	2046 ± 725	2096 ± 579	2017 ± 590	2062 ± 575	1997 ± 639	1911 ± 523	1833 ± 564
PVRI (dynes·s·cm^{-5}·m^{-2})	296 ± 203	308 ± 179	344 ± 345	427 ± 382	341 ± 261	290 ± 237	278 ± 207

EHFO, external high-frequency oscillation; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index.
Hemodynamic values were assessed prior to EHFO (baseline) and at 10 min, 30 min, 1 h, and 2 h after EHFO, and at 5 min and 1 h after the termination of EHFO.
Each value represents the mean ± SD. Differences from baseline: * $P < 0.05$; ** $P < 0.01$.

Table 3. Changes in blood gas analysis and respiratory rate

	Baseline	After initiation of EHFO				After termination of EHFO	
		10 min	30 min	1 h	2 h	5 min	1 h
$Paco_2$ (mmHg)	39 ± 10	39 ± 7	39 ± 8	40 ± 8	39 ± 7	37 ± 7	39 ± 5
Pao_2 (mmHg)	70 ± 4	79 ± 22	86 ± 18	95 ± 23**	104 ± 29**	106 ± 26**	130 ± 45**
RR (breaths·min^{-1})	28 ± 3	—	—	—	—	22 ± 3**	23 ± 2**

EHFO, external high-frequency oscillation; RR, respiratory rate; $Paco_2$, partial pressure of arterial carbon dioxide; Pao_2 partial pressure of arterial oxygen.
Blood gas values and respiratory rate were assessed prior to EHFO (baseline) and at 10 min, 30 min, 1 h, and 2 h after EHFO, and at 5 min and 1 h after the termination of EHFO.
Each value represents the mean ± SD. Differences from baseline; * $P < 0.05$; ** $P < 0.01$.

Blood gas analysis and respiratory rate (Table 3)

No severe hypoxemia (pulse oximetry <80%) occurred, and mild hypoxemia (<90%) never lasted more than 5 min during the study period. Mild hypoxemia was observed in only one patient. The lowest level of Pao_2 was 52 mmHg, and the lowest level of pulse oximetry was 85%. No adverse effects were recognized for the duration of the study.

Pao_2 was significantly higher at 1 h after EHFO than at baseline. This change continued for 1 h after the termination of EHFO. Arterial CO_2 pressure ($Paco_2$) did not, however, change significantly during the study. $Paco_2$ in 5 patients who had hypocapnia ($Paco_2$ < 35 mmHg) at study entry increased slightly during the study. Furthermore, another 2 patients who had hypercapnia ($Paco_2$ > 50 mmHg) experienced a decrease in $Paco_2$ to the normal range.

Discussion

This study yielded two major findings. The first important finding was that the cardiac index and arterial oxygen content increased in patients with cardiogenic pulmonary edema in response to EHFO treatment. The second was that hemodynamic parameters other than the cardiac and stroke volume indices did not change. These findings demonstrate either improved inotropic function of the left ventricle or reduced left ventricular afterload with EHFO.

Two potential mechanisms may explain how EHFO improves left ventricular function: (1) by increasing arterial oxygen content and, thereby, oxygen delivery to vital organs and therefore improving ventricular oxygenation and inotropic function; or (2) by decreasing left ventricular afterload. In our study, arterial oxygen content increased significantly. Furthermore, left ven-

tricular afterload presumably decreased since cardiac output increased significantly without a change in systemic arterial pressure.

Penny et al. [10,11] achieved increased pulmonary blood flow in patients after total cavopulmonary anastomoses and after the Fontan procedure using EHFO. The authors consider the reduction in mean airway pressure and the increased systemic venous return to be responsible for the increased pulmonary blood flow. Because we did not measure pulmonary blood flow, we cannot verify that the increased cardiac output was caused by increased pulmonary blood flow. Since the cardiac output and stroke volume increased significantly without a change in other hemodynamic parameters, EHFO appears to exert hemodynamic benefits by producing maximal improvements in cardiac output in the setting of cardiac failure [12].

Because high-frequency ventilation may result in lower intrathoracic pressure than conventional positive pressure ventilation, it may also have less influence on cardiovascular dynamics. However, problems associated with the use of high-frequency ventilation include the need for endotracheal intubation, alterations in baseline lung volume, and dehumidification of the respiratory system [13–15]. Even when used with an adaptive mouthpiece, difficulties in warming and humidifying the air persisted [16]. EHFO can enhance gas exchange without the complications associated with both conventional positive pressure ventilation and high-frequency ventilation. Previous studies in which EHFO was applied to animals have reported that gas exchange could be enhanced despite a reduction in spontaneous ventilation [17–19]. EHFO may also be more effective in enhancing gas exchange than conventional ventilation in the presence of increased elastic recoil [7]. High-frequency ventilation with its lower airway pressure is associated with significantly less impairment of cardiovascular function than conventional positive pressure ventilation in dogs with induced global myocardial ischemia [20]. In particular, cardiac output in high-frequency ventilation is significantly higher than that in positive pressure ventilation. This effect is attributable to alterations in stroke volume. The increased cardiac output observed during our study was primarily caused by alterations in stroke volume. Stroke volume is influenced by physiological factors that alter preload, afterload, and contractility.

Patients with acute heart failure have an increased amount of lung water, reductions in lung volume and lung compliance, and increased airway resistance [21,22]. Myocardial function may also be improved through a reduction in left ventricular afterload resulting from an increase in intrathoracic pressure [2]. Several investigators have noted a reduction in respiratory work as an advantage of CPAP therapy [23,24]. Because we did not measure transpulmonary pressure change or tidal volume, we cannot directly confirm that respiratory work decreased during either treatment. However, a decreased respiratory rate with subjectively determined less labored breathing is indirect objective evidence of decreased work of breathing. Diminished expiratory lung volumes are associated with decreased lung compliance, which increases the elastic work of breathing. To minimize this work, patients take shallow, frequent breaths which may further decrease lung volume [25]. This explains the observation that patients with caridogenic pulmonary edema often have an increased respiratory rate. The reduction in respiratory rate seen in normal subjects while maintaining gas exchange at frequencies of 30 or 60 oscillations·min^{-1} implies that gas exchange was taking place during respiratory muscle rest [8]. It seems that the significantly decreased respiratory rate was attributable to improved lung volume and oxygenation. Decreased spontaneous respiratory rate could be also responsible for the increased $Paco_2$ during the study period in 5 patients with hypocapnia.

One of the concerns encountered in the present study was the possible interactions between vasoactive medications and EHFO, since all patients were treated with intravenous nitroglycerin, dopamine, and/or dobutamine. Because the study was initiated when the dose of vasoactive medications had been stable for at least 4 h, we assumed relatively mild effects of vasoactive medications. However, the changes in hemodynamic parameters which persisted for 1 h after the termination of EHFO may be related to the vasoactive medications.

The setting of EHFO was made at a frequency range of 60 oscillations·min^{-1}, an amplitude of 36 cmH_2O (−26 to +10 cmH_2O), and an I/E ratio of 1:1. A previous study suggests that the EHFO is equally effective at a frequency of 60–140 oscillations·min^{-1} [26]. The frequency chosen should be determined in accordance with the comfort of the patient during application of the oscillator. On the other hand, amplitude should be selected individually, on the basis of severity of disease and compliance of the chest wall. Lean patients would require lower amplitudes than obese patients, and patients with less impairment would require a lower amplitude than severely impaired patients. In this study, we used a fixed amplitude for the purpose of uniformity. Further testing will establish the range of setups that allows adjustment to the individual patient. The I/E ratio used in our study was 1:1. Apparently, a lower I/E ratio, enabling a longer expiratory phase, would be more natural in this type of patient. The effect of the device is to create a negative distending pressure and a positive compression pressure that gives an amplitude of 36 cmH_2O (−26 to +10). This amplitude generates a

respiratory cycle that is totally controlled by the device. The subject can occasionally use his own spontaneous drive to breathe, the effect of which is, however, negligible within the total framework of ventilatory output. Thus, the improved ventilation induced by EHFO may be due solely to the device.

In conclusion, while the cuirass is attached, a pause in ventilation can easily be taken to allow patients to communicate with staff and take oral fluids. No harmful side effects were seen with the use of the cuirass. EHFO opens a new range of potential applications in clinical chest medicine. This modality may be effectively used in the management of respiratory failure due to severe cardiogenic pulmonary edema, particularly to obviate endotracheal intubation and mechanical ventilation in such patients.

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