Nitric oxide and high frequency jet ventilation in a patient with bilateral bronchopleural fistulae and ARDS

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Purpose: To describe a method of delivering nitric oxide during high frequency jet ventilation.

Clinical Features: A 63-yr-old man underwent reduction pneumoplasty for bullous emphysema. Postoperatively, ventilation was inadequate, secondary to bilateral high output bronchopleural fistulae. High frequency jet ventilation was initiated and achieved adequate ventilation (pH>7.2). Over the following 24 hr, progressive hypoxemia ($Sa0_2$ < 86%) developed along with the acute respiratory distress syndrome. Nitric oxide was delivered by continuous flow at the patient Y-connector during combined high frequency jet and conventional ventilation (two conventional low volume breaths/minute). Substantial improvement in oxygenation (FiO_2 0.8 0.5, SaO_2 > 92%) was noted initially and was sustained over 72 hr. Subsequently, the patient was weaned to conventional ventilation without difficulty. Mechanical ventilation was discontinued on postoperative day sixteen.

Conclusion: The simultaneous use of nitric oxide and high-frequency jet ventilation was used safely and effectively in this patient as a method of support for acute respiratory distress syndrome with co-existing large bilateral bronchopleural fistulae.

Objectif : Décrire une méthode d'administration de l'oxyde nitrique pendant la ventilation en jet à haute fréquence.

Éléments cliniques : Un homme de 63 ans devait subir une pneumoplastie de réduction pour emphysème bulleux. Après l'opération, la ventilation était inadéquate, situation secondaire à des fistules bilatérales bronchopleurales à haut débit. La ventilation en jet à haute fréquence a été amorcée et a permis une respiration suffisante (pH > 7,2). Pendant les 24 h suivantes, une hypoxémie progressive ($Sa0_2$ < 86 %) s'est développée avec le syndrome de détresse respiratoire aiguë. On a administré de l'oxyde nitrique à débit continu au moyen du connecteur en Y du ventilateur pendant la ventilation en jet à haute fréquence combinée à la ventilation traditionnelle (deux respirations à bas volume/minute). Une amélioration importante de l'oxygénation (FiO_2 0,8 ± 0,5, SaO_2 > 92 %) a été notée au début et maintenue pendant 72 h. Par la suite, le patient a été sevré sans difficulté pour ne recevoir que la ventilation classique. La ventilation mécanique a été cessée le seizième jour postopératoire.

Conclusion : L'utilisation simultanée d'oxyde nitrique et de ventilation en jet à haute fréquence a été utilisée de façon sécuritaire et efficace chez ce patient comme une méthode de soutien du syndrome de détresse respiratoire aiguë coexistant avec de grandes fistules broncho-pleurales bilatérales.

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THE simultaneous use of nitric oxide (NO) and jet ventilation has been documented in only one previous case report.[1] The combined use of NO with high frequency oscillation ventilation (HFOV) has been well established in the neonatal intensive care unit; however, HFOV is rarely used in the adult setting. Occasionally, jet ventilation is used, with variable efficacy, for adult patients who are difficult to ventilate. We describe a case in which simultaneous HFJV and NO were safely used in a post-operative patient with acute respiratory distress syndrome (ARDS) and large bilateral bronchopleural fistulae.

Case report

A 63-yr-old, 45.9 kg man with severe emphysema and massive bilateral bullae was scheduled for bilateral bullectomy. He had a 53-pack year smoking history with documented chronic obstructive pulmonary disease (COPD) for the previous ten years. Preoperative pulmonary function tests revealed a one-second forced expiratory volume (FEV_1) of 0.84 litres. His FEV_1/FVC (forced vital capacity) was 54% and residual volume (RV) was measured at 125% of predicted (Table I).

The patient had been admitted to a peripheral hospital ten weeks prior to surgery with respiratory failure requiring ventilatory support. Bilateral thoracostomy tube placement was required for pneumothoraces and prolonged air leak. Mechanical ventilation was eventually discontinued and he was transferred to our hospital for assessment. Pulmonary function tests were obtained after removal of the chest tube and are shown in Table I. Preoperative arterial blood gases were pH 7.41, PO_2 66 mmHg, PCO_2 44 mmHg, HCO_3^- 28 meq·L^{-1}, and oxygen saturation (SaO_2) 93% while breathing room air. Computed tomography (CT) scan of the chest revealed extensive bullous disease. After assessment, he was discharged home for six weeks of rehabilitation prior to a planned reduction pneumoplasty procedure.

On the day of the procedure a thoracic epidural (T_{7-8}) and radial arterial catheter were inserted. General anesthesia was induced with 100 µg fentanyl, 100 mg propofol and muscle relaxation with 50 mg rocuronium. A #37 French double-lumen endotracheal tube was placed and its position confirmed by bronchoscopy. Anesthesia was maintained with isoflurane (0.2-0.5%), propofol infusion (10-50 µg·kg^{-1}·min^{-1}), and intermittent doses of rocuronium. Bilateral bullectomy was performed, through a median sternotomy incision, using sequential one-lung ventilation. Two chest tubes were placed in each hemithorax. The double lumen endotracheal tube was exchanged for a standard size #8.0 endotracheal tube at the end of the procedure. The intra-operative course was complicated by persistent episodes of hypotension and desaturation (SaO_2 < 80%); therefore, he was brought to the intensive care unit (ICU) postoperatively. On arrival, the blood pressure was 76/56 mmHg with a pulse rate of 108 per minute. A pulmonary artery catheter was inserted which revealed a cardiac index of 2.01 L·min^{-1}·m^{-2}, central venous pressure (CVP) 11 mmHg, pulmonary capillary wedge pressure (PCWP) 12 mmHg, and systemic vascular resistance index of 2023 dynes·sec·$cm^{-5}m^{-2}$. Volume resuscitation and inotropic support were initiated. A 12-lead electrocardiogram showed widespread ST-segment elevation (1-2 mm), which was interpreted as pericardial reaction to surgery. On postoperative day one (POD#1) a mild elevation of troponin I = 4.1 (µg·L^{-1}) was noted suggesting a small subendocardial myocardial infarction had occurred. An echocardiogram revealed no pericardial fluid and normal ventricular function. However, the patient continued to require inotropic support to maintain blood pressure and cardiac index. He was initially administered 100 mg hydrocortisone *iv* q8h steroids until postoperative day six; thereafter, high dose methylprednisolone was initiated as per the Meduri[2] protocol for treatment of ARDS.

On arrival in the ICU, pressure control ventilation was initiated with a peak inspiratory pressure (PIP) of 26 cm H_2O, respiratory rate 15 min^{-1}, positive end expiratory pressure (PEEP) of 5 cm H_2O, and FiO_2 of 1.0. Initial blood gas analysis in the ICU revealed a pH of 7.28, PO_2 47, PCO_2 57, HCO_3^- 26, and SaO_2 80% (Table II). A chest x-ray revealed collapse of the right upper lobe, which re-expanded after bronchoscopy and lavage. High output air leaks were evident, severely impairing effective ventilation: delivered tidal volumes were 600 ml and expired volumes of only 100 ml were measured. Ventilation continued to be compromised.

Measures attempted to control fistulae flow included the following: reduction of chest tube suction, applying a small amount of continuous positive pressure to the chest tube underwater seal, decreasing inspiratory flow rates and mean airway pressures on pressure control ventilation. However, these techniques actually exacerbated the respiratory acidosis and resulted in marked subcutaneous emphysema. Extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) are not available at our institution and it was felt that the patient would have been at a prohibitively high risk for inter-hospital transport.

On POD #2 ventilation was provided by combined high frequency jet ventilation (CHFV)[3] in an effort to reduce the leak via the bronchopleural fistulae. Deep

sedation (5-15 mg·hr^{-1} morphine and 2-4 mg·hr^{-1} midazolam) and intermittent paralysis with 10 mg vecuronium were required. A jet rate of 100 min^{-1}, with a conventional intermittent mandatory ventilation rate of two low tidal volume (300 ml) breaths per minute, and driving pressure of 25 cm H_2O were initiated. The bilateral chest tube leak lessened and blood gases improved substantially: pH 7.41, PO_2 70 mmHg, PCO_2 42 mmHg, HCO_3^- 26 meq·L^{-1}, and SaO_2 94% with FiO_2 of 0.8. The driving pressure was reduced in an attempt to further decrease the bronchopleural leak.

On POD#3 ventilation deteriorated again and chest x-rays revealed development of bilateral airspace disease consistent with ARDS (PCWP=12). Blood gases continued to deteriorate and on POD #7 they were pH 7.14, PCO_2 93 mmHg, PO_2 93 mmHg, HCO_3^- 30 meq·L^{-1}, SaO_2 94% with FIO_2 of 0.8 and PEEP of 5 cm H_2O. Whenever the PEEP was increased, the output from the bilateral bronchopleural fistulae also increased dramatically. The concern of oxygen toxicity with ongoing persistently high FiO_2 requirements and deteriorating respiratory acidosis prompted the idea of delivering inhaled nitric oxide while continuing with the HFJV. The experimental nature of the proposed ventilation technique was discussed with the patient's family. There was no English literature available for technical guidance. Other tertiary care teaching hospitals throughout the area were contacted for advice, but none had attempted the simultaneous use of NO and HFJV. The integrated CHFJV-NO injection system we assembled is described below (Figure).

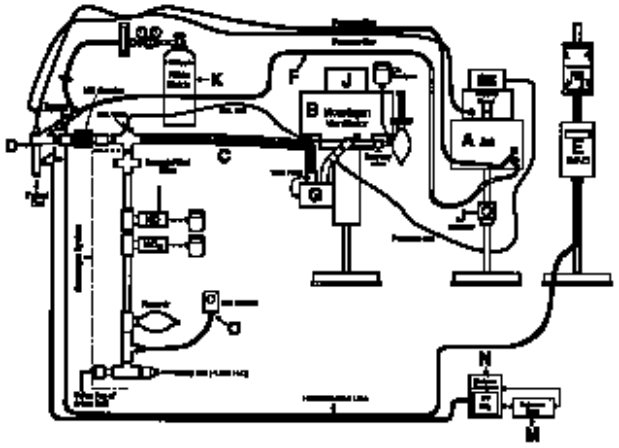

FIGURE Legend for Diagram
A. Healthdyne Impulse High Frequency Jet Ventilator
B. Monaghan 225 SIMV Ventilator
C. External IMV circuit
D. Portex Jet connector
E. IVAC infusion pump
F. Jet line of the circuit
G. Fisher-Paykel MR 450 Servo Humidifier
H. Novametrix Pneumoguard Model 1200
I. Distal exhalation valve NO sampling site
J. Bird Oxygen Blenders on each ventilator
K. Nitric Oxide (1000 ppm)
L. Patient "Y" connection
M. Siemens 300 Nitric Oxide Ventilator
N. Micro Medical Microgas analyzers
O. Active suction system

The Healthdyne Impulse High Frequency Jet Ventilator (A) was used in tandem with a Monaghan 225 SIMV Ventilator (B) and external IMV (intermittent mandatory ventilation) circuit (C). A Portex Jet connector (D) was attached to the existing single lumen endotracheal tube. Humidification was provided by instilling 20 ml·hr^{-1} of normal saline via an IVAC® infusion pump (E) into the jet line of the circuit (F).

The Monaghan 225 was used to provide a low level of PEEP (5 cm H_20), a ventilation rate of 2-4 per minute, and a continuous entrainment flow for the jet breaths. Gas from this ventilator was humidified by a Fisher-Paykel MR 450 Servo Humidifier (G). The FiO_2 was titrated by Bird Oxygen Blenders on each ventilator (J). Proximal airway pressures were monitored with a Novametrix Pneumoguard Model 1200 (H).

Nitric Oxide (1000 ppm) (K) was delivered by a constant flow (3 lpm) to the Jet line (F). The inhaled nitric oxide (NO) and nitrogen dioxide (NO_2) were initially measured at two points: at the patient "Y" connection (L) and distal to the exhalation valve (I). The measured values of inhaled NO were nominal (1-2 ppm) compared to the expired concentrations (10-20 ppm). Changes in ventilation and NO flow resulted in insignificant changes in the measured values at the patient "Y" connector, whereas expected changes were noted in the measured levels in the expired side. We assumed this was due to insufficient mixing time of the gases on the inspiratory side. The inspired measurements were therefore discontinued after approximately 24 hr.

The inspired gas concentrations were measured by the NO and NO_2 monitoring system of the Siemens 300 Nitric Oxide Ventilator (M). The exhaled gases were analyzed for NO and NO_2 with Micro Medical Microgas electrochemical analyzers (N). Exhaled gases and all escaping gases from the chest tube drainage system were scavenged by an active suction system (O).

TABLE I Pre-operative Pulmonary Function Tests

Spirometry	*Predicted Value*	*Observed*	*% Predicted*
FVC (L)	2.85	1.54	54
FEV_1 (L)	2.29	0.84	36
FEV_1/FVC	80	54	67
FEF_{25-75} (L/S)	2.46	0.34	13
Lung Volumes	Predicted Value	Observed	% Predicted
total lung capacity (L)	4.77	4.28	89
functional residual capacity (L)	2.83	2.98	105
residual volume (L)	1.92	2.4	125
Diffusion	Predicted Value	Observed	% Predicted
DLCO	21.92	4.95	22
DL/VA	4.6	2.11	45

TABLE II Blood Gas Values

Conditions	*Blood Gas Analysis*
Preoperative values	pH 7.41, PO_2 66, PCO_2 44, HCO_3^- 28, SaO_2 93%
PCV: PIP 26, RR15, PEEP 5, FiO_2 1.0	pH 7.28, PO_2 47, PCO_2 57, HCO_3^- 26, SaO_2 80%
CHFV: CMV 2, V_T 300 ml, PEEP 5, Jet Freq. 100, DP 25, $Fi0_2$ 0.8	pH 7.41, PO_2 70, PCO_2 42, HCO_3^- 26, SaO_2 94%
POD#3 same ventilation as above; CXR now shows ARDS	pH 7.14, PO_2 93, PCO_2 93, HCO_3^- 30, SaO_2 94%
CHFV and NO (20 ppm): Jet Freq. 100, DP 25, $Fi0_2$ 0.5	pH 7.35, PO_2 64, PCO_2 49, HCO_3^- 27, SaO_2 92%
POD#12: PSV 10, PEEP 7, FiO_2 0.5	pH 7.41, PO_2 78, PCO_2 51, HCO_3^- 32, SaO_2 95%

FiO_2= fraction of inspired oxygen; PEEP= positive end-expiratory pressure; PCV= pressure control ventilation; PSV= pressure support ventilation (cm H_2O); CHFV= combined high frequency ventilation; DP= driving pressure; PIP= peak inspiratory pressure (cm H_2O); RR= respiratory rate; CMV= controlled mandatory ventilation; V_T= tidal volume; CXR= chest x-ray; ARDS= adult respiratory distress syndrome

With the addition of NO at 20 ppm, both oxygenation and ventilation improved so that 12 hr after the initiation of NO, FiO_2 was reduced to 50% with blood gas analysis revealing pH 7.35, PO_2 64 mmHg, PCO_2 49 mmHg, HCO_3^- 27 meq·L^{-1}on the same ventilation parameters. On POD#10 blood gases had improved substantially and the NO was gradually weaned over the course of 24 hr. The air leak from the chest tubes had also decreased substantially and pressure control ventilation was resumed. On POD#12 sedation was reduced and the patient was placed on pressure support ventilation of 10, PEEP of 7, FiO_2 of 0.5 with resultant minute ventilation of 8.1 litres. Blood gases revealed pH 7.41, PO_2 78 mmHg, PCO_2 51 mmHg, HCO_3^- 32 meq·$L^{-1}$and SaO_2 of 95%. With sedation reduced, a right-sided motor deficit was detected and CT scan of the head revealed a left parietal temporal infarct. On POD#15 a tracheostomy was performed. On POD#16 tracheostomy mask trials of spontaneous breathing were started and on POD#19 the patient was able to sustain spontaneous breathing. The patient was eventually discharged to a peripheral hospital for continued rehabilitation.

Discussion

Published case series describing the use of HFJV as a ventilation mode for patients with bronchopleural fistulae have demonstrated variable success in improvement of gas exchange.[4] Improvement appears to be correlated with the presence of large, proximal, bilateral fistulae in lungs with normal or increased compliance.[4] The profound loss of tidal volume through both sets of chest tubes with rising $PaCO_2$ levels prompted an urgent trial of CHFV (a term that describes using both jet and conventional ventilation simultaneously), which rapidly produced acceptable $C0_2$ elimination and oxygenation. We accepted a pH >7.2 (permissive hypercapnia) in an attempt to reduce the driving and distending pressures both as a protective ventilation strategy[5] and also to allow healing of the fistulae. Unfortunately, ARDS developed and gas exchange deteriorated again. Although there are no trials

demonstrating a mortality benefit of NO for ARDS, it is a commonly utilized support measure for patients with ARDS and refractory hypoxemia. The relatively small size of our patient (45.9 kg), using combined conventional ventilation, allowing permissive hypercapnia and the proximal location of the bronchopleural fistulae may have contributed to the success of the HFJV in improving ventilation in this case.

Combining these two therapies led to a number of concerns. One problem was the ability to measure the dynamic levels of NO and NO_2 accurately in the inspired and expired gases, as well as in the ambient atmosphere. The administration of NO at high levels (i.e. > 40 ppm) is associated with lung injury and thus close monitoring is essential.[6] The ability to monitor respiratory gases accurately while using HFJV is problematic. Rapid response chemiluminescence analysis was not available but would be preferable, particularly during jet ventilation, in which wide swings in inspiratory flow may entrain dangerously high peak NO levels. The biological long-term effects of the possibly large regional swings in NO concentrations during HFJV require further study before they are implemented into routine practice. The large chest tube leaks led to concern regarding adequate scavenging of NO to protect bedside staff. The system as outlined above was developed and implemented. Another problem, specific to the use of HFJV, was providing adequate humidification. Adding saline to the jet line has been known to cause mucosal dessication as saline droplets are propelled into the airways. There were also concerns that the measurement of airway pressures at the jet connector were not a true reflection of intrapulmonary pressures. Despite these known deficiencies, the results were encouraging with a rapid improvement in oxygenation. Eventually, discontinuation of mechanical ventilatory support was accomplished.

Conclusion

The combined use of HFJV and nitric oxide has been infrequently reported.[1] We report the technical aspects of its successful use in a severely ill man who had large bilateral bronchopleural fistulae and who subsequently developed severe ARDS.

The primary concern with delivering this therapy was with safety of the patient and bedside staff. The difficulty in establishing predictable NO levels while using jet ventilation is a severe limitation of this technique. Neither HFJV for treatment of bronchopleural fistulae nor nitric oxide therapy for ARDS has been shown to improve patient outcome. Nevertheless, when faced with deteriorating blood gases using conventional therapy, an alternative strategy is often implemented. The use of this combined therapy, with its known deficiencies, must be cautiously approached until randomized outcome studies are available.

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