Respiratory Support Strategies in AIDS

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Introduction

The first cases of acquired immunodeficiency syndrome (AIDS) were reported by the Centers for Disease Control (CDC) in 1981 (1). Later on the causative virus was discovered and initially called the human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV III/LAV) by scientists at the Pasteur Institute (2) and the National Institutes of Health (3), respectively, and successively renamed human immunodeficiency virus (HIV). It quickly became evident that the disease was a worldwide problem and that persons outside the originally described risk groups (intravenous drug abusers and male homosexuals) could also be afflicted (4). AIDS consists of a profound immunosuppression, predominantly of cell-mediated immunity, that leads to a variety of opportunistic diseases, particularly certain infections and neoplasms. The main cause of the immune defect in AIDS is a quantitative and qualitative deficiency in the subset of thymus-derived (T) lymphocytes termed the T4 population. These cells are defined phenotypically by the presence of the CD4 surface molecule, which is the cellular receptor for HIV. Virtually any human cell that expresses CD4 receptors can be infected; among them the monocyte-macrophage lineage is of particular importance. Once the T4-lymphocyte count drops to 200 cells/μl or less, the chances of developing an opportunistic infection such as *Pneumocystis carinii* pneumonia are high, and this level of T4 cells is prognostic of a serious clinical complication.

The lung is the principal target organ of the infectious complications of AIDS and why this occurs is not entirely evident. Part of the explanation lies in the fact that lungs are the more frequent portal of entry of many infectious agents. Besides, the lungs may be predisposed to infectious complications because their immunologic capabilities may be even more suppressed than those of other organs. This is probably due to a direct infection of alveolar macrophages with HIV (5) and to a decreased production of soluble factors by lymphocytes (6). The spectrum of pulmonary disorders associated with HIV infection includes both infectious and noninfectious diseases (Table 1).

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Table 1. More frequent pulmonary disorders of HIV infection [Modified from Murray and Mills (7)]

Infections
Viruses
CMV, EBV, VZV, HSV, HIV
Bacteria
Pyogenic organisms
Mycobacterium tubercolosis, MAC
Fungi
Candida species, *Cryptococcus neoformans*, Aspergillus
Pneumocystis carinii
Protozoars
Toxoplasma gondii
Malignancies
Non-Hodgkin's lymphoma, Kaposi's sarcoma
Interstitial pneumonias

Pneumocystis carinii pneumonia

Pneumocystis carinii pneumonia (PCP) is the most commonly reported serious opportunistic infection in adult patients with AIDS. It is the index diagnosis for 66% of patients and occurs during the course of their illness in more than 80% of patients with AIDS (7). *Pneumocystis carinii* has been classified as both a parasite and a fungus, although the more recent opinion favored its inclusion with fungi (Table 1). *Pneumocystis* is virtually exclusively a pulmonary pathogen and its transmission is predominantly by the airborne route as either small particle aerosols or droplet nuclei. Although most cases of PCP are thought to result from reactivation of latent infection, there are several instances of small outbreaks of infection that could be attributed to airborne transmission of infection (8-11).

The histopathology of *P. carinii* is distinctive. Alveoli are filled with an acellular, eosinophilic, proteinaceous material that contains cysts and trophozoites of the organism with few inflammatory cells within the alveoli. The interstitial spaces contain predominantly mononuclear inflammatory cells.

The pathophysiologic abnormalities are characterized by impaired gas exchange, primarily from ventilation-perfusion mismatching or right-to-left shunts from impaired ventilation of alveoli filled with microorganisms or inflammatory debris. Most patients are hypoxemic and hypocarbic; more severely ill patients may become hypercarbic as respiratory failure worsens, and pulmonary compliance is markedly reduced.

PCP occurs only in immunosuppressed patients with a CD4 lymphocyte count below 200/mm^3 (12).

Diagnosis is usually made by broncho-alveolar lavage with a sensitivity of 86%. Other diagnostic tools are the examination of Gram-stained specimens

obtained by sputum induction or, less frequently, the transbronchial biopsy (sensitivity 87%).

In a 3-year period (1991-1994) we admitted in our ICU dedicated to infectious diseases 38 patients with AIDS and respiratory failure due to *P. carinii*. PCP represents in this population more than a half (55%) of the total number of episodes of acute respiratory failure requiring mechanical ventilation. Other causes of respiratory failure were *Staphylococcus a.* (17%), *Pseudomonas a.* (13%) and *Aspergillus f.* (16%). CMV was also detected on 16% of BAL samples, usually associated to other microorganisms.

Patients with a terminal illness who develop respiratory failure are often reluctant to undergo endotracheal intubation and mechanical ventilation, even when respiratory failure is acute, potentially reversible, and not a direct manifestation of the disease. They have an understandable fear of spending their final days attached to a machine that deprives them of autonomy and of the ability to communicate with others. After endotracheal intubation patients are unable to verbalize, and many patients experience pain and discomfort. Not surprisingly, many patients who have been previously intubated often refuse to repeat this experience. Besides, when a patient with AIDS develops acute respiratory failure, the physician may not have a clear understanding of the possible outcome and has the difficult task of assessing the risk vs benefits of an invasive treatment that will affect the patient's quality of life.

Patient and family support in the decision-making may also be difficult to achieve, particularly when ventilatory assistance is urgently needed. Furthermore, patient may become ventilator dependent and the decision to withdraw life support is difficult and has an emotional cost for all those who are involved.

Besides, the high financial cost to the hospital for supporting patients with respiratory failure and mechanical assistance is not fully recovered by the new diagnosis-related regional reimbursment (DRG).

Noninvasive ventilation

The concept of noninvasive mechanical ventilation by full face or nasal mask was initially developed for patients with neuromuscular disease (13) or chronic obstructive lung disease (14) necessitating rest of fatigued respiratory muscles.

More recently several authors applied continuous positive airway pressure (CPAP) to hypoxemic patients with *Pneumocystis carinii* pneumonia. CPAP improves oxygenation by the same mechanism whether delivered by endotracheal tube or mask. Functional residual capacity and lung compliance rise, $\dot{V}/Q$ matching improves, and shunt decreases (15, 16). CPAP reexpands collapsed alveoli by preventing early airway closure and increasing ventilation to areas of low $\dot{V}/Q$.

Gregg et al. (17) applied 5 cmH_2O CPAP by face mask to 18 patients with PCP with a mean pre-treatment $PaO_2/FiO_2 = 75$. All patients experienced relief of dyspnea, improved PaO_2/FiO_2 up to 180, and reduced work of breathing within 2 h from the beginning of treatment. Mask CPAP therapy lasted an average of 4.5 days and the authors underlined how all patients were able to speak and cough. Side effects were represented by dry mouth, necrosis of the bridge of the nose (27%) and conjunctivitis (12%). Two patients experienced recurrent gastric distension and one had pneumothorax. ICU mortality in this population was 37% and hospital mortality 55%. The reported mortality for patients with AIDS and PCP requiring intubation and mechanical ventilation in a total of more than 200 patients evaluated in the literature ranges from 84% to 91% (17-23). Gregg et al. concluded that CPAP by mask could identify a less severely ill or more responsive group of patients.

In a study performed in 1991 in conscious and collaborative patients with AIDS and PCP, Miller and Semple (24) demonstrated the efficacy of CPAP ventilation by an improvement of oxygenation and a reduction of respiratory rate and respiratory work. Gachot et al. (25) compared patients with PCP treated with CPAP by mask or with intubation and conventional mechanical ventilation and observed again that CPAP allows identification of a less acutely ill subset of patients, and avoids intubation and mechanical ventilation in many of them (19-25). In 1990 Brochard et al. (26) published a paper in which they demonstrated that pressure support ventilation (PSV) by face mask can obviate the need for conventional mechanical ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. Inspiratory pressure support is a method of ventilatory assistance designed to deliver a preset level of positive pressure during spontaneous inspiration. The patient's spontaneous inspiratory activity regulates the frequency and duration of inspiratory assistance. During PSV the assistance is cycled according to the inspiratory flow and stops before the flow drops to zero. The authors were able to show that PSV by mask was able to ameliorate gas exchange and to also reduce inspiratory effort evaluated by trans-diaphragmatic pressure time index and diaphragmatic EEG, provided that a tight fitted face mask was used.

The efficacy of this form of ventilation was successively confirmed in both acute and stable COPD patient by others (27-30). A tight mask is a major concern for patients ventilated for several days: facial pressure necrosis at the site of mask contact with ulcers of the bridge of the nose are frequent complications of mask ventilation causing patient discomfort.

We have recently demonstrated (31) that the mask can be loosened to improve comfort without altering the significant respiratory effort reduction and gas exchange improvement usually seen during mask ventilation. This was made possible by using a time-cycled instead of a conventional flow-cycled pressure support ventilation technique. The Siemens Servo Ventilator C permits the modification of the maximum pressurization time during PSV by adjusting the

RR knob. We set RR at 60 to achieve a maximum inspiratory time of 0.8 s corresponding to 80% of a controlled breath. Conventional flow-cycled PSV could not be used in the presence of air leaks because the flow does not drop below the preset expiratory trigger threshold (25% of inspiratory flow with Servo Ventilator). Inspiratory time is prolonged and inspiratory "hang up" and patient-machine asynchronism occur. Table 2 summarizes the results of the study.

Table 2. Data are means ± SE (*p < .05 **p < .01 vs SB p < .05 vs PSVfc)

	ΔPes (cmH_2O)	PTPes (cmH_2O.s/min)	RR(es-aw) (bpm)	SaO_2 (%)	PaO_2/FiO_2	$PaCO_2$ (mmHg)
SB	16 ± 3	392 ± 63	–	89 ± 3	148 ± 22	30.6 ± 3.4
PSVfc	15 ± 2	342 ± 58	9 ± 2	95 ± 1	–	–
PSVtc	11 ± 2*	230 ± 29**	1 ± 0.6	96 ± 1*	222 ± 39*	30.6 ± 3.3

SB, Spontaneous breathing; PSVfc, flow-cycled PVS; PSVtc, time-cycled PSV; RR(es-aw), difference between respiratory rate calculated on esophageal and airway pressure curve

In conclusion this study demonstrated that respiratory effort reduction and gas exchange improvement can be achieved during mask ventilation with air leaks provided that a time-cycled PSV is used.

Therefore since 1993, mask ventilation represents the first step treatment in the ventilatory management of patients with AIDS and respiratory insufficiency in our department.

In our last (unpublished) trial we considered 11 patients with AIDS and respiratory failure (most PCP) meeting the conventional criteria for intubation and mechanical ventilation (i.e., PaO_2/FiO_2 = 109 ± 20; RR = 40 bpm; and bilateral diffuse alveolar-interstitial pulmonary infiltrates). In these patients we were able to demonstrate a rapid improvement of oxygenation after mask ventilation with PSV (PaO_2/FiO_2 = 173 ± 64 at 1 h and 190 ± 70 at 24 h). Three out of 11 patients (27%) avoided tracheal intubation and were successively discharged from the ICU. The remaining eight patients were intubated and five of them died (63%), confirming the high mortality rate of intubated patients with AIDS and severe respiratory insufficiency (more recent reported mortality rate in literature = 89%) (32).

Our results indicate that mask ventilation is safe, well tolerated and able to avoid the need for tracheal intubation in about 30% of treated patients. It can effectively improve gas exchange and possibly prevent respiratory muscle fatigue by decreasing the workload of the respiratory muscles when adequate gas volumes are delivered.

Permissive hypercapnic ventilation

Once mask ventilation has failed and patients have to be intubated because of worsening of respiratory failure, permissive hypercapnic ventilation (PHC) is used as ventilatory treatment of choice in our department.

PHC was first introduced into clinical practice by Hickling et al. in 1990 (33). They suggested that peak inspiratory pressure limitation (PIP < 40 cmH_2O) led to a lower hospital mortality rate in 50 patients with ARDS when compared to mortality rate estimated by APACHE II scoring system or by the "ventilator score". Reduction of peak inspiratory pressure was obtained by reducing tidal volume, allowing spontaneous breathing with SIMV and disregarding hypercapnia. They had moved from animal studies which suggested that the use of large tidal volumes and high peak inspiratory pressures during mechanical ventilation resulted in the development of acute lung injury with the production of hyaline membranes and granulocyte infiltration (34, 35).

The following few randomized studies confirmed an improved outcome, even if not with the dramatic reduction described by Hickling (36, 37).

According to Tuxen (38) the ventilatory strategy for PHC can be summarized as follows:

1. PEEP should be titrated to the point of maximal alveolar recruitment as determined by lung mechanics (inflection point on the P-V static curve).
2. After optimal PEEP has been determined, tidal volume should be gradually reduced from 7 ml/kg to as low as 4 ml/kg in order to maintain the plateau pressure (Pplat) < 30 cmH_2O.
3. Suggestions about respiratory rate are less clear; some authors recommend mechanical ventilator rates < 30 bpm while Hickling reported intermittent mandatory rates of 14 to 20 bpm.
4. Whichever approach to ventilator rate is chosen, hypercapnia of greater or lesser degree will occur. To counteract hypercapnia one can sedate and cool the patient, reduce CO_2 production by paralysis and restriction of glucose intake and give sodium bicarbonate to correct a pH < 7.25.
5. Concerning oxygenation, FiO_2 should not exceed 0.6 and mean airway pressures should be elevated accordingly by increasing inspiratory time rather than tidal volume or external PEEP.

Adverse effects of PHC include cerebral vasodilatation, high cardiac output state with maintenance of blood pressure and enhanced hypoxic vasoconstriction with increased pulmonary vascular resistance.

Avoidance of alveolar overdistension through volume or pressure limitation has a significant support based on animal models and deleterious effects of the associated hypercarbia in severe lung injury do not appear to be an important limiting factor in preliminary human clinical trials. At present there are no data on the use of PHC in AIDS patients with PCP or other opportunistic pulmonary infections. However, we believe that the severe prognosis of these patients and the predisposition to develop life-threatening pneumothorax during mechanical

ventilation should encourage the use of PHC even without conclusive experimental results.

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