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Abstracts


Twenty-two pediatric patients with AIDS required assisted ventilation during 27 pediatric ICU (PICU) admissions. Patients were retrospectively divided on the basis of whether they required assisted ventilation for acute respiratory failure (ARF) or for another reason. Sixteen (59%) courses of assisted ventilation were for ARF. The PICU mortality rate was 81% for the ARF group. Eleven (41%) courses of assisted ventilation were for reasons not involving ARF. The PICU mortality rate for the group without ARF was 9%, significantly lower (p < 0.01) than for the ARF group. Pneumocystis carinii pneumonia (PCP) was documented in 48% of admissions. Occurrence of PCP did not affect mortality, nor was it more likely in those with than without ARF. Two patients with ARF survived to discharge from the hospital. Both died within 1 y of ARF. Thus, the short-term prognosis for pediatric AIDS patients requiring assisted ventilation for ARF is extremely poor.


The objective of this study was to test the safety of withholding anticoagulant therapy in patients with clinically suspected pulmonary embolism who have normal perfusion lung scans, regardless of the clinical manifestations. Anticoagulant therapy was withheld or withdrawn in 515 consecutive patients except in patients in whom deep-vein thrombosis was detected. Only three of the 515 patients had symptomatic venous thromboembolism on follow-up. The frequency of symptomatic pulmonary embolism on follow-up was one of 515 patients. With knowledge of the normal findings by perfusion scanning, an alternative diagnosis was established in 361 of the 515 patients. Cause of symptoms remained uncertain in 148 patients. It is safe to withhold anticoagulant therapy in patients with suspected pulmonary embolism and normal perfusion scans, regardless of the clinical manifestations. The finding of a normal perfusion scan excludes the presence of clinically important pulmonary embolism and makes pulmonary angiography unnecessary.


We retrospectively reviewed the records of 18 children with acquired immunodeficiency syndrome (AIDS) who required mechanical ventilation for respiratory failure. These patients represented 35% of the patients seen with pulmonary disease and AIDS. The most common causes of respiratory failure were Pneumocystis carinii pneumonia (77%) and bacterial pneumonia (33%). Bronchial lavage by fiberoptic bronchoscopy or endotracheal tube suctioning in mechanically ventilated children with AIDS had a high yield for P carinii. Eight of 18 (44%) children survived the episode of respiratory failure and were weaned from the ventilator. However, four of eight survivors died within 6 months. Arterial oxygen tension on admission and maximum peak inspiratory pressure on the ventilator did not differ between survivors and nonsurvivors. We conclude that children with AIDS who are mechanically ventilated can be weaned from the respirator but that the subsequent course remains poor.


Endotracheal intubation is not without complications, among the most serious of these being misplacement of the endotracheal (ET) tube. Unrecognized esophageal placement is a lethal complication, but even when placed in the trachea, ET tubes can be displaced distally and enter a mainstem bronchus. Correct positioning of an ET tube is usually defined as the placement of the tube within the trachea approximately 5 cm above the carina. Chest x-ray is the most common and a reliable method of demonstrating correct positioning, particularly in ICU patients. Using transillumination by means of a flexible stylet (lightwand), we investigated whether transillumination could position an ET tube consistently within 5 ± 2 cm of the carina. Ten human cadavers of varied weight and body habitus were intubated under direct vision and 10 mL of a radiopaque dye was injected down the tube as a marker for the carina. A premeasured flexible lighted stylet was then inserted into the in-place tube so that the bulb was positioned at the tube's distal opening. The brightest transilluminated glow produced by the bulb was then positioned at the sternal notch. A chest x-ray was taken and the distance of the tube tip from the carina was calculated. In each case the tube tip could be placed consistently at a level 5 ± 1 cm from the carina by observing the maximal transilluminated glow at the sternal notch. We
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In an attempt to identify predictors of long-term compliance with nasal continuous positive airway pressure (CPAP), we reviewed the records of 125 patients with obstructive sleep apnea (OSA) referred to our center for nasal CPAP trials. Severity of sleep apnea, sleep staging, daytime hypersomnolence, effectiveness of nasal CPAP, previous palatal surgery, and adverse reactions were compared in compliant and noncompliant patients. Nineteen patients did not tolerate a nasal CPAP trial in the laboratory or refused home nasal CPAP therapy. Ten patients were unavailable for follow-up. Of the remaining 96 patients, 23 (24%) had discontinued therapy, while 73 (76%) were still using nasal CPAP at 14.5 ± 10.7 months (mean ± SD). There were no statistically significant differences between the compliant and noncompliant patients in baseline apnea plus hypopnea index (AHI), baseline sleep staging, AHI while receiving nasal CPAP, sleep staging while receiving nasal CPAP, or frequency of adverse reactions during therapy. Severe daytime sleepiness was present in 65 of the 73 compliant patients and in 12 of the 23 noncompliant patients (p < 0.05). Ten of 43 in the compliant group had previous palatal surgery compared with 10 of 23 noncompliant patients (p < 0.05).

Our data confirm earlier observations in smaller samples that compliant and noncompliant patients have equally severe sleep apnea and good initial responses to nasal CPAP. Long-term compliance with nasal CPAP may be associated with the severity of daytime hypersomnolence on presentation. Previous palatal surgery was more frequent in patients who did not tolerate long-term nasal CPAP therapy.


This is a study of the effect of nocturnal nasal intermittent positive pressure ventilation (NIPPV) on symptoms of chronic alveolar hypoventilation (CAH), sleep oxygen saturation (S\textsubscript{aO\textsubscript{2}}), and frequency of hospitalization of patients with progressive neuromuscular respiratory insufficiency or restrictive lung disease from thoracic wall deformity. The nocturnal use of NIPPV is explored in combination with other noninvasive methods of supported ventilation for daytime support as alternatives to tracheostomy and long-term tracheostomy intermittent positive pressure ventilation (TIPPV). Sixteen patients with < 400 mL of vital capacity (VC) supine and < 15 minutes of autonomous respiration (free time) maintained a mean S\textsubscript{aO\textsubscript{2}} of 95.9 ± 2.6% (SD) during sleep on NIPPV without added oxygen. Seventeen other patients with adequate free time for a sleep trial unaided had an average S\textsubscript{aO\textsubscript{2}} of 81.8 ± 11.0%, which improved to 94.1 ± 3.4% on NIPPV alone. The average length of use of NIPPV by the 42 patients who have used it for one month or more is 21 (3-67) months. All 34 patients who were not dependent on ventilatory support 24 hours a day demonstrated significant improvement and in most cases normalization of ABG when off aid. Thirteen patients were converted from IPPV via an endotracheal tube or TIPPV to NIPPV. Long-term use of a custom molded thermoplastic nasal interface for the delivery of NIPPV is reported for 17 patients. Unnecessary morbidity and hospitalizations can be avoided by early awareness and appropriate management of CAH. NIPPV can be an effective alternative to TIPPV, body ventilators, or oxygen therapy.


To evaluate the long-term effect of prematurity and/or hyaline membrane disease (HMD) on pulmonary function and airway reactivity, we studied 49
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prematurely born children aged 10 to 13 years. They were divided into three groups according to birth weight and HMD status: Groups I and II comprised the children weighing less than 1,500 g at birth, and Group III those whose birth weight exceeded 1,500 g. Children without HMD at birth were classified as Group I and those with HMD as Group II or III. We performed both pulmonary function tests and methacholine (MCh) challenges and compared the results with those of 27 age-matched controls born at term. We found that FEVI and RV/TLC ratios were significantly different from control values in the groups with birth weights less than 1,500 g, regardless of their HMD status (Groups I and II). In Group I, results for FEV25-75% %Vmax50% and Dlco were lower than those of controls. Airway reactivity was significantly increased in Groups I and II. A 20% drop in FEVI after MCh challenge was found in 88%, 62%, 53%, and 36% of children in Groups I, II, and III and controls, respectively, and a 35% drop in SGaw occurred in 87%, 88%, 53%, and 59%. We conclude that prematurity and not HMD per se leads to long-term pulmonary abnormalities and to an increase in nonspecific airway reactivity.


High frequency jet ventilation (HFJV) was used to treat 176 infants who were either failing to respond to conventional mechanical ventilation (CMV) or demonstrating pulmonary air leak. The median birthweight for infants treated with HFJV was 1530 g, median gestational age was 31 weeks. Median duration of therapy with HFJV was 3.0, with a range of 0.1 to 27 days. During the first 24 hours of treatment, mean airway pressure decreased from 16.2 ± 0.3 (Mean ± SEM) cm H2O to 12.2 ± 0.3 cm H2O, while mean PAo2 increased from 65.3 ± 3.0 torr to 93.3 ± 3.0 torr during the same time period. Simultaneously, mean PaCO2 decreased from 46.4 ± 1.5 torr to 36.6 ± 1.0 torr, although peak inflating pressure decreased from 34.3 ± 0.7 cm H2O to 30.1 ± 0.8 cm H2O. Ninety-five (54%) infants treated with HFJV survived. Of 123 infants with RDS 75 (61%) survived. The rate of complications for HFJV patients was similar to that seen with CMV in our nursery. This study suggests that HFJV provides improved oxygenation and ventilation of infants at lower mean and peak pressures compared to conventional mechanical ventilation. HFJV combined with CMV may be a valuable adjunct to therapy in infants with severe lung disease.


We have examined the effects of combinations of three bronchodilator drugs in 37 patients with poorly reversible asthma. In each case FEVI was less than 90% predicted before administration of the third drug. Nineteen patients took increasing doses of salbutamol by inhalation followed by 160 μg ipratropium bromide and intravenous aminophylline, 5-6 mg kg. FEVI increased by at least 200 mL in 18 patients after salbutamol. Subsequently, ipratropium bromide increased FEVI by 200 mL in 3 patients while aminophylline did not produce a further 200 mL rise in any patient in this group. Nine patients were given aminophylline followed by ipratropium bromide and salbutamol and 9 took ipratropium bromide and then aminophylline and salbutamol. Eleven of the 18 patients in these latter two groups had a 200 mL increase in FEVI using salbutamol as the third drug. Significant increases in pulse rate were only seen after aminophylline or salbutamol administered as the third drug. These results suggest that maximal bronchodilatation in poorly reversible asthma can usually be achieved by increasing doses of beta agonist up to a therapeutic plateau. A further response, if required, may be achieved in some patients with ipratropium bromide.


Pulmonary function tests were carried out in 20 consecutive patients with pulmonary embolism (PE), diagnosed on the basis of a positive ventilation-perfusion lung scan carried out within 72 h of admission. Changes in forced expiratory volume in one second (FEVI), forced vital capacity (FVC) and arterial blood gas tensions were too variable to be helpful diagnostically. In contrast, transfer factor (diffusing capacity) of the lung (Dlco) was significantly reduced in all cases and, in spite of a period of anticoagulation, tended to remain subnormal during a follow-up period of up to 3 years. Lung scans, however, tended to return to normal within 3 months of the incident. Thus, a reduction of Dlco to below 75% of the predicted normal was found in all cases with abnormal lung scans and such measurements provide a useful and simple screening test for PE; a normal Dlco would effectively exclude such a diagnosis. The failure of Dlco to return to normal in the majority of cases suggests persistence of the underlying physiological defect, in spite of normalization of symptoms and lung scans following anticoagulation.
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The increase in morbidity and mortality attributable to chronic obstructive pulmonary disease (COPD) has focused attention on environmental and host factors causally associated with the clinical entities included under the rubric of this term with a view to early preventive intervention. Despite the biologic plausibility of inhaled agents being causally implicated, only the role of tobacco smoke has been accepted beyond doubt. However, evidence implicating occupational exposures has accumulated, in particular over the last 2 y from: (1) community-based studies (in which larger study populations provide greater power than the usually smaller workforce-based studies); (2) longitudinal studies of lung function (which enhance the signal of interest, namely the effects of the occupational exposures, and diminish the noise due to between-individual differences: (3) pathology studies (in which the outcome of interest is the quantitative measurement of emphysema), and (4) cohort mortality studies of all or specific causes of death. This evidence, reviewed here according to accepted criteria for establishing causality, leaves little doubt that occupational exposure to dust and/or to dust and fumes may be causally implicated in the genesis of COPD. As with tobacco exposure, both bronchitis (mucus hypersecretion) and airflow limitation are recognized as causally related to exposure, but not necessarily to each other. As with tobacco exposure, though effects are in general dose related to exposure, there is evidence for individual suscepti-

ability. As with tobacco exposure, a possible host factor is the reactivity of airways to inhaled materials. Future research should focus on the interrelationships of acute and chronic airway responses of all types to inhaled agents including those encountered at work, and this information should be incorporated into current concepts of the origins and natural history of COPD.


This study utilized computerized tomography (CT) to evaluate the effects of uvulopalatopharyngoplasty (UPPP) on upper airway (UA) dimen-

Recently reported data from a general population study in Tucson, Arizona, have shown that subjects who have an asthmatic bronchitic type of chronic airways obstruction have a much more benign course than equally impaired subjects who have the typical smoking-induced, and presumably emphysematous, form of disease. These data are reviewed briefly. Findings in these subjects are then compared with those in COPD patients enrolled in an emphysema clinic in Chicago many years ago; patients with asthmatic features had been systematically excluded from the Chicago series. The rate of decline in FEV₁ and mortality of Arizona subjects considered to have typical COPD were remarkably similar to those in the Chicago series after accounting for age and initial FEV₁, but Arizona subjects with features suggesting chronic asthmatic bronchitis had a much more favorable prognosis than either of the COPD groups. These different forms of chronic airways obstruction should be distinguished in clinical or epidemiologic studies of airway obstructive disorders.


Women have lower quit rates in smoking cessation than men. There are several factors suggested that are relevant to women's difficulties in smoking programs. One factor cited is the problem that women experience during withdrawal. Similar physiological and psychological symptoms are reported after smoking cessation and during menstrual cycle changes. In this study we evaluated the association between withdrawal and reports of menstrual distress. Results showed that a significant correlation existed between menstrual distress symptoms and initial smoking withdrawal symptoms. Women who quit smoking in the last phase (Phase 2) of their menstrual cycle experienced greater withdrawal than those who quit in the early phase (Phase 1) of the cycle. When these results were compared with male quitters, the Phase 2 women experienced significantly greater withdrawal than males. These results suggest that women may have specific biological needs that should be addressed in smoking treatment programs.


Serum antibodies to the fusion (F) and large glycoprotein (G) of respiratory syncytial virus in the serum of 57 infected infants were measured by enzyme linked immunosorbent assay (ELISA). Most serum samples taken at the time of admission to hospital contained antibodies to both glycoproteins, and overall there was no significant evidence of a selective deficiency of antibody to either viral antigen. Less than a quarter of the infants showed rising IgG antibody titres to either glycoprotein after infection, whereas over three quarters produced an IgM response. There was a significant correlation between IgG response to viral glycoproteins and the age of the infant. The correlation of age with the IgM response was less pronounced, and there was no correlation between serum IgG antibody derived transplacentally in the acute phase of infection and IgM response to either glycoprotein. Neither IgG or IgM responses correlated with a clinical assessment of the severity of infection in the infants. IgM responses, however, were weakly correlated with reduced secretion of infectious virus in the upper respiratory tract.
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Alternative Methods of Humidification during Use of Nasal CPAP

David A Strumpf MD, Carol C Carlisle BA RN, Susan C Beadles CTTT, and Richard P Millman MD

In 13 sleep apnea patients with severe nasal symptoms from the use of nasal CPAP and a consequent humidity deficit in inspired air, we compared the use of an artificial nose and a chin strap to the use of an in-line passover humidifier.

METHODS: In a 3-week study, the patients randomly used the chin strap or artificial nose the first week, then switched to the other device the second week, and finally used the in-line humidifier the third week. After each week, they answered questionnaires about ease of use, comfort, and symptoms with each device—and expressed their personal preferences. RESULTS: Most patients had some nasal discomfort or symptoms when using the in-line humidifier, but 8 of the 13 (62%) preferred it to the chin strap or artificial nose. CONCLUSIONS: The majority of these sleep apnea patients preferred the in-line humidifier to the other devices for improving humidification of their inspired air, but it was not uniformly acceptable. Further work should be done to develop a more effective, less expensive, less bulky humidification system for use with nasal CPAP. (Respir Care 1990;35:217-221.)

Introduction

Obstructive sleep apnea (OSA) is a syndrome characterized by transient upper-airway obstruction during sleep, resulting in repeated episodes of oxygen desaturation, CO2 retention, and sleep fragmentation. OSA is more common in the presence of obesity, produces daytime hypersomnolence and personality changes, and can lead to cor pulmonale in severe cases. The diagnosis is established by polysomnography, with an apneic episode defined as (1) complete cessation of airflow for 10 seconds or more, resulting in a drop in oxygen saturation of 4 percentage points, and (2) electroencephalographic evidence of arousal or awakening. Similarly, a hypopnea is defined as a 50% reduction in airflow, with associated desaturation and arousal. The apnea-hypopnea index is found by summing the apneic and hypopneic events and dividing the total by the total sleep time (in hours); the accepted criterion for a positive study of OSA is an apnea-hypopnea index of more than five events/hour.

Nasal continuous positive airway pressure nasal (CPAP) has been shown to be an excellent first-line therapy for patients with OSA, being effective in as many as 85% of patients. While it is generally well tolerated, nasal CPAP is not without complications. Serious complications, including reversible upper-airway obstruction and bilateral conjunctivitis have been described. More common are complaints of nasal discomfort—typically dryness, burning, and congestion. We have previously reported a case of massive epistaxis resulting from erosion of the nasal mucosa in a patient who used nasal CPAP nightly. Anecdotal information indicates that a number of methods have been employed to try to minimize these nasal...
problems, including decongestants, topical nasal solutions containing either steroids or emollients, and room humidifiers. In-line humidifiers have also been employed with good success, but these devices are expensive and bulky. In addition, many patients complain about both the noise these devices create and the condensation of moisture on the face.

Because of the foregoing problems, we evaluated two alternative methods of humidification in nasal CPAP patients who were currently using an in-line humidifier to treat severe nasal symptoms.

**Methods**

We asked 37 patients with OSA who were currently using Cascade Junior in-line humidifiers* to participate in the study. Of these, 19 responded affirmatively, of whom 6 subsequently withdrew due to noncompliance or conflicting plans. The remaining 13 patients made up our study group.

All subjects were drawn from patient records either at the Rhode Island Hospital Sleep Apnea Laboratory (Providence RI) or Amcare Medical Services (Newton MA). There was a marked male predominance, with the group having 10 males and 3 females. Their mean ± standard deviation age was 52.8 ± 3.2 years. Their apnea-hypopnea index was 82.8 ± 19.5 events/hour. All these patients were currently using SleepEasy II or III nasal CPAP systems. Nasal CPAP had been in use for 12.6 ± 1.9 months, and CPAP levels ranged from 7.5 to 15.0 cm H2O. All the patients were known to have had severe nasal problems, including epistaxis, nasal congestion, and burning with the use of nasal CPAP alone—and the addition of the in-line humidifier had allowed them to continue using CPAP.

The study was conducted in late October and November 1988, when there was a decline in ambient temperature and the heating of homes reduced indoor humidity. Because the patients were located over a large area, five respiratory clinicians (RRT or CRTT) were necessary to carry out the study. After instruction by this paper's authors, the respiratory clinicians went to the homes of the subjects and instructed them in the use of the two alternative humidification devices—an artificial nose and a chin strap.

The artificial nose is a passive moisture- and heat-retention device that collects heat and moisture from the patient's exhaled gases and returns them on the subsequent inhalation. In Figure 1, the arrow shows the artificial nose in the breathing circuit. The device requires daily cleaning, but with proper care can be expected to last up to 6 months. The chin strap (Fig. 2) prevents involuntary opening of the mouth during

*Suppliers are identified in the Product Sources section at the end of the text.

Fig. 1. Subject wearing a nasal CPAP mask connected with tubing to a SleepEasy III CPAP generator. An in-line artificial nose is indicated by the arrow.

Fig. 2. Here the subject has a chin strap (marked by the arrow) holding his mouth closed, with the aim of improving the humidification of his inspired air.
sleep and may minimize loss of upper-airway moisture and consequent drying and associated problems.

All subjects were randomized and began the study concurrently, using either the artificial nose or chin strap for one week and then crossing over to use the alternate device the second week. In the third week they all resumed use of the Cascade Junior humidifier, shown in Figure 3 to be in-line near the SleepEasy CPAP blower. Humidification with the Cascade Junior device is achieved by passing gas from the CPAP generator over a reservoir containing sterile water. (The tower was removed from the Cascade in all cases.)

Fig. 3. In this setup, humidification is provided by an in-line Cascade Junior humidifier (arrow) placed next to the SleepEasy CPAP blower.

Weekly telephone calls were made to the patients by two of the authors (DS, CC) to enhance compliance, and after completion of each week of the study all patients completed and returned a 15-item questionnaire. Information requested included the number of nights each device was used, overall comfort, ease of application of the device, effect on perceived sleep quality, and nasal symptoms. In addition, the third questionnaire asked the subjects to rate the devices in order of preference. After completion of the study, each subject resumed use of the preferred device.

Table 1. Subjective Reports of 13 Patients Who Had Used Three Different Methods of Humidification during Nasal CPAP*

<table>
<thead>
<tr>
<th></th>
<th>Artificial Nose</th>
<th>Chin Strap</th>
<th>Cascade Junior Humidifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to use</td>
<td>12</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Comfortable to use</td>
<td>10</td>
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<tr>
<td>Uncomfortable to use</td>
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<td>9</td>
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<td>Persistent nasal symptoms</td>
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<td>11</td>
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<tr>
<td>Increased nasal discomfort</td>
<td>9</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Worsened sleep quality</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Preferred method of humidification</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Good alternative for travel</td>
<td>3</td>
<td>2</td>
<td>0</td>
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*Each number indicates the number of patients giving a positive response.

Results

All the patients returned the three questionnaires. Evaluation of the replies revealed no apparent differences based on the order in which the devices were used. Patient responses are summarized in Table 1.

Cascade Junior Humidifier

All 13 subjects had noted symptomatic improvement after starting use of the Cascade Junior humidifier before the study. However, during the Cascade phase of the study, 10 of the 13 still complained of one or more of the following symptoms: nasal stuffiness, dryness, or burning. Despite this, when they were asked to compare the Cascade with the artificial nose and the chin strap, 8 of the 13 subjects (62%) preferred the Cascade. No patient suffered from epistaxis while using the Cascade humidifier.

Chin Strap

Eight subjects found the chin strap easy to use, and it was the preferred method of humidification.
in three subjects. Two subjects specifically noted that the chin strap was a good alternative for use when traveling. Nine subjects felt that the chin strap was uncomfortable, but only one noted a worsening of sleep quality while using it. Six subjects reported an increase in nasal discomfort while using the chin strap, and two of these six developed epistaxis.

Artificial Nose

Twelve subjects found the artificial nose easy to use, and two rated it as their preferred method of humidification. Three subjects preferred it as an alternative for travel. Nine subjects reported an increase in nasal discomfort with the artificial nose, and one developed epistaxis. Three subjects felt that the device was uncomfortable to use, but, again, only one complained of difficulty sleeping with it.

Discussion

In this comparison of patients' subjective evaluations of an in-line humidifier, an artificial nose, and a chin strap as methods of humidification during nasal CPAP use, the majority of the patients felt that neither the artificial nose nor the chin strap was as effective as the in-line humidifier.

Nasal CPAP has gained wide acceptance for the treatment of obstructive sleep apnea since its use was first reported in 1981. Most authors cite nasal discomfort as the principal side effect of this therapy. However, little has been written concerning methods of overcoming this problem. McEvoy and Thornton reported that three of seven patients treated with nasal CPAP for 1-18 months complained of nasal discomfort; however, no specific remedy was instituted. Sullivan et al found it unnecessary to humidify inspired air in any of 35 patients treated with nasal CPAP for up to 30 months; in fact, they noted that some patients who had complained of a sore throat as part of their pre-treatment symptom complex experienced relief of these symptoms on nasal CPAP. Sanders et al found that 68% of their patients complained of nasal congestion on CPAP, but these symptoms were manageable with saline sprays or room vaporizers.

In our experience, nasal discomfort has been a significant problem among CPAP users despite the routine use of topical nasal corticosteroid inhalers and saline nasal sprays. This problem has been most severe during the cold, dry fall and winter months, and the local New England climate may explain the higher degree of intolerance here than has been reported by others.

Despite its effectiveness, the Puritan-Bennett Cascade Junior humidifier has not been uniformly accepted by our patients, 77% of whom continue to report nasal discomfort while using it. Two other factors that have limited patient acceptance of this in-line humidifier are its size and cost.

Both alternative methods that we studied were associated with an increase in nasal symptoms in many of the patients; however, five patients preferred either the artificial nose or the chin strap to the Cascade Junior or felt that they were equivalent. Those who did not like the chin strap found it either uncomfortable or ineffective; perhaps a modified design that allowed the strap to be more securely fitted might be better tolerated. The artificial nose, while generally easy to use and comfortable, was simply not effective in the majority of patients.

Clearly, further studies are needed to determine better ways of providing humidity to CPAP users. We studied patients with profound nasal problems, and perhaps less expensive and bulky devices (such as the artificial nose or chin strap) might control nasal problems in less severely affected patients and could be tried first. In our study, the chin strap and artificial nose did lessen the burden of traveling with nasal CPAP in a select number of individuals, but neither device equaled the overall effectiveness of the in-line humidifier. Although we feel that the direct method of humidification (such as use of the Cascade Junior humidifier) is the most effective in these patients, it is apparent that a less cumbersome device is needed to maximize patient acceptance.

ACKNOWLEDGMENTS

The authors thank the respiratory care clinicians with Amcare Medical for their help in the study. We also thank Respironics for supplying the artificial noses and the chin straps.

PRODUCT SOURCES

In-Line Humidifier:
Cascade Junior, Puritan-Bennett, Boulder CO
CPAP System:
SleepEasy II & III, Respironics, Monroeville PA
Artificial Nose:
Model 6-270, Ohmeda, Lafayette CO

Chin Strap
Model 302175, Respironics, Monroeville PA

REFERENCES

Management of Respiratory Failure in the 1990s:
An Introduction

David J Pierson MD

Presented in this issue of the Journal are five articles developed from the fifth annual symposium, "New Horizons in Respiratory Care," held December 3, 1989, at the Annual Meeting and Exhibition of the American Association for Respiratory Care in Anaheim, California. Like that of its predecessors, this symposium's purpose was to provide information and insight on topics of concern to clinicians working throughout the profession. As in past years, participants were selected not only for their knowledge of the subject but also for their personal experience and insight. This year, however, the Program Committee asked also for imagination—charging each speaker-author to include not only the topic's relevant history and present state of the art but also his prediction of what the coming decade may bring. This year's papers are thus broader in scope and by necessity more speculative than their predecessors.

The topics selected are five aspects of the management of respiratory failure, four of them set in the intensive care unit (ICU) and one in the rapidly expanding arena of home care:

- Extracorporeal oxygenation and CO₂ removal
- The ventilator of the 1990s
- Pharmacologic approaches to the adult respiratory distress syndrome (ARDS)
- Home mechanical ventilation in the 1990s
- The quest for a blood substitute

Each presenter at the Symposium was given five specific tasks. First, he should clearly identify the issue or problem raised by the title as it pertains to the practice of respiratory care. Second, he should summarize the claims being made or possibilities being raised: 'the talk on the street' about what the technique or agent is alleged to do or about to be able to do. A concise review of presently available data—the current state of the art—should come next, followed by the presenter's own synthesis of what it all really means. Finally, each speaker-author was asked to speculate on the future, and offer predictions of where the technique, agent, or care area is most likely to go from here. Will it enter the mainstream of accepted respiratory care practice or will it end up gathering dust in the profession's vast warehouse of abandoned modalities, along with so many other promising developments that proved with time to be unnecessary, unacceptably dangerous, or too expensive to use?

What is extracorporeal oxygenation and CO₂ removal (ECCO₂R)? Clinicians caring for patients with severe hypoxemic respiratory failure have been hearing for 3 or 4 years about a new technique from Italy for resting the lungs and supporting gas exchange. Is it really new or is it just 25-year-old extracorporeal membrane oxygenation (ECMO) resurrected? Standard ECMO was abandoned in the management of adults with ARDS after a multicenter NIH-sponsored study showed it to offer no survival benefit as compared with conventional ventilator therapy. Does this new version mandate another look? In fact, another look is already under way, and its preliminary results provide some interesting insight not only into the clinical promise of ECCO₂R but also into improvements in care that may be possible using protocol-based management.
Ventilators for use in the ICU have evolved rapidly and dramatically in the last two decades, most recently with the emergence of the microprocessor-based ventilator and its expanded capabilities and flexibility. What can the ventilators of 1990 do that their predecessors could not, and what further capabilities are likely to become available at the bedside in the next decade? What will the next generation of ventilators look like? How will the clinician use (or perhaps more correctly 'interact with') them? How will they be incorporated into monitoring systems, data processing, and recordkeeping? How will the patient’s safety be ensured as the ventilator assumes more and more control of moment-to-moment management? These questions are of vital concern to everyone in the ICU, and they can be answered with more certainty and less conjecture than one might imagine.

When ARDS was first described more than 20 years ago, one half to two thirds of all patients with this syndrome died; and this remains the case today despite an enormous amount of basic and applied research into its pathophysiology and management. Much has been learned about the predispositions and mediators of the lung injury of ARDS, and this knowledge suggests a number of ways in which pharmaceutical agents might be able to prevent or attenuate this injury. What are the aspects of ARDS that might be amenable to modification by drugs? What drugs have already been tried, and what has been learned? What agents, old and new, is the clinician likely to be using in the management of patients with ARDS at the end of the 1990s?

Mechanical ventilation outside the ICU is a health care modality of increasing importance worldwide. It may take the form of life support for patients with high cervical spinal cord transection or ventilator support for those who have recovered from any acute illness but still require mechanical ventilation, or of elective therapy aimed at resting fatigued respiratory muscles for only a portion of each day, as in muscular dystrophy or severe kyphoscoliosis. What has been the history of home mechanical ventilation, and what systems have evolved to provide it in different social and cultural settings? What is its current status in the United States, and what is likely to happen during the next decade in terms of numbers and types of patients, home care services and reimbursement, and resources for ventilator-assisted individuals and their families? And how can this country’s health care system benefit from an examination of the problems encountered and solutions devised elsewhere in the world?

Patients with severe ARDS may experience critical tissue hypoxia despite high inspired-oxygen concentrations, the use of positive end-expiratory pressure, and red blood cell transfusion. Life-saving transfusions may be unavailable or refused by patients with profound anemia. In acute myocardial or cerebrovascular ischemia, crippling or fatal tissue loss may occur because of inadequate access of that tissue to oxygen. In each of these circumstances, the availability of a red blood cell substitute or “artificial blood” might mean the difference between death and survival. Substances with key properties of hemoglobin and red blood cells have been under study for 25 years. What has been learned, and what is the likelihood that a safe, effective blood substitute will become available for clinical use before the year 2000?

These were difficult assignments, but the authors have risen commendably to their tasks. In the five articles that follow, the authors provide helpful summaries, thoughtful discussions, and stimulating glimpses of the future roles that their topics may play in the management of respiratory failure in the 1990s.
Extracorporeal CO₂ Removal Therapy for Adult Respiratory Distress Syndrome Patients

Alan H Morris MD, C Jane Wallace RN, Terry P Clemmer MD, James F Orme Jr MD, Lindell K Weaver MD, Nathan C Dean MD, Samuel Butler MD, Mary R Suchyta DO, Thomas D East PhD, and Dean F Sittig PhD

Introduction

Patients with adult respiratory distress syndrome (ARDS)¹⁻⁵ have a high mortality,⁶⁻¹¹ although those who do survive generally resume productive lives without pulmonary limitations.¹²⁻¹⁶ In spite of many technical advances in intensive care, the ARDS mortality of > 60% does not appear to have changed during the past 15-20 years.⁶⁻⁹,¹⁷ Very few randomized clinical trials of therapy for ARDS have been performed, and studies continue to be plagued by two major problems: no widely applied standard definition of ARDS¹⁸,¹⁹ and no standardization of specific or supportive therapy. Thus, patient selection and subsequent treatment vary from center to center and in different clinical studies. The hallmark of the syndrome is severe refractory arterial hypoxemia, a result of intrapulmonic right-to-left shunting. The definition of ARDS usually includes severe arterial hypoxemia refractory to oxygen administration, bilateral chest radiograph infiltrates, respiratory distress manifest by dyspnea and tachypnea, and absence of elevated pulmonary artery wedge pressures. Unfortunately, the variability in the selection of ARDS patients and in their therapy in different clinical studies makes comparisons of study results imprecise and difficult to interpret.

Therapy

Treatment of ARDS can be specific (eg, draining closed-space infections) but usually is only supportive. Major elements of pulmonary care include oxygen administration, maneuvers to reduce right-to-left shunting (increasing functional residual capacity by increasing mean transthoracic pressure),²⁰ and support of ventilation and acid-base balance. Attention to cardiac output, fluid therapy, electrolyte management, and nutrition are required as well. Mechanical ventilatory support techniques used in the treatment of ARDS include assist-control, continuous positive-pressure, pressure-support, pressure-release, high-frequency, intermittent mandatory, inverse-ratio, and pressure-controlled inverse-ratio ventilation. Differences in survival due to different mechanical ventilation techniques have not yet been convincingly demonstrated.

The collaborative National Institutes of Health extracorporeal membrane oxygenation (ECMO) trial
of the 1970s employed high-flow venoarterial bypass (Fig. 1) in addition to traditional ventilatory support as a means of correcting life-threatening hypoxemia (Table 1).\(^{10,21}\) Traditional ventilatory support used for the patient’s natural lung included the application of PEEP, oxygen, tidal volume \((V_T)\) of at least 500 mL\(_\text{A} \) and ventilatory rate \((V_R)\) of at least 15/min (Table 2). Survival rates were disappointing and were almost identical in those patients treated with ECMO (9.5%) and in those in the control group treated with conventional therapy (8.3%). These results interrupted the widespread application of ECMO therapy for ARDS in adults. Subsequent experimental pursuit of extracorporeal support focused upon removal of carbon dioxide \((\text{CO}_2)\) through low-flow venovenous

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**Fig. 1.** Configuration of a venoarterial extracorporeal membrane oxygenation system. (Modified from Yukihiko N. Manual on artificial organs. Vol 11: The oxygenator. St Louis MO: CV Mosby Co, 1973:62.)

**Table 1.** Criteria for Entry into the RFP-NHLI-73-20 Collaborative Study of Extracorporeal Support for Respiratory Insufficiency, for Patients with a \(P_{A\text{O}_2}\) of 50 Torr or Less in Three Successive Analyses.\(^{10,21}\)

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<th>(Q_s/Q_t)</th>
<th>(P_{A\text{CO}_2}) (torr)</th>
<th>ICU Care (h)</th>
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<td>(\geq 5)</td>
<td>(\geq 0.3)</td>
<td>30-45</td>
<td>(\geq 48)</td>
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**Abbreviations Used in this Paper**

- ARDS = Adult respiratory distress syndrome
- CPAP = Continuous positive airway pressure
- CPPV = Continuous positive pressure ventilation
- ECMO = Extracorporeal membrane oxygenation
- \(F_{1\text{O}_2}\) = Fractional inspired oxygen concentration
- IMV = Intermittent mandatory ventilation
- LFPPV = Low-frequency positive-pressure ventilation
- PEEP = Positive end-expiratory pressure
- PCIRV = Pressure-controlled inverse-ratio ventilation
- \(P_{\text{peak}}\) = Peak pressure
- \(Q_s/Q_t\) = Right-to-left shunt fraction
- \(Q_s\) = Cardiac output
- \(V_R\) = Ventilatory rate
- \(V_T\) = Tidal volume

*For further information on SI (le Système International d’Unités), see Respir Care 1988;33:861-873 (October 1988) and Respir Care 1989;34:145 (February 1989—correction).*

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**Table 1.** Criteria for Entry into the RFP-NHLI-73-20 Collaborative Study of Extracorporeal Support for Respiratory Insufficiency, for Patients with a \(P_{A\text{O}_2}\) of 50 Torr or Less in Three Successive Analyses.\(^{10,21}\)

<table>
<thead>
<tr>
<th>Entry Type</th>
<th>Testing Time (h)</th>
<th>(F_{1\text{O}_2})</th>
<th>PEEP (cm H(_2\text{O}))</th>
<th>(Q_s/Q_t)</th>
<th>(P_{A\text{CO}_2}) (torr)</th>
<th>ICU Care (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>2</td>
<td>1.00</td>
<td>(\geq 5)</td>
<td>–</td>
<td>30-45</td>
<td>–</td>
</tr>
<tr>
<td>Slow</td>
<td>12</td>
<td>(\geq 0.60)</td>
<td>(\geq 5)</td>
<td>(\geq 0.3)</td>
<td>30-45</td>
<td>(\geq 48)</td>
</tr>
</tbody>
</table>
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Fig. 2. Configuration of system for patient support with low-flow positive-pressure ventilation (LFPPV) and extracorporeal CO₂ removal (ECCO₂R). DC = drainage catheter; RC = return catheter; ITC = intratracheal catheter for O₂ flow (~1 L/min); ML = membrane lung; RP = roller pump; R = venous reservoir; H = humidifier; GI = gas inlet; GO = gas outlet; GF = gas flow monitor. (Modified from Reference 28.)

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support (Fig. 2) as a means of resting the natural lung (Table 2). A remarkable survival of 77% has been reported in a nonrandomized, uncontrolled application in ARDS patients meeting ECMO criteria. 22 High-flow venovenous support of oxygenation in severely ill ARDS patients with major barotrauma who met rapid-entry ECMO criteria resulted in survival of 3 of 6 patients in an uncontrolled application. 23

The 77% survival followed the application of a sequential 3-step therapy program: 22 pressure-controlled inverse-ratio ventilation (PCIRV), continuous positive airway pressure (CPAP) if the patient improved with PCIRV, and low-frequency positive-pressure ventilation with extracorporeal CO₂ removal (LFPPV-ECCO₂R) (Fig. 2, Table 2) if the patient failed to improve with PCIRV. During LFPPV-ECCO₂R, CO₂ was removed with a low blood-flow (25-30% of the cardiac output) venovenous extracorporeal circulation. Arterial oxygenation was achieved primarily through the natural lung by a variant of apneic oxygenation, utilizing low-flow O₂ (~1 L/min) through an intratracheal cannula. This contrasts with the venaarterial approach used in the ECMO study (Fig. 1), which employed traditional ventilatory support (VT ≥ 0.5L, VR ≥ 15/min) for the natural lung and achieved oxygenation primarily through the extracorporeal membrane lung (Table 2).

Table 2. Comparison of Goals and Treatment Characteristics for Extracorporeal Support for ARDS in the ECMO vs the LFPPV-ECCO₂R Studies

<table>
<thead>
<tr>
<th>Goals</th>
<th>ECMO</th>
<th>LFPPV-ECCO₂R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Lung Ventilation</td>
<td>Minimize FiO₂</td>
<td>Minimize FiO₂</td>
</tr>
<tr>
<td></td>
<td>Ventilate in traditional manner</td>
<td>Lung rest*</td>
</tr>
<tr>
<td>Extracorporeal</td>
<td>Oxygenation of arterial blood</td>
<td>CO₂ removal*</td>
</tr>
<tr>
<td></td>
<td>(in order to rest lung)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Characteristics</th>
<th>(mean)</th>
<th>(representative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Lung Ventilation</td>
<td>VT = 0.6L†</td>
<td>VT = 0.2 L</td>
</tr>
<tr>
<td>Ppeak = 50 cm H₂O</td>
<td>Ppeak = 35-40 cm H₂O</td>
<td></td>
</tr>
<tr>
<td>PEEP = 10 cm H₂O</td>
<td>PEEP = 17 cm H₂O</td>
<td></td>
</tr>
<tr>
<td>VR = 15/min</td>
<td>VR = 2-4/min</td>
<td></td>
</tr>
<tr>
<td>Natural Lung Perfusion</td>
<td>~0.1 Qt</td>
<td>all Qt</td>
</tr>
</tbody>
</table>

*The two major differences of goals between the Rx in Milan and that used in the NIH ECMO trial in the 1970s.
†VT = tidal volume, Ppeak = peak ventilator pressure, PEEP = positive end-expiratory pressure, VR = ventilatory rate, and Qt = cardiac output.
injured ARDS lung sustains overexpansion (hyper-inflation) of and profound damage to the remaining small fraction of compliant lung still capable of gas exchange, thus superimposing an iatrogenic lung injury upon ARDS. In several normal mammals, severe lung damage followed uncomplicated ventilation with positive airway pressure either with \( P_{\text{peak}} > 30 \text{ cm H}_2\text{O} \) or \( V_T = 50 \text{ mL/kg} \) (Table 3). Lower \( P_{\text{peak}} \) does not appear to lead to lung damage because goats ventilated with room air at \( P_{\text{peak}} = 13 \text{ cm H}_2\text{O} \) for 2 weeks \(^{30} \) and dogs ventilated with \( P_{\text{peak}} = 23 \text{ cm H}_2\text{O} \) and 6-10 cm H\(_2\)O \(^{11} \) sustained no harmful effects. The induced increase in lung volume rather than the positive pressure itself appeared to be responsible for the lung damage. \(^{32} \)

It is disturbing to consider the possibility, compatible with animal study results but yet unproved in humans, that traditional ventilatory support may propagate lung injury in ARDS. This possible iatrogenic lung damage due to regional overdistention of compliant lung tissue represents a perception of barotrauma different from that traditionally defined by the presence of air in extrapulmonary tissues or spaces (eg, pneumothorax and pulmonary interstitial emphysema).

The reduced \( P_{\text{peak}} \) provided by PCIRV or by LFPPV-ECCO\(_2\)R may eliminate this regional lung overdistention in a way similar to the ‘lung rest’ program used in the apparently successful but nonrandomized neonatal ECMO therapy study. Representative neonatal values were: \( P_{\text{peak}} = 20 \text{ cm H}_2\text{O} \), PEEP \( = 4 \text{ cm H}_2\text{O} \), VR \( = 10/\text{min} \) and \( F_{\text{O}_2} = 0.3 \). Increased survival of PCIRV + LFPPV-ECCO\(_2\)R in a randomized, prospective clinical trial will be compatible with but will not prove the hypothesis that the lung is ‘overstretched’ during conventional management. Alternate mechanisms will have to be considered. Pulmonary blood flow is preserved in LFPPV-ECCO\(_2\)R (a venoarterial bypass) in contrast to ECMO (a venoarterial cardiopulmonary bypass), which markedly reduces pulmonary blood flow (Figs. 1 & 2; Table 2). Pulmonary blood flow may be an important determinant of lung response to injury, \(^{34,35} \) and this possibility must be retained as one of the potential explanations of differences between the outcomes of ECCO\(_2\)R and ECMO.

In 1986, survival of ARDS patients meeting ECMO criteria (Table 1) who had been supported with LFPPV-ECCO\(_2\)R (without PCIRV) was reported to be 49%. \(^{28} \) Although this is similar to the survival of ARDS patients in general, it is much higher than the 9% survival observed in the 1970s in the NIH collaborative ECMO trial for the subset of ARDS patients meeting ECMO blood-gas entry criteria. \(^{10,21} \) The two studies are not easily compared, however, because of the uncontrolled nature of reported ECCO\(_2\)R studies and because of the differences between the 1980 Italian and 1975 American clinical environments. The reported survival rates for LFPPV-ECCO\(_2\)R have, therefore, not been accepted as proof of the efficacy of this therapy.

**Statistical Considerations**

A prospective, randomized, controlled clinical trial is necessary to determine if PCIRV + LFPPV-ECCO\(_2\)R increases survival in patients with ARDS who meet ECMO criteria. Clinical results now available in the literature do not define the advisability or effectiveness of the therapy. \(^{36,37} \)

The use of tests to search for low-probability problems is usually fruitless. For example, the use of lung scans to find evidence of pulmonary embolism in normal college athletes is inappropriate because the likelihood (prior probability) of this disease being present is so low. Most of us recognize that, in such a group, a lung scan positive for pulmonary embolism would more likely be a false positive than a true positive. Thus, the predictive value of a positive test (the probability that a positive result is a true positive) would be too low to lead to meaningful action. \(^{38} \) In a similar manner, the predictive value of a positive

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**Table 3. Evidence of Severe Lung Damage in Normal Mammals from High Peak Airway Pressures**

<table>
<thead>
<tr>
<th>Animal</th>
<th>( P_{\text{peak}}^* ) (cm H(_2)O)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>Rats</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>Rats</td>
<td>( \geq 30 )</td>
<td>26</td>
</tr>
<tr>
<td>Dogs (open chest)</td>
<td>( &lt; 30 (V_T = 50 \text{ mL/kg}) )†</td>
<td>27</td>
</tr>
</tbody>
</table>

\(*P_{\text{peak}} = \text{peak inflating pressure.} \)

†\( V_T = \text{tidal volume.} \)
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Fig. 3. Predictive value of a positive trial (the probability of a true positive result) as a function of prior probability for a specificity (1-p) of 0.95 (ie, p = 0.05). (Modified from Reference 39.)

clinical trial is a function of the prior probability that the hypothesis being tested is true. The likelihood (prior probability) that a hypothesis, such as “PCIRV + LFPPV-ECCO₂R increases survival,” is correct must be sizeable if the results of a clinical trial are to be interpreted with confidence. The preliminary report of increased survival, though not from a randomized study, is crucial because it increases the prior probability that PCIRV + LFPPV-ECCO₂R is actually a superior therapy. In our thinking, this increases the prior probability from about 0.01 in 1979 to a prior probability in 1989 that can reasonably be assumed to be as high as 0.5. Figure 3 illustrates the relationship among specificity, prior probability, and predictive value.

With a prior probability of only 0.01, it would have been unreasonable to carry out a randomized clinical trial 10 years ago. A positive clinical-trial result at that time would have had only a 0.13 probability of being a true positive (and a 0.87 probability of being a false positive), and the results would not have led to any change in medical practice. In contrast, with a prior probability of 0.5, a positive clinical-trial result will now have a 0.93 probability of being a true positive and only a 0.07 probability of being a false positive. If the current randomized clinical trial produces a significant difference in patient outcome, this increased prior probability assures that such a difference can now be interpreted with a level of confidence high enough to lead to changes in medical practice.

Study Design: Randomized Clinical Trial

A randomized, prospective single-center clinical trial is currently being carried out at the Shock Trauma/Intermountain Respiratory ICU at the LDS Hospital (University of Utah). Patients are randomly assigned to two groups: traditional therapy or the 3-step therapeutic program that includes PCIRV + LFPPV-ECCO₂R. The clinical-trial design is seen in Figure 4. ARDS patients who meet ECMO entry criteria and are without characteristics that would cause them to be excluded are enrolled after signing informed consent. The ECMO exclusion criteria are intended to ensure that patients who complete the clinical trial are not likely to have underlying conditions, other than ARDS, that would preclude survival. We expect that 40 randomized patients, stratified by age (≤ 40 y or > 40 y) and
by the presence or absence of trauma, will be necessary. Blinded randomization with blocking is being used.

**Protocol Control of Therapy**

In medical practice today, variations in patient care can be seen not only among hospitals but even among ICUs within a single hospital and among physicians within an ICU. In fact, a particular physician may treat patients with similar problems and similar physiologic indicators differently. Protocols can dramatically alter the number and magnitude of therapy changes commonly encountered in clinical settings in which different physician treatment styles are used in the same patient. Further, careful protocol application can markedly increase the credibility and interpretability of clinical trial results.

We established a protocol-controlled critical care environment to ensure uniformity of care, equal intensity and frequency of monitoring, and a consistent decision-making logic for ARDS patients randomized to the two different therapies in our clinical trial. Published protocols for respiratory management of ARDS lacked the detail and specific instructions we needed. We, therefore, developed detailed specific protocols for all modes of respiratory management of arterial hypoxemia in patients with ARDS.

Therapy for arterial hypoxemia is guided, for both traditional treatment and PCIRV + LFPPV-ECCO₂R, with specific, quantitative, detailed protocols. Paper-based flow diagrams outline the logic and specific directions for therapy, thus providing a bedside guide that can be followed by the nurse, respiratory therapist, or physician. The flow-diagram protocols meet four basic investigative needs of our current clinical trial:

1. Use of uniform logic in decision making;
2. Examination of a uniform database for decision making;
3. Equal frequency of monitoring (ie, interrogation of the database); and
4. Equal intensity of care for all patients (eg, equal time intervals and equal increments between changes in therapy).

A therapy consensus committee initially consisted of 14 physicians, 3 nurses, and 1 PhD candidate in Medical Informatics. The physicians were members of the Pulmonary, Critical Care, and Anesthesia Departments of the LDS Hospital and the University of Utah and included two research associates from Dr Gattinoni’s group at the University of Milan. We were subsequently joined by a PhD bioengineer (TE) and were able to work with a group of about 7 physicians, after achieving acceptance of the protocols in the ICU. Primary responsibility for data acquisition fell to the respiratory therapists. Clinical application of the protocols was then a team effort, with the ICU respiratory therapists and nurses playing central roles. We worked 3½ years to develop the protocols (about 40,000 person-hours). All physicians agreed to forego personal bias and style and accept the ARDS therapy consensus recommendations that were incorporated into the flow-diagram protocols. The protocols include literature as well as local-expert information.

We have used the flow-diagram protocols successfully for more than 12,000 hours (representing approximately 12,000 decisions) of patient care. We believe that our experience establishes the feasibility of controlling the respiratory therapy of arterial hypoxemia in severely ill ARDS patients with bedside protocol instructions to clinical care team members. The protocols successfully control therapy 85% of the 24-hour day. (An obligate fraction of time exists during which protocols must be suspended for diagnostic or treatment procedures, such as x-rays or surgery.) This contrasts with the common medical wisdom that protocol control of therapy of such complicated ICU patients is impossible.

Utilizing the HELP computer system, we have used computerized versions of the protocols to control respiratory therapy of arterial hypoxemia, for about 6,000 hours. These computerized protocols are automatically activated when new information enters the patient’s data file (eg, from the blood gas laboratory or from the respiratory therapist’s ventilator check). The protocols generate therapy instructions, which are displayed to the clinical care team on the patient’s bedside computer terminal. We are currently controlling therapy, with the computerized version of the protocols, about 92% of the 24-hour day (ie, around the clock). Computerized protocol control is not only possible but appears feasible and more accurate than bedside interpretation of paper-based protocol flow diagrams.
To date, we have randomized 26 patients meeting ECMO criteria; 9 (35%) have survived. Survival rates in both control-therapy and new-therapy patient groups exceed the 9% expected for ARDS patients meeting ECMO criteria, but more patients must be randomized before a difference in mortality between the two therapy groups can be definitively assessed.

**In Summary: What Should We Do?**

The high (77%) survival in patients with severe ARDS has renewed worldwide interest in the use of extracorporeal support. The procedure is followed by survival in some patients; however, it is expensive and personnel intensive, requires a large well-trained team, and carries a significant risk of bleeding. If this technique proves superior, it should be widely employed. If not, it should be restricted to investigative applications. Whether the unexpected 35% survival in our clinical trial so far (four times the expected 9%, for ARDS patients meeting ECMO entry criteria) is due to patient selection, therapeutic or clinical environment changes, use of detailed protocols for respiratory care or other factors, is not yet known. Regardless of the cause, this 35% survival emphasizes the importance and necessity of well-controlled, randomized clinical trials with precise patient selection and treatment protocols for the definition of appropriate ARDS therapy.

New developments in extracorporeal support include heparin-bonded circuits, smaller partial-support devices, and percutaneous cannulae. In the future, extracorporeal circulation without systemic heparinization and the associated high risk of bleeding may be possible. Less invasive partial support of patients at an earlier stage of the illness may become common. The impact of extracorporeal support upon survival of ARDS has, however, not been definitely determined. Because the role of extracorporeal support in medical care is not yet defined, it is not currently recommended as a therapy, except for controlled clinical evaluations.

**REFERENCES**

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The Ventilator of the 1990s

Thomas D East PhD

Introduction

Vesalius could never have imagined what he started when, in 1555, he first described positive pressure ventilation:¹

But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air.

He would be shocked by the proliferation of techniques and devices designed to provide positive-pressure mechanical ventilation. Despite Vesalius's early observations, mechanical ventilators were not in evidence until the 1940s,² and it was not until the late 1960s and early 1970s that positive end-expiratory pressure (PEEP) was popularized as a treatment for adult respiratory distress syndrome (ARDS).³⁴ In the 1970s and early 1980s, an 'explosion' of positive-pressure mechanical ventilation techniques and devices occurred, and the later 1980s heralded the introduction of the microprocessor-based mechanical ventilator. In this paper, I engage in conjecture—'educated' guesswork, if you will—about mechanical ventilation in the 1990s.

Ventilator Design and Construction

The ventilator of the 1990s will be smaller, lighter in weight, and quieter than its predecessors and will use mostly digital electronics. As of 1989, most intensive care ventilators sold are microprocessor-based; however, early into the 1990s all of them will be. Digital electronics are not inherently better than analog electronics for ventilator operation (in fact, analog circuits may be more reliable in some circumstances), but digital systems are more versatile. A microprocessor-controlled ventilator can be easily modified by a simple software change to provide almost any new mode of ventilation and to collect information from a variety of sensors. This information can be displayed, stored, or manipulated in a variety of ways—limited only by the imagination of the software engineer. The power and flexibility of the microprocessor allows a redesign of the operator interface of the ventilator. The ventilator of the 1990s will not have the bewildering array of knobs that characterizes the intensive care ventilator of the 1980s.

The operator will gain access to controls and settings via the microprocessor using a device such as a keyboard, touch screen, mouse, or track ball or through speech recognition. Speech output will be used to respond to verbal requests when the user is busy and cannot see the display panel on the ventilator.

The primary disadvantages of using a microprocessor to operate a ventilator are related to safety and quality control. It has been well documented in aerospace and defense applications that a critical device cannot be dependent on just a single microprocessor operating independently.⁵ To be safe enough for use in a life-support device, an independent 'watch dog' system must be present to verify correct

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microprocessor performance. If the watch dog system detects a failure, the ventilator should enter a safe default mode of operation independent of the microprocessor. An even more ideal situation would be to have completely redundant systems—simultaneously operating microprocessors so that a backup can take over operation in the event of a failure.

Power fluctuations and failures can be a serious problem for microprocessor systems. When the power fails, all of the volatile random access memory (RAM) is lost, and lost with the RAM are all of the ventilator settings, monitored data, and alarm information. The solution is to have battery backup power for the RAM and thus be able to maintain the essential information, such as ventilator settings. Microprocessor-based ventilators of the 1980s incorporate such safety systems in some form; however, the ventilators of the 1990s must have improved safety systems, even though such systems increase ventilator cost and complexity.

Software quality control is an issue that is being debated throughout the microcomputer-based medical devices industry. In 1986, a software error in the Therac 25 linear accelerator allowed it to deliver 25 times the lethal dose of radiation in less than 1 second—causing the death of one patient and severely injuring two others. In 1987, the Food and Drug Administration (FDA) published a list of products known to have been withdrawn from the market because of software errors. The list, which is probably not complete, includes certain models of infusion pumps, surgical lasers, pacemakers, blood analyzers, ultrasound scanners, pediatric spirometers, cardiopulmonary function analyzers, and cardiac output computers. In response to a number of serious and fatal hardware and software failures in a variety of devices, the FDA has begun to regulate software to be used in microprocessor-based medical devices. All software for a life-support device must be extensively checked for software ‘bugs’ before being sent to the clinician. It is inappropriate for the intensive care unit (ICU) to be the testing ground for new software releases. In the 1990s, more and more emphasis will be placed on software validation and quality control.

Modes

Many of the modes of mechanical ventilation available on the intensive care ventilators of the 1980s

<table>
<thead>
<tr>
<th>Abbreviations Used in this Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS = Adult respiratory distress syndrome</td>
</tr>
<tr>
<td>CPAP = Continuous positive airway pressure</td>
</tr>
<tr>
<td>ECMO = Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>FiO2 = Fractional concentration of inspired oxygen</td>
</tr>
<tr>
<td>I:E = Inspiratory-to-expiratory time</td>
</tr>
<tr>
<td>IEEE = Institute of Electrical and Electronics Engineers</td>
</tr>
<tr>
<td>LCD = Liquid-crystal display</td>
</tr>
<tr>
<td>MIB = Medical information bus</td>
</tr>
<tr>
<td>PaO2 = Arterial oxygen tension</td>
</tr>
<tr>
<td>PEEP = Positive end-expiratory pressure</td>
</tr>
<tr>
<td>PetCO2 = End-tidal carbon dioxide tension</td>
</tr>
<tr>
<td>PCIRV = Pressure-controlled inverse-ratio ventilation</td>
</tr>
<tr>
<td>SIMV = Synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>SpO2 = Oxygen saturation as measured via pulse oximetry</td>
</tr>
</tbody>
</table>

are listed in Table 1. In addition, such modes as pressure-release ventilation are being reported in the research literature.

The ventilator of the 1990s will continue to provide all of these modes and perhaps provide a few more. However, the proliferation of new modes will not continue because the scientific and clinical communities are insisting that it be shown in prospective randomized clinical trials that new modes of ventilation significantly improve patient care before

Table 1. A Listing of Modes of Ventilation Available on Ventilators in 1989

<table>
<thead>
<tr>
<th>Assist/Control (Volume Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume Control + Sigh</td>
</tr>
<tr>
<td>Intermittent Mandatory Ventilation (IMV)</td>
</tr>
<tr>
<td>Synchronized IMV (SIMV)</td>
</tr>
<tr>
<td>Pressure Control</td>
</tr>
<tr>
<td>Pressure Control with Inverse Inspiratory-Expiratory Time Ratios (PCIRV)</td>
</tr>
<tr>
<td>Pressure Support</td>
</tr>
<tr>
<td>Continuous Positive Airway Pressure (CPAP)</td>
</tr>
<tr>
<td>Mandatory Minute Ventilation (MMV)</td>
</tr>
<tr>
<td>SIMV + Pressure Support</td>
</tr>
<tr>
<td>SIMV + Pressure Control</td>
</tr>
<tr>
<td>MMV + Pressure Support</td>
</tr>
<tr>
<td>Manual</td>
</tr>
<tr>
<td>High Frequency</td>
</tr>
<tr>
<td>Volume Control + High Frequency</td>
</tr>
</tbody>
</table>
these modes are released to the general public. The trend will be toward the unification of existing modes of ventilation into a small subset of universally applicable modes. One can easily imagine a merger of pressure-support, pressure-control, pressure-controlled inverse-ratio, mandatory minute ventilation plus pressure support, and synchronized intermittent mandatory ventilation plus pressure control as one mode—pressure-assisted ventilation—in which the presence and number of controlled breaths are determined by feedback from measures of ventilation and oxygenation, with the remainder of the breaths being pressure-supported. Such a mode, with the correct gas delivery system, could be merged with pressure-release ventilation. This trend reflects the general move toward a small, compact, computer-controlled mechanical ventilator that is simpler to use.

**Monitoring**

The most obvious new direction in mechanical ventilators is in monitoring. Already, most of the major manufacturers offer, on either the ventilator or an interfaced computer, extensive data collection and display both in textual and graphic form. The early 1990s will be marked by the widespread application of microcomputers to display the large amount of information available from the ventilator.

Monitors of gas exchange and hemodynamics will be merged into the data collection system of the ventilator to provide a central display of all vital information. Ventilators may have plug-in modules for pulse oximetry, CO₂ analysis, and noninvasive blood pressure measurement. Manufacturers will also provide a communication interface so that the information may be assimilated into the ventilator display from external monitors.

Cathode ray tubes, liquid crystal displays (LCD), flat-panel plasma-discharge display devices, and twisted crystal displays are available for displaying information. All of these devices are in use, and the device that can display the most graphic information in the smallest package will become the most popular. As the user interface evolves, the computer display will become much more vital and will occupy a proportionally larger percentage of the device panel. A balance between providing large, high-resolution graphics of excellent quality and constructing small compact ventilators must be struck. For example, a 21-in high-resolution-graphics color monitor occupies a volume of 5.4 ft³! The most likely result will be widespread use of the flat-panel displays—the LCD, plasma discharge, or twisted crystal displays. These displays offer reasonable graphics displays with a large viewing area but at small expense in terms of physical size. A 21-in-square flat-panel display may occupy as little as 0.25 ft².

All of the existing monitoring packages as of 1989 allow the user to select a combination of as many as 20-30 different variables for graphic trending. These systems display all of the data coming from the ventilator either in raw form or as moving averages. Little or no attempt is made to remove artifact from the signals or to provide higher level interpretation of the data. Gardner and Clemmer have pointed out that there is an information overload in the ICU. The overload makes it impossible for the clinician to assimilate effectively all of the information that is presented to him and to make a correct decision. The presence of 20-30 more new variables will only compound the problem. The monitoring systems of the 1990s must process the available information, provide a higher level of interpretation, and display the results in a simple form.

All data coming from the ventilator should be validated and the artifact rejected before the data are displayed to the user. This is a complex issue because many so-called artifacts are real events (eg, suctioning, drug nebulization, and patient movement) rather than being noise inherent in the sensing systems. These real events are typically not recorded or acted upon in decision making. Extensive work remains to be done in defining this type of data validation. The respiratory care community should demand that only high quality data important to decision making be displayed on the monitoring systems.

Trend plots, bar graphs, and other traditional forms of data display can be helpful; however, they do not ease the information overload. In the future, icon-based displays may simplify the interpretation of data. The display in its simplest form would be a picture of the patient and ventilator: The patient's color would indicate the oxygenation-ventilation status. At a glance, it would be immediately obvious that a blue patient is in deep trouble and that an immediate response is necessary. The human mind processes such images more efficiently than it does a textual display.
of pulse-oximetry oxygen saturation (eg, \( S_{\text{PO}_2} = 80\% \)). If the clinician wants more information, he selects the patient icon; consequently, a window pops up that contains the current specific information. If a trend is desired, a soft key can be activated to bring up a color-coded, traditional trend plot.

Automated interpretation of complex data—such as pressure-volume and expired CO\(_2\) curves—should be provided. Rather than just displaying these curves in different forms, the ventilator should provide an interpretation and possible diagnoses ranked according to probability of occurrence. For example, if a CO\(_2\) waveform with a sloping phase III is seen, the system should respond by indicating that the patient has alveolar dead space with sequential emptying, with the most likely cause being obstructive lung disease and a less likely cause being mechanical ventilation with small tidal volumes.

Alarms will be much more sophisticated. For example, if the patient becomes disconnected from the ventilator, should the ventilator respond with a low airway-pressure message, a low airway-pressure alarm, a low expired-minute-volume display, a low expired minute-volume alarm, a low end-tidal CO\(_2\) (\( P_{\text{ETCO}_2} \)) display, a low \( P_{\text{ETCO}_2} \) alarm, a low \( S_{\text{PO}_2} \) display, a low \( S_{\text{PO}_2} \) alarm, and an apnea alarm? No! The system should interpret all of these conditions, conclude that the patient has become disconnected from the ventilator, locate the problem, flash up a picture of the circuit with the fault isolated, indicate that the patient has become disconnected, and suggest a solution.

**Communication**

Most ventilators as of 1989 provide some form of communication port to send ventilator data to the outside world. All of the microprocessor-based ventilators of the 1990s will provide a digital interface from which an array of variables can be obtained with every breath. The Puritan-Bennett 7200 ventilator can send more than 100 pieces of information out the digital port with every breath! In the future, each manufacturer will have its own hardware and software communication standards that will work well if one wants to communicate among that manufacturer's devices—an acceptable situation if one's institution purchases equipment from a single manufacturer. However, most institutions have a mixture of makes and models of equipment. How can one obtain information from Siemens, Puritan-Bennett, Hamilton, and Ohmeda ventilators and the 'stat' blood gas lab? No good answer to this problem now exists, and it is a major stumbling block to the installation of a hospital-wide automated respiratory care charting system.

A committee of the Institute of Electrical and Electronics Engineers (IEEE) has been developing a standard method for communicating between medical devices—to allow devices of all makes to communicate with each other. This hardware and software standard known as the medical information bus (MIB) has been approved by the committee, after 5 years of deliberation. It seems likely that at least 2 more years will pass before the MIB standard is adopted and put into use.

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**Fig. 1.** Diagram of the Medical Information Bus (MIB) as implemented at the LDS Hospital in Salt Lake City, Utah. DCC = Device Communications Controller. MCC = Master Communications Controller.
Gardner et al decided several years ago that many things could be learned by actually using the proposed MIB, and they have proceeded to implement the 1986 IEEE MIB standard 1073.1 at the LDS Hospital in Salt Lake City, Utah (Fig. 1). The MIB has been successful at the LDS Hospital for I.V. pumps and pulse oximeters and for the measurement of mixed-venous oxygen saturation and gastric pH. We have been working on the MIB interface for the Puritan-Bennett 7200 and Siemens 900C ventilators.

Immediately apparent is the huge volume of information coming from the ventilator. Approximately 1500 pages (6 megabytes) of breath-to-breath data is sent from the Puritan-Bennett 7200 ventilator every 24 hours—bogging down the MIB and overloading the central computer. The second serious problem is that very little data validation or artifact removal is done before data are sent out of the digital port of the ventilator. To prospectively decide which data are good or bad is very difficult. Figure 2 is an example of data collected by the MIB vs that collected by the respiratory therapist. It is obvious that many events were not considered to be important and are not logged during the manual charting procedure. Figure 3 shows that some important things were mistakenly not entered during the manual charting. I have observed clinicians reacting to figures such as Figure 2 by indicating strongly that they do not want the "extra garbage" contained in the MIB data.

Such a reaction implies that standards are needed for all respiratory care data collection. Important
variables need to be clearly defined, not only for
decision making but also for the legal record. The
valid range and a definition of a significant change
should be established for each variable. I would
challenge the respiratory care community to establish
these standards—rather than leaving such decisions
to the individual manufacturer. Perhaps a nationwide
committee should be formed to establish minimum
standards for respiratory care data with which all
manufacturers must comply. It is only through such
standardization efforts that the concept of automated
respiratory care charting and computer-aided
management of mechanical ventilators can ultimately
be implemented effectively throughout a hospital and
across the country.

Automated Charting

It is clear that the ventilators of the 1990s will
provide respiratory care charting in some form. Some
ventilators already provide rough respiratory care
charting systems. The issues surrounding the MIB,
which were discussed in the section on communi-
cation, play a vital role in automated charting.
Machine-specific charting works well if there is only
one type of ventilator in the hospital—unlikely in
most institutions. If a hospital-wide charting system
that automatically gathers high quality data from all
ventilators is desired, a communication MIB and
respiratory care data standard are required. The MIB
data can then be printed and displayed in a variety
of forms depending on institutional and individual
needs. Such a system could be used as the basis for
charge capture for respiratory care billing. Each
service or treatment charted would be assigned a
charge, and a particular patient would be charged
only for the specific services or treatments received.
The hospital-wide respiratory care charting system
at LDS Hospital, which is based on manual charting
procedures, has been shown to improve efficiency,
charge capture, and departmental management. In
addition to providing for routine charting, such an
integrated system can provide management reports
for staff scheduling, duty assignment/history, labora-
tory data, physicians’ rounds reports, and quality
assurance, and can alert clinicians to the need
to modify FIO2, PEEP, peak airway pressure, tracheal
tube-cuff pressure, or airway temperature in response
to blood gas and microbiology data.

By the late 1990s, ventilators should all be
interfaced to the MIB, and integrated respiratory care
charting and management should be part of a hospital-
wide system.

Computer-Aided Management

A number of publications have shown that closed-
loop control of mechanical ventilation, with the
computer directly adjusting the ventilator settings
(respiratory rate, tidal volume, PEEP, pressure-control
level, the ratio of inspiratory-to-expiratory time [I:E],
and fractional concentration of inspired oxygen
[FIO2]), has been successful in animals. However,
little application of this technology has been made
to patient care—primarily, I believe, because of safety
issues. It has been impossible to guarantee that the
sensors measuring oxygenation and ventilation are
accurate and reliable enough to allow complete
computer control. Even in the 1990s, sensor
technology may not progress to the point that it will
be safe to have a ventilator totally controlled by
computer.

Data exist to show that expert systems can be used
successfully to manage mechanical ventilation in an
open-loop fashion. In these systems, the computer
makes a suggestion to the clinician who must then
make the final decision and adjust the ventilator.
Computerized protocols for the management of
oxygenation (control of FIO2, PEEP, pressure-control
level, and I:E) have been developed for volume
control, PCIRV, SIMV, and CPAP modes of
mechanical ventilation. A therapy consensus
commitee of 14 physicians, 3 nurses, 2 respiratory
therapists, and 2 doctors of philosophy worked 3½
years to develop these flow-diagram protocols. The
committee members were from the Departments of
Pulmonary, Critical Care Medicine, Medical
Informatics, Respiratory Care, and Anesthesia at LDS
Hospital and the University of Utah and included
two physician research associates from Dr Gattinoni’s
group at the University of Milan. All physicians agreed
to forego personal bias and style and to accept the
consensus recommendations for ARDS therapy that
were incorporated into the protocol logic. The
protocols included input from surveys of the literature
as well as local expert information.

The protocols were computerized to improve their
reliability and ease of use. The computerized protocols
were implemented in the HELP system, a comprehensive, hospital-wide, integrated data and decision support system.\textsuperscript{23,24} The overall structure of the computer implementation of the protocols is shown in Figure 4. The protocols are “data driven” because entry of a piece of important information into the system (eg, an arterial blood gas value or $S_{PO_2}$ value) can trigger execution of the protocols. The protocols first categorize the patient’s arterial oxygenation, ventilation, and acid-base status. It is much more efficient for the computer protocols to operate on categorical variables rather than to deal always with continuous variables. Five categories have been defined for arterial oxygenation: super-satisfactory, satisfactory, acceptable, marginal, and threatening. The $P_{aO_2}$ thresholds that define these categories depend on the barotrauma status of the patient. These thresholds are shown in the flow diagrams as conditionals on $P_{aO_2}$ (ie, “Is $P_{aO_2} < 55$?”). Similar categories have been established for pH. Once the categorizations have been made, the appropriate sections of the protocols are invoked, and computer instructions are generated.

The clinical staff interacts with the HELP system via the bedside terminal to receive the computer instructions. The other functions available at the bedside are review of the current patient database (eg, laboratory test results and vital signs), suspension of protocol, barotrauma classification (identification of the existence and type of barotrauma), execution of the protocols based on bedside pulse-oximetry-determined oxygen category, manual activation of the protocols based on the current HELP patient database, and patient enrollment. All of the instructions generated, intermediate data categorization, actual therapy decisions made, reasons for protocol suspension, and reasons for rejection of computer instructions are stored in the patient file in the same format as other patient data. Data storage in the patient database allows use of the unique tools available in the HELP system to integrate the protocol performance information with all of the other online patient information.

The protocols in paper flow-diagram form have been used for over 12,000 hours in 43 ARDS patients who met extracorporeal membrane oxygenation (ECMO) criteria, of whom 41\% survived. Anticipated survival from historical data is 9.5\% for ARDS patients meeting ECMO criteria.\textsuperscript{25} Although this is a moderate-sized group, the fourfold increase in survival is surprising. These protocols assured uniformity of care and reduced patient perturbations (eg, episodes of high peak pressure and high $F_{O_2}$ exposure). The results clearly establish the feasibility of managing the arterial hypoxemia of severely ill ARDS patients by guiding decision making of physicians, nurses, and respiratory therapists at the patient’s bedside. This contrasts with the common medical wisdom that protocol control of therapy of such complicated ICU patients is impossible.\textsuperscript{26}

The computer protocols were used simultaneously with the paper protocols for 3,388 hours between
9/4/88 and 5/3/89 in 11 patients who met ECMO criteria. A total of 1,986 computer protocol decisions were made—1,485 (75%) of which agreed with the actual therapy decisions made.

The computer performance has improved dramatically over time by reduction of incomplete, erroneous, and unstable patient data (human errors) through education and training, and by elimination of computer software failures. In our last 8 patients, 1,327 of 1,436 computer decisions (92%) agreed with actual therapy decisions (Fig. 5). The success of these computer protocols clearly establishes the feasibility of controlling the therapy of severely ill patients by guiding decision making of physicians, nurses, and respiratory therapists at the patient’s bedside.

By the mid-1990s, such protocols will be aiding the clinician in limited aspects of respiratory care decision making. By the late 1990s, more comprehensive protocols will cover a large portion of respiratory care patient management. Only time will tell whether protocols such as these will have the positive impact on patient survival that they seem to promise at the present time.

Impact on Respiratory Care

Whenever the issues of automated respiratory care charting and computer-aided management of mechanical ventilation are raised, the question inevitably asked is, “Will these systems eliminate the respiratory therapist?” To answer this question, let us consider that the evolution of mechanical ventilators is not too different from that of modern aircraft. Thirty years ago all aircraft were flown by hand, and most of the gauges were mechanical. Today the sophisticated jet fighter is totally computerized. The computer not only controls the F-16 fighter but also makes it aerodynamically stable. This implies that the aircraft would not fly at all if it were not for the computer. The plane can fly literally thousands of miles and land all under complete computer control. Yet, the pilot has not been removed. In fact, two pilots are required on scheduled commercial airlines. Whenever one reads of an airline mishap in which disaster was narrowly averted, one does not hear about the computer saving lives. It is the human being, the pilot, who takes over in the crisis situations, using the most powerful computer in the world, the human mind, to safely guide the aircraft.

The modern ICU is not really that much different from a high performance jet fighter. Devices provide vast amounts of information to the respiratory therapist who must comprehend the information and safely control the ventilator. The computer will not replace the respiratory care specialist, rather it will enhance the specialist’s abilities. The evolution to an automated computerized charting system and to computer-aided management of ventilation will change the nature of the respiratory therapist’s job. The fighter pilot of today is not trained the same
way the World War II fighter pilot was trained. Today's pilot must know and understand the computerized instruments and systems and the complex interactions within the system. As we have introduced these new respiratory care concepts in the ICU at the LDS hospital, we have seen the respiratory therapist become the pivotal person in operating the computer protocols and the MIB. Possessing a great deal of knowledge about the computerized system and the way the protocols function, the therapist is the expert, the pilot, of the highly sophisticated mechanical ventilator. The respiratory therapist is also an essential part of the decision-making team taking care of the patient. If anything, the amount of time the therapist spends with the patient has increased. The era of the respiratory therapist who only does incentive spirometry and collects some data from the ventilator is gone. The new tasks facing the respiratory therapist are even more challenging. The therapist must ensure the safe and correct operation of these complex new systems and safely guide the system by hand to avert disaster in the event of a malfunction. The respiratory therapist will be the pilot of ventilators of the 1990s.

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Pharmacologic Strategies for Treating the Adult Respiratory Distress Syndrome

Richard J Maunder MD and Leonard D Hudson MD

Introduction

The adult respiratory distress syndrome (ARDS) occurs in an estimated 150,000 patients annually in the United States, most often in association with sepsis, major trauma, or aspiration of gastric contents. The syndrome is characterized by the development of acute respiratory failure with hypoxemia and low lung compliance due to altered permeability of the gas exchange barrier and loss of surfactant function. Examination of lung tissue reveals the presence of inflammatory cells, alveolar and interstitial deposition of fibrin, protein-rich edema, and loss of pulmonary microvasculature. Despite advances in the understanding of ARDS pathophysiology and improvements in ICU monitoring and respiratory care, the mortality associated with ARDS exceeds 50% and has not changed since the syndrome was first described by Ashbaugh and Petty over 20 years ago.

The treatment of ARDS is primarily supportive, consisting of oxygen therapy, mechanical ventilation, and positive end-expiratory pressure (PEEP). To date, although many pharmacologic interventions have been tried, no specific treatment has proven successful. In this paper, we review the drugs that have been utilized in the treatment of acute lung injury, including those that have been subjected to rigorous clinical trials in human beings as well as those that have been used in the laboratory or have been the subject of anecdotal reports in the literature. Pharmacotherapy may be directed at the physiologic derangements that characterize ARDS, at the inflammatory events thought to be responsible for the initiation and perpetuation of lung injury, or at prevention of complications (in particular, infectious complications that account for the high mortality).

Drugs To Correct Disordered Physiology in ARDS

A number of physiologic abnormalities develop during the course of respiratory failure. Hypoxemia develops as a result of alveolar edema and collapse, airflow limitation, and abnormal hypoxic pulmonary vasoconstriction. Additionally, many patients develop right-heart failure and reduced cardiac output because of increased pulmonary vascular resistance from both active vasoconstriction and obliteration of the pulmonary vasculature by microthrombi. A variety of agents have been employed in an effort to reverse these physiologic abnormalities in patients with ARDS.

Drugs To Correct Hypoxemia

Surfactant Replacement. The success of exogenous surfactant administration in the management of neonates with respiratory distress syndrome

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A version of this paper was presented by Dr Hudson in the Schering Symposium New Horizons in Respiratory Care "Management of Respiratory Failure in the 1990s" during the 1989 Annual Meeting of the AARC in Anaheim, California.

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PHARMACOLOGIC STRATEGIES FOR ARDS

Abbreviations Used in this Paper

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>alpha-PI</td>
<td>Alpha-proteinase inhibitor</td>
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<tr>
<td>ARDS</td>
<td>Adult respiratory distress syndrome</td>
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<tr>
<td>auto-PEEP</td>
<td>Unintentional (spontaneous) PEEP</td>
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<tr>
<td>IRDS</td>
<td>Respiratory distress syndrome of infants</td>
</tr>
<tr>
<td>Pao_2</td>
<td>Arterial oxygen tension</td>
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<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
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(IRDS) has led to much interest in this form of therapy for adults with respiratory failure. The available products range from artificial phospholipid preparations to natural surfactants derived from bovine or porcine lung or even from human amniotic fluid.

Despite the success of trials in IRDS, there are many potential problems with surfactant replacement therapy for adult respiratory failure. It appears from experimental work that the proteins present in natural surfactant are crucial for the spreading of surfactant across the alveolar epithelial surface and for effective surfactant function in vivo. Thus, a natural product rather than one synthesized from phospholipids alone may be necessary. Although the antigenicity of natural surfactant products has not presented a problem in treating neonates, there are two reasons that this may not be the case in adults. First, the immune system is relatively undeveloped in newborns, especially those born prematurely, so the response to foreign antigens present in bovine or porcine surfactant is likely to be absent or significantly blunted. Second, the fact that IRDS is caused by surfactant deficiency, a problem that is rapidly corrected in most infants after delivery, means that only a single dose may be necessary. In ARDS, there is every reason to expect that the inflammatory milieu that induces surfactant dysfunction in the first place will be present to inactivate exogenously administered surfactant, so that repeated dosing may be necessary, enhancing the likelihood of an antibody response.

Another problem to be overcome before surfactant therapy for ARDS can be widely applied is related to the method of drug delivery. In neonates, surfactant is given as a liquid bolus as the infant takes his first breath before the lungs are filled with air. In adults, the volume of surfactant required to provide therapeutic benefit has been estimated to be as much as 250-300 mL. To deliver this as a bolus would almost certainly compromise a patient already experiencing respiratory distress. A number of investigators are currently (1989-90) working on development of an optimal delivery system; results available thus far suggest that an aerosol delivery system may be the most effective.

Surfactant replacement therapy has shown promise in certain animal models of ARDS, but results are variable. A handful of medical centers are testing surfactant products in humans, but no controlled trials have been performed. In selected cases, surfactant therapy has led to transient improvements in compliance and oxygenation. Much effort is being devoted to the synthesis of a surfactant product that combines the phospholipid component with human recombinant surfactant proteins. Such products are likely to be tested in the near future and show great promise as a potential breakthrough in the management of patients with ARDS.

Reduction of Lung Edema. Because pulmonary edema is a prominent feature of ARDS, it makes sense that drugs to reduce the accumulation of edema fluid in the lung would be useful. Intensive diuretic therapy has been utilized by some workers in an effort to 'dry out' the lungs and improve gas exchange. Such efforts have met with limited success. Although radiographic improvement may occur, and the Pao_2 may increase slightly, the hazard exists that volume depletion may decrease cardiac output, ultimately impairing tissue oxygen delivery. This is especially true in ARDS patients with sepsis or recent traumatic injuries in whom intravascular volume may already be low due to altered vascular permeability. Other authors have advocated the use of vasoactive and inotropic agents to maintain cardiac output while minimizing pulmonary intravascular pressures, thereby reducing the movement of fluid into the lung interstitium. The use of dopamine and nitroprusside has been shown to improve oxygenation and tissue oxygen delivery in experimental animals. Another approach to reducing lung edema involves the use of beta agonists such as terbutaline to enhance the clearance of alveolar edema by epithelial cells. Although Berthiaume et al have demonstrated accelerated liquid clearance from the lung in sheep treated with terbutaline, this therapy has not yet been applied in humans.

Bronchodilator Therapy. Airflow limitation is not often considered a part of the pathophysiology that
occurs in ARDS, yet work in experimental animals and a recent report in patients with ARDS suggests that reversible airflow obstruction is extremely common. The administration of metaproterenol by aerosol in ventilated patients with ARDS has been shown to significantly reduce airflow resistance. Although in theory this would be expected to improve ventilation and oxygenation, to lower airway pressures, and to lessen the risk of auto-PEEP, important clinical benefit has not been demonstrated.

**Promotion of Ventilation/Perfusion Matching**. Reflex vasoconstriction in response to regional hypoxia is probably impaired in ARDS and may contribute to increased shunt. Almitrine has been used in patients with chronic obstructive lung disease and in ARDS to augment the pulmonary vascular response to regional hypoxia, improving ventilation-perfusion matching and increasing oxygenation. In a study reported from France, the effect was variable, but $P_{aO_2}$ improved in most ARDS patients treated with the drug. There was a slight but nonsignificant increase in pulmonary artery pressure and no significant change in cardiac output. Almitrine has not yet been marketed in the United States, but it shows promise as a temporizing agent in patients with severe ARDS.

**Drugs To Correct Pulmonary Hypertension and Right-Heart Failure**

**Vasodilators**. As described earlier, nitroprusside and other vasodilators have been utilized in ARDS patients in an effort to reduce afterload, augmenting cardiac output while at the same time lowering pulmonary intravascular pressures. However, nitroprusside is a nonselective vasodilator with systemic as well as pulmonary effects. Systemic hypotension can be a limiting factor, particularly for the treatment of patients with sepsis, burns, or trauma who are already vasodilated peripherally. Furthermore, nitroprusside has been shown to impair hypoxic pulmonary vasoconstriction and may worsen arterial oxygenation. Nitroglycerine has less of an effect on the hypoxic vascular response, and hydralazine appears to have little if any effect. However, both of these agents have systemic vascular effects as well, again making hypotension a limitation to their use.

Prostaglandin $E_1$ (PGE$_1$) is a vasodilator prostaglandin with weak anti-inflammatory properties that is metabolized by the lung with nearly complete clearance in a single pass through the lung. As a result, PGE$_1$ acts as a pure pulmonary vasodilator. PGE$_1$ has been tested in ARDS patients by a number of investigators and has been shown to lower pulmonary vascular resistance and increase cardiac output in these patients. Although one early report suggested improved survival in ARDS patients treated with PGE$_1$, results of a recent multicenter trial showed no effect on outcome. The effect of PGE$_1$ on hypoxic pulmonary vasoconstriction is not known.

**Inotropic Agents**. The use of inotropic agents to maintain cardiac output in the face of hypovolemia was discussed earlier. There has also been interest in using inotropes to treat right-heart failure in ARDS, although limited data are available. Dobutamine offers advantages over dopamine for the treatment of right-heart failure in that it augments contractility while lowering pulmonary vascular pressures, thereby reducing right ventricular afterload and left ventricular preload. Dobutamine also has less of an effect on heart rate than dopamine, allowing more time for ventricular filling, an important compensatory factor in cor pulmonale. Amrinone and milrinone have also been used for inotropic support in critically ill patients, but use in patients with pulmonary hypertension and respiratory failure is limited.

**Anticoagulant and Fibrinolytic Agents**. Intravascular and extravascular activation of the clotting cascade has been demonstrated in ARDS, and intravascular thrombosis can be seen by angiography and histopathologic examination. Although their contribution is not clearly understood, coagulation proteins appear to play a major role in inflammatory lung injury and in the systemic response to sepsis and trauma. Therapy with protein C, an endogenous anticoagulant, has been shown to enhance survival in septic mice, and fibrinolytic therapy with urokinase has been shown to protect against the development of lung injury in a rat trauma model. Anticoagulants (such as heparin or protein C) or fibrinolytic agents (such as streptokinase, urokinase, or tissue plasminogen activator) have not been used in humans at risk for or with established ARDS. Obviously, there are risks in treating patients with recent major injury or with disseminated intravascular coagulopathy. However, this approach is likely to be tested in the next year or two, particularly in patients with sepsis.
Drugs To Reduce Alveolar Inflammation

**Nonspecific Anti-inflammatory Agents.** Corticosteroids have been widely used in the treatment of ARDS. However, several well-conducted clinical trials have failed to demonstrate any benefit of steroids in ARDS.\(^{12-14}\) Not only is early high-dose steroid therapy of no benefit in established ARDS, steroid therapy prior to ARDS in patients with sepsis, major surgery, or trauma does not prevent or lessen the severity of respiratory failure. In some series, results suggest that steroid therapy may increase the risk of infectious complications.\(^{12-14}\) Each of these trials has limited corticosteroid administration to the very earliest stages of lung injury. It is possible that the selective use of sustained high-dose corticosteroids in patients with severe, nonresolving ARDS may be beneficial as suggested by two uncontrolled studies.\(^{15,16}\)

Ibuprofen has been studied in animals and in a small number of human beings at risk for ARDS because of sepsis. This nonsteroidal anti-inflammatory drug appears to have beneficial effects, but it is not clear whether improvements in pulmonary vascular resistance, airflow resistance, and outcome are due to the action of the drug on inflammatory cells or the influence of cyclo-oxygenase inhibition on pulmonary physiologic responses.

Pentoxifylline is a drug that is marketed for use in human beings with peripheral vascular disease, but it has gained popularity in recent years as an agent with diverse anti-inflammatory properties that may be useful in treating patients with acute lung injury.\(^{17}\) Pentoxifylline has been shown to reduce neutrophil adherence and leukostasis and to blunt the response of neutrophils to inflammatory cytokines such as tumor necrosis factor. In experimental models of pulmonary injury, the drug has improved lung edema, protein leak, and even survival. To date, no ARDS studies have been done in patients, but there is great interest in pentoxifylline among intensivists—making it likely that this agent will be tested in the near future.

**Scavengers of Inflammatory Products.** Another approach to treating inflammatory lung injury is to block injurious mediators after their release from inflammatory cells. Alpha\(_1\)-proteinase inhibitor (alpha\(_1\)-PI), now available for use in patients with congenital alpha\(_1\)-antitrypsin deficiency, is one drug that has been tested in small series of patients with ARDS or a risk for ARDS. Although plasma levels of alpha\(_1\)-PI can be augmented by intravenous administration, the effect on alveolar fluid levels is less clear. From other work, it appears that a large quantity of functional alpha\(_1\)-PI is present within the lung during ARDS, so it is unlikely that this product or synthetic antiproteases will offer additional benefit.

Antioxidants such as superoxide dismutase and catalase have been administered in a number of animal studies with mixed results. The most promising work with antioxidants involves the use of liposome-encapsulated antioxidants, which appear to reach intracellular locations.\(^{18}\) Liposome-encapsulated superoxide dismutase plus catalase has been shown to prevent lung injury following sepsis in baboons and following hyperoxia in mice. However, the technology of liposome-encapsulation is cumbersome and expensive, so wide clinical application is unlikely in the near future. N-acetylcysteine, an antioxidant currently used to treat acetaminophen overdose, has been shown to lessen the lung injury associated with sepsis and with bleomycin injury in animals.\(^{19,20}\) Clinical trials in human beings with ARDS are currently under way.

Pharmacologic agents with specific effects on a variety of inflammatory mediators have been advocated by ARDS researchers. Platelet-activating factor antagonists have been shown to preserve blood pressure and hypoxic pulmonary vasoconstriction in septic rats.\(^{21}\) Although conflicting reports exist, these agents do not appear to have a beneficial effect on vascular permeability. Biotechnology firms have developed monoclonal antibodies directed against specific proinflammatory factors thought to be involved in acute lung injury. Monoclonal antibodies against tumor necrosis factor have been demonstrated to reduce the shock, organ failure, and mortality associated with sepsis in baboons.\(^{22}\) Anti-endotoxin therapy has been tested in several trials. Although the results are not yet available from recent studies in which monoclonal antibodies were employed, very promising results have been reported using polyclonal antisera in patients in septic shock, with significantly improved survival and shock reversal.\(^{23}\) Antibodies against the proinflammatory complement fragment C5a were found to reduce hypoxemia and lung edema in a primate model of sepsis, but human studies have not been performed.\(^{24}\)
Drugs To Prevent ARDS Complications

Drugs in this category are directed primarily at preventing the infectious complications that account for the majority of ARDS deaths. Most infections in ARDS patients involve the respiratory tract, so the prevention of airway colonization and pneumonia has a high priority. An Australian group, having observed that herpes simplex virus was present in 30-70% of ARDS patients, went on to study the effect of therapy with acyclovir, an antiviral agent, in patients with ARDS. Although acyclovir therapy successfully sterilized the respiratory tract and reduced the incidence of positive cultures to 17%, no benefit in terms of ARDS severity, duration, or outcome was observed.

Bacterial rather than viral infection of the lower respiratory tract is probably the greatest problem in ARDS. This is presumed to be due to impaired local and systemic host defenses and the propensity toward colonization with nosocomial pathogens that are increasingly resistant to treatment. One route of respiratory tract colonization is through regurgitation and aspiration of bacteria from the gastric reservoir in patients with gastric tubes and impaired consciousness. The use of sucralfate rather than antacids or H-2 blockers for prophylaxis against stress mucosal ulceration has been shown to result in a significantly lower incidence of lower respiratory tract infections and reduced mortality in mechanically ventilated ICU patients. This effect may be due in part to the preservation of gastric acidity, which prevents proliferation of bacteria within the stomach, but sucralfate appears to exert a direct antimicrobial effect as well. At least two European studies have reported that the use of topical antibiotics to decontaminate the oropharynx and gastrointestinal tract reduces the incidence of pneumonia in ICU patients. However, to date, these studies have not shown a reduction in mortality. None of these trials has been conducted in a population of ARDS patients, so the extrapolation of results to patients with acute lung injury must be made with caution.

Another approach to preventing or ameliorating infectious complications is represented by immunotherapy. Pseudomonas immune globulin has been shown to improve the outcome of Pseudomonas pneumonia in animals, and a human trial is currently in progress. This persistent and difficult-to-treat organism is the most frequently isolated gram-negative pathogen seen in ARDS, and its presence in this patient population is nearly always associated with a fatal outcome. The use of anti-endotoxin therapy in patients with established sepsis was discussed earlier. The prophylactic application of immunotherapy in ARDS patients—that is enhancement of the immune response prior to the development of overwhelming infections or sepsis—may offer an even more effective strategy than treatment after the fact.

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Mechanical Ventilation and Respiratory Care in the Home in the 1990s: Some Personal Observations

Allen I Goldberg MD

I. The Challenge of Home Mechanical Ventilation

Modern practices of pulmonology, critical care, and rehabilitation have made long-term mechanical ventilation a present reality. However, each ventilator-dependent person finds a different situation depending upon where he lives. Not all nations are at the same stage of evolution with regard to approaches designed to help the ventilator-assisted person return home. How programs develop and function today is very different depending upon the country and the specific region.

What programs have different nations put in place for persons who require prolonged mechanical ventilation? When did it become necessary for these programs to develop? Who has been essential to their creation? Where and how did the initial programs find their support? Why have these programs evolved the way they have?

Program Solutions: U.S.A., France, and England

The historical origins of home mechanical ventilation programs are found in the world-wide experience with poliomyelitis. Every nation had survivors who required prolonged hospitalization. Among them were the first generation of ventilator-assisted patients—some of whom remained for years in special ‘polio’ centers. Home mechanical ventilation was a direct outcome of efforts by medical leaders and ventilator users in these centers. Whether such patients were ever discharged home depended on what happened in and to those polio centers.

United States

The polio centers were phased out in the mid-50s after the discovery of the polio vaccine. The voluntary organization (National Foundation-March of Dimes), which had established the polio centers, then redirected its mission to birth defects. Much of the clinical expertise developed during the polio era led to the techniques and technologies used today in modern intensive care, pulmonary, and rehabilitative medicine. However, with several notable exceptions, the U.S. was not to see a direct continuation of the home care experiences from that period to present-day practice. There was to be a hiatus until progress in medicine, surgery, anesthesia, and critical care created a second generation of patients in need of long-term mechanical ventilation.

The U.S. exceptions were the publically financed polio centers that remained open: Goldwater Memorial Hospital, New York City, New York; Rancho Los Amigos, Downey, California; and the Institute for Research and Rehabilitation, Houston, Texas. Each developed respiratory rehabilitation and home mechanical ventilation programs for polio patients and others with neuromuscular diseases. The experiences in such centers and with other isolated individual cases in the U.S. and around the world

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were documented by a unique consumer (user) network in the publication Rehabilitation Gazette. This documentation was to provide the inspiration for a new generation of medical leaders and ICU ventilator users who were to attempt new demonstrations of home mechanical ventilation.

In 1982, U.S. Surgeon General C Everett Koop brought the issue of developing programs for ventilator-dependent children to national prominence as a case-example of children with special needs. In 1983, the U.S. Department of Health and Human Services, Public Health Service, Division of Maternal and Child Health, sponsored four special projects of regional and national significance to create and evaluate home care models for these children. In 1984 and 1985, two major studies of current status, problems, and dimensions of life-sustaining technologies were authorized by the U.S. Congress, Office of Technology Assessment (OTA). In 1986, the Secretary of Health and Human Services convened a major task force to study the needs of technology-dependent children. In 1989, the Health Care Financing Administration designated several demonstration programs for elderly persons requiring prolonged mechanical ventilation.

The U.S. has not yet developed an integrated systems approach to home mechanical ventilation. Funding for the home care of ventilator-assisted persons is often determined on an individual-case basis. Most programs are based at centers whose leaders have attempted to develop local solutions. Home care services and funding are fragmented and poorly coordinated. Many agencies, voluntary associations, and proprietary organizations are involved, but no uniform systems management exists to take advantage of scale economies, learning-curve efficiencies, and quality control technologies.

France

Because polio vaccination was not initially mandatory in France, their need for polio treatment centers continued and new polio patients were admitted well into the 1960s. These centers, which were eventually incorporated into the intensive care units, became 'home' to the patients who filled their beds. In Lyon (Sedallion Pavilion, Croix-Rousse) and Paris (Breznin Pavilion, Raymond Poincare, Garches) polio survivors and physicians together took the initiative to make possible home mechanical ventilation.

Many early leaders of intensive care medicine in France were students of the directors of original polio centers. Their early experiences with prolonged mechanical ventilation made them comfortable with the concept of home mechanical ventilation. They were motivated by social concerns for their patients and the need to make acute care resources available to new patients. They enlisted the involvement of regional government officials and finance authorities who were interested in new and better ways to extend the value and range of their own health care budgets.

France has a cultural tradition of serving the public good with voluntary associations established under the law of 1901. Thus, it was only natural for regional associations to develop ICUs from these original polio centers—initially for social reasons and medical purposes—and to allow services to be extended to new patients with similar needs but with conditions other than polio. Prominent political figures were included among the leaders who directed the establishment and growth of these associations. The original associations became models for other regions facing similar problems; these other regions adapted the model to their unique localities. Eventually, a major government-sponsored study recommended this approach to meet the large and growing demand for home oxygen, the extension of regional associations to all of France, and the creation of a national federation of the regional associations (ANTADIR).

Currently, over 20,000 ventilator-assisted and/or oxygen-dependent patients obtain home care services from community-based regional associations that are linked to local associations serving a variety of social needs and to centers of expertise at regional (university) medical centers. These programs provide equipment, supplies, and comprehensive surveillance; they have been established through the collaborative effort of health care professionals, patients and families, funding authorities, and governmental officials. They fully coordinate, integrate, and provide the social, technologic, and health care services necessary for successful home mechanical ventilation.

England

The Responaut Program evolved (in the 1960s) from England’s first intensive care unit at the St
Thomas Hospital in London. Incorporated into this original ICU was a former polio unit with beds occupied by polio survivors who still required mechanical ventilation. Home care was established through the cooperative ingenuity and tireless efforts of these patients and their physicians. The dramatization of their cause to political leaders led to a major national study: The Responaut Study. The Responaut program enabled these original patients to return (with personal care attendants) to the community or to their families. Services were then extended to other patients with neuromuscular diseases whose lives were being sustained by medical technology.

The Responauts also created a voluntary association (PRUPA) responsible for the development of a home care program at the Phipps Respiratory Unit at St Thomas. From this base unit of expertise, the Responaut Program provides a growing number of patients throughout England and beyond with a comprehensive home maintenance service that meets health, social, and equipment needs. The Responaut program is linked to other voluntary organizations in England (that serve persons with disabilities) to make comprehensive services available to ventilator-assisted individuals in the community.

Program solutions in countries other than the U.S. have shown that demonstrations and studies are prerequisite to the public policy determination and health care financing authorization needed to stimulate major program development. Model programs operational today were developed in ways that were appropriate to the cultural traditions of each country.

Program Evolution

What is in place in each nation fits the political, economic, social, and cultural realities of the country and the regional peculiarities of each locality. In addition, there seems to be a predictable pattern of evolution of home mechanical ventilation around the world. There are certain predeterminants and steps that occur before major programs develop.

Medical Progress

Medical techniques and technologies must have developed to a point where patients with critical illnesses can be saved, stabilized, and offered the home care alternative. Progress in acute intensive care and rehabilitation creates this patient population in the first place. New medical practices and devices stimulate home care: prolonged mechanical ventilation, the portable ventilator, the oxygen concentrator, the nasal mask, and the transtracheal catheter.

A Critical Number of Patients

A critical number of patients is required to make a program worthwhile and necessary. Although isolated cases may, for humane reasons, qualify for discharge to home, projected cost savings are required before programs can develop. Acute care beds must have become limited because of prolonged occupancy by such patients, and hospitals must be facing economic loss from inadequate reimbursement. Financial authorities must anticipate sufficient economic returns for funding program development because home mechanical ventilation programs develop only when associated with larger social or financial issues.

Level of Awareness

Patients, families, physicians, and all others involved must become aware that home mechanical ventilation is a possible, safe, and preferable alternative and must become committed to program development. Building awareness among the medical community and the public is often accomplished by convening conferences to share models and experiences.

Degree of Acceptability

Many categories of people and organizations must accept home mechanical ventilation and become involved if the concept is to become a reality. All have their own requirements for participation. A mechanism must be established for them to work together for program planning, implementation, and evaluation.

Skillful Leadership

Most home ventilation programs are the outgrowth of leadership efforts by doctors, patients and families,
and other key persons (eg, hospital administrators, government officials) who see the potential of the home option and dedicate an enormous amount of time and energy to this challenge. Programs can benefit from the insights and skills of political leaders.

**Trigger Events**

Although some programs just 'happen' as a result of the tireless efforts of their founders, more often a 'special event' unexpectedly occurs or is planned by design. The need for home mechanical ventilation is sometimes made evident by a 'crisis'—often in the form of a special case, event, or person's achieving notoriety.

**Collective Action**

Once the advantages of home care become evident, collaboration is required, with participation of all essential persons and organizations at the decision-making, action-taking level. They have to be involved at the outset of program planning and must assume ownership of the concept.

**Trial and Demonstration**

None of the original programs mentioned were established overnight. Each grew after model development, initial trial, demonstration, re-evaluation, and modification. All key persons and organizations participated at each step, and formal studies or major investigations were required.

**Educational Efforts**

A major commitment to education had to be undertaken before home mechanical ventilation could proceed. Patients, families, and professional caregivers had to understand what was required at home. Participating persons and organizations need this understanding to motivate involvement and commitment.

**Documentation and Advocacy**

As the value of isolated experiences was demonstrated and documented, program considerations began. The same questions were asked each time: How many patients are there? Where are they? Who is taking care of them? How much does it cost? What outcomes are desired? Information had to be collected, processed, and reported to answer these questions and to satisfy those who would make program development a reality. Then, through advocacy efforts, the information had to be used to elicit proper attention to the issue.

**Program Uniqueness**

Although similarities exist in the evolution of home mechanical ventilation around the world, programs between and within nations have not developed in the same way or to the same extent. Although what programs accomplish may be similar, the means may not be. The degree to which home care concepts are developed and the manner in which actual programs operate vary throughout the world, with differences in several key areas.

**Critical Level of Need**

The actual number of ventilator-assisted patients in any given country or area is a reflection of the progress that has occurred in acute care and rehabilitative practice. As health care professionals are trained and intensive care units established, more patients who require life-sustaining technology survive. A natural consequence is that a greater number of 'expensive care' beds become occupied by these patients; bed utilization and economic issues eventually attract the attention of physicians, hospital administrators, government officials, and health care financial authorities.

**Essential Level of Acceptance**

Medical leaders and others have had different attitudes concerning the approaches to be used in the long-term management of patients who require mechanical ventilation. Even among experts, agreement on a definition of prolonged mechanical ventilation, standards of practice, or guidelines for care is hard to establish. Differences in medical management preference is a reflection of differences among professional disciplines. How programs
develop depends upon the orientation of the medical leadership. Program differences depend upon whether the founding physicians are hospital or community oriented, and whether their professional training has been in intensive care, pulmonology, or rehabilitation.

**Medicine and Culture**

Medical practice among nations varies dramatically. What is considered illness in one country may not be in another. A preferred treatment in one nation may be considered unacceptable or even an example of malpractice in another. How a nation views a person who requires prolonged mechanical ventilation (ie, by what means and where they should be managed) is a dramatic example of how culture and tradition affect the value judgments of doctors, patients, and other members of society. Culture determines whether people think it is worthwhile to live on a ventilator, whether such a ventilator-dependent person is sick, and whether such a person's needs are appropriately served outside a hospital.

**Dramatization of the Problem**

Oftentimes the preferences and beliefs of ventilator-assisted persons and their families concerning home mechanical ventilation must be brought to the attention of leaders and key officials who must then be 'encouraged' to do something. Some attention-attracting devices have included conducting a key media event (eg, the Responauts' invasion of 10 Downing Street), securing the interest of an important public official (eg, Katie Beckett and President Reagan), and eliciting the involvement of a public figure. Sometimes attention has been drawn less dramatically, but nevertheless effectively, eg, conducting a major study (ANTADIR Study) or convening a major conference (Surgeon General's Workshop).

**Understanding the Issues**

To elicit the interest and involvement of leaders and key officials in home mechanical ventilation, broad-based educational initiatives must be launched. A key physician, ventilator user, or official in a position of power must recognize this need and plan a major lecture, conference, publication, or other information-generating activity. One example is the task force of the American College of Chest Physicians that generated guidelines for home mechanical ventilation. Strategies used to create awareness and to stimulate local and regional activities for learning more about the problem have included project grants, technology assessment studies, special-purpose workshops, and designated task forces.

**Information Networking**

Initial home mechanical ventilation experiences may be isolated events. However, nations that have experienced progress in establishing home mechanical ventilation have had networking mechanisms available for the sharing of experiences, with information disseminated through major studies, publications, and international conferences.

**Organizational Development**

Those nations with exceptional home mechanical ventilation programs have program leaders and managers who understand and practice the principles of successful organization development. These programs realize the highest human potential of each interdisciplinary team member, demonstrate a passion for excellence, and utilize so-called vanguard principles of organization design and management. These successful programs have grown because team members understand and serve the needs of the persons they treat (their 'shareholders'); they are deeply committed to people. Each program has adapted organization development practices in ways that reflect and respond to the culture and traditions of their nation.

**Management of Operations**

The countries with outstanding home mechanical ventilation in place have programs whose leaders and managers understand and apply advanced practices of systems management. From the onset, France has responded to the need for cost-containment. As a result, one can observe creative applications of management information systems and market channel...
management—including ordering, inventory, distribution, accounting, and finance functions.

Political and Social Realities

Because of the complexity of the system that must be put into place, all political constituencies and social structures must be considered. Those nations with advanced approaches benefit from insights because efforts were made to find and develop the right alliances. Programs were designed by leaders and political officials who consequently shared a sense of ownership and made certain that the system meshed with acceptable ways of doing things.

Economic Considerations

All over the world, public policy experts are concerned about the exploding costs of long-term health care. They are searching for less costly alternatives, and home care is of major interest. However, this has happened only recently. The long tradition of hospital-based medical models in the U.S., Europe, and elsewhere has only been questioned since space utilization, prolonged length of stay, and budget contraints have become issues for debate.

Each nation has put into place a program that fits the health care financing and delivery systems unique to that country and the regional or local setting. In some settings, it has been more appropriate to develop the program from a hospital-based unit as an outgrowth of a center of excellence (eg, Responaut Program).28 In other locations, community settings that integrate the centers of expertise and regional funding authorities have been preferred (eg, French associations).25 In the U.S., sources of patients, distribution of equipment and supplies, and mechanisms of health care financing are fragmented and difficult to integrate.27 As a result, the scale economies of a comprehensive systems operation do not exist, resulting in an alarming rise in costs that endangers the future of home mechanical ventilation.

Program Recommendations

The programs that will be put into place around the world will be essentially the same: The elements and evolutionary steps will be variations on a theme.

The mechanisms will be unique to each nation's experience. However, basic to the successful implementation of home mechanical ventilation in any country or region are the following:

• Collective Leadership—Home mechanical ventilation requires the involvement of a broad-based constituency and the representation of committed leaders.

• Political, Economic and Social Sensitivity—The implementation of home mechanical ventilation must be accomplished in stages at designated centers of excellence where the political, economic, and social preferences of each nation, region, and specific locality are considered.

• Cultural Responsiveness—Home mechanical ventilation programs must be designed to reflect the values, beliefs, attitudes, and behavioral norms of each nation, responding to unique cultural traditions.

• System Design and Operation—To accomplish the dual challenges of quality assurance and cost-containment, home mechanical ventilation programs must utilize advanced concepts of organization design and management practice.

Our nation, as well as others, is undergoing a major transformation of its health care system—with the potential for both danger to and progress in home mechanical ventilation. Although home mechanical ventilation is an important concern to some, it is a relatively minor issue in the total health care picture. Those of us wishing to see progress in this area must assume leadership roles and take appropriate steps to make our concern an issue considered by others—or it will not become one. Our efforts must focus upon making home mechanical ventilation part of the larger health care, social, and financial picture. In fact, the complexities of the problems associated with gaining acceptance for and implementing home mechanical ventilation are such that once those problems are resolved, home mechanical ventilation will be able to serve as a model for other important medical and societal challenges facing us today.

II. Home Respiratory Care: New Roles
   for Health Care Professionals

All those concerned about respiratory home health care must confront complex medical, technical,
organizational, social, financial, and ethical issues in the decade ahead.

The Mission

The final product must be defined from the perspectives of all concerned parties: payors, providers, distributors, and users. It should be a comprehensive, coordinated integrated systems-management approach for providing respiratory care and support services to persons who require the prolonged use of mechanical aids for breathing and who choose to live at home or in a home-like environment in the community. The system must meet predetermined needs as articulated by all beneficiaries. It must be based on a social-wellness model, with the inherent flexibility to meet the requirement of each individual case and locality.

Desired Outcomes

The desired outcomes of such a system are:
- family-centered care relying on self-help networks;
- caregiving by family members, neighbors, and friends, supplemented by professional staff and personal attendants;
- home care equipment provided, maintained, and repaired on an emergency and routine basis;
- equipment surveillance, support, and tracking in place;
- direct physician participation and involvement;
- individualized case management to monitor, evaluate, and modify care programs for clinical appropriateness and medical necessity;
- independently managed care to assure program design for safety (reduce liability risk); flexibility to adapt to needs of each user (improve resource utilization); quality services from suppliers, distributors, and providers (quality assurance); operational efficiencies and accountabilities to contain costs within limitations of capitated payments (reduce financial risk); and
- documentation registry for cost-accounting and financial projection; quality control and assurance programs; review of medical, psychosocial, and economic outcomes; program re-evaluation and modification; and education, research, and policy formulation.

Specific Mechanisms

Specific mechanisms designed to produce the desired outcomes are:
1. designated organizations for respiratory home care in defined geographic areas;
2. centers of excellence to serve the base units of expertise for initial evaluation, medical stabilization, preparation for home, major clinical re-evaluation, and education and research;
3. integrated management systems to channel multiple payors, providers, suppliers, and distributors to end-users—providing incentives for participation, quality control, safety, operational efficiencies, and cost-containment; and
4. management information systems that incorporate, process, and provide documentation required by all beneficiaries.

Human Resources

To describe the human resources that will be required, future medical issues must be understood. The number of candidates for home respiratory care will increase—but the increase will be small. Care will have to be provided within a limited (capitated) payment structure. Economic and social pressures will be exerted to select home care for patients and families who may not be suited for such care. Home care candidates may require more complex care because of their condition and age. More medical management decisions and treatment modifications may be done in the home. Home health care providers and clients will have to be aware of what is involved, accept what is required, and be properly prepared. Home respiratory care, which today is an extension of the acute care mindset, will develop a more scientific foundation based on peer-reviewed research. The medical model now used will evolve into a social-wellness model.

The necessary human resources will be suitable home care candidates who meet predetermined criteria for home care (clinically appropriate, exhibiting medical necessity); families who accept and are prepared to provide care; trained professionals including home care physicians and respiratory care practitioners; selected personal attendants; medical-technical experts to provide equipment support (ie,
surveillance, maintenance, and emergency repair; administrative staff with expertise in case-management; managed-care professionals skilled in operations of integrated management systems; finance experts who represent ultimate payors (employers, labor unions, consumers) and who work collaboratively on creative financing; and policy officials (public and private sector) who accept the need for innovation in home care and are willing to participate in its evolution prior to policy formulation.

Material Resources

To describe the material resources required, technical issues must be understood. Devices designed for home use must meet safety standards now being developed by the American Society for Testing and Materials (ASTM).46 Home-care support services for these devices must meet standards also being developed by ASTM47 and those already established by the Joint Committee on Health Care Organizations (JCAHO).48 Home care equipment and practices will also have to conform to guidelines from several consensus activities.34-36 Mechanical aids for breathing and applications will evolve that are more suitable for use in the home. Home care techniques and technologies will be simplified to permit ease of learning and use (eg, transtracheal oxygen and nasal mask ventilation).39-55

The necessary material resources will be:
1. home care equipment and supplies (including noninvasive clinical monitors) designed and manufactured for ease of training, simplicity of cleaning and operation, and robust performance—within limits of capitated payments;
2. support mechanisms (equipment delivery, surveillance, maintenance, repair) to assure safety in the home and flexibility to meet individual case requirements;
3. management information systems to collect clinical, administrative, and technical data for evaluation of equipment performance, outcomes of care, quality of services, and cost experiences;
4. educational programs to provide training and preparation for patients and family members, professionals, personal attendants, and technical-administrative support personnel;
5. flexible financial packages featuring relevant cost accounting from many reimbursement sources; and
6. material management systems (purchasing, inventory control, tracking) to take advantage of cost-economies and cost-efficiencies.

Roles, Responsibilities, and Relationships

For program planning to occur, the following questions must be asked: Who will be involved? What will they be accountable for? How will they work with others? Because of complexity, the need for flexibility, and the unique requirements of each individual case, home care requires a comprehensive written plan. The home care plan must explicitly outline the roles, responsibilities, and relationships of each participant.

Participants in home respiratory care will be:
1. the patient and family member (team members with authority)—assuming clinical care and case-management responsibilities, relying on self-help resources;
2. the home health physician—functioning as a direct care provider and/or managed-care professional, accountable for all medical decisions and implementation;
3. the home health professionals (specialists or generalists) from nursing and allied health professions—functioning as direct-care providers and/or case managers;
4. the home health personal attendant—providing both personal and medical care under direct supervision of a trained practitioner and the client (a cost-saving option extending the caregiver pool);
5. the medical-technical specialist—providing equipment support and surveillance;
6. the community-based support service providers of health care, social service, educational, or vocational services;
7. the managed-care experts for clinical care and integrated management systems—responsible for monitoring and coordinating reimbursement, services, and care—a resource independent but accountable to all other parties;
8. the manufacturers—responsible for the design and production of robust equipment that meets
safety needs and performance requirements in the home;
9. the supplier/distributor—providing equipment, supplies, and support services that are flexible and adaptable to unique case requirements; and
10. the reimbursement authorities—providing partial or total funding options, accountable to the ultimate payor or a managed-care program.

Communication and Linkages

To understand communication among the participants and interparticipant linkage, certain organizational issues must be appreciated. Future home care services will be packaged into management systems that contract with preferred provider organizations. The loose fragmentation of services and funding common today will evolve into integrated systems linking payors and designated providers who will participate in a system that they perceive as beneficial. Mega-organizations will result from acquisitions and mergers established for management efficiencies. In one form or another, a managed-care approach will be used to coordinate the activities of all participants and to assure performance accountability. Managed care will assure that quality of service will not be compromised despite the requirements for cost-containment.

Adequate communication and coordination among essential home care participants will require:
• a tracking system for equipment performance, clinical surveillance, and outcome analysis;
• a management information system for materials management (logistics, operations), cost accounting, financial projections; and
• a managed-care designee for case coordination and communication.

If the ultimate user does not assume a direct managed-care role, he or she must work interactively with the professional who does. The patient and family often have important insights that unfortunately are not always taken into account.

External Environmental Factors

Any systems approach must consider pervasive variables—political, economic, sociodemographic, and cultural factors—in the external environment that have a major impact upon what is or is not possible. These must be understood within the context of social, financial, and ethical issues of the future.

Social Issues

The ultimate user (patient or family member) will be better educated and more aware of health issues, will assume more responsibility (self-help), and will demand a central role for the family (family-centered care).

The family is evolving and will be extended to include others (friends, neighbors). Families will prefer nonprofessional caregivers who are directly accountable to them (client-maintained plan).

It will be necessary to provide the patient and family with more options and resources, adapting to changing and diverse lifestyles and evolving demographic patterns (eg, low birthrate and increased number of elderly citizens). Home respiratory services must support community-based alternatives to the home (eg, group living arrangements with shared services, hospice, respite).

Financial Issues

Capitation (ie, institution of a uniform payment schedule) will become universal and the rate of growth of health care allocations will be reduced. Home respiratory care will represent only a small ‘piece of the pie.’ Programs will have to fight for financial resources and live within pre-established financial constraints.

Financial accountability (cost accounting) and operational efficiencies (management information systems) will permit both quality service and cost containment. Both will be demanded by a marketplace consisting of buyers with increased awareness (employers, labor unions, consumers, health maintenance organizations).

Ethical Issues

Because of limited resources, the home respiratory care option may be denied to potential beneficiaries. So-called warehousing in large institutions may be
preferred by payors because of cost-efficiencies that can be achieved. In addition to economic reasons, home care may also be denied due to age or health status. How will the criteria be determined and by whom? What process will be used to decide which monies will be allocated? Who will decide which patients will go home, and on what basis will the decision be made?

How can the marketplace provide profit incentives to investors and participants? Considering the social nature of the home care services required, by what means can we foster participation and ensure appropriate ethical behavior?

Can the marketplace serve the population requiring home care without regulatory and voluntary initiatives? How will this balance be equitably achieved?

**Political Factors**

Government policy reflects public opinion. Since 1980, private-sector solutions have been preferred to government regulation and intervention—a consensus for less government. Now the pendulum is swinging back.

Public policy reflects administration philosophy. The federal government has favored state initiatives within the constraints of federal oversight (HCFA waiver policy).

The health care industry is more regulated than most. Therefore, natural market tendencies regarding supply, demand, and pricing are constrained.

Health care and social issues have been targeted by the current administration for political attention. However, specific focus is defined by political forces (AIDS, long-term care, catastrophic care). All constituencies must be proactive and vocal to benefit. Special interest groups might do better as part of a larger constituency.

Political leaders change, but governmental infrastructure remains. Proper roles must be defined for public officials and bureaucratic authorities (eg, governance).

**Economic Factors**

Health care costs have risen in absolute and relative terms to a level and rate not acceptable to payors or users. Costs will be fixed (capitated), rates of growth limited, allocations defined, and expenditures monitored.

Aware, proactive buyers of services will be more demanding of what they purchase (quality, cost). Informed buyers and marketplace forces will select survivors.

Physicians will get more involved in home care because there will be an oversupply of physicians. However, it is uncertain who in the future will augment the limited pool of direct caregivers that currently consists of nurses, allied health personnel, and medical-technical experts.

Hospitals have excess capacity; home care will be one strategy to extend resources. There will be fierce competition in the marketplace among providers; only those who operate efficiently will survive.

Medical malpractice insurance (tort liability) costs are currently out of control and are no longer considered a cost of doing business.

**Sociodemographic Factors**

The size and proportion of age groups will change, and each group will have different needs and will demand different health resources.

Societal expectations of health care will change—from curative to caring, sickness to wellness, authoritarian to participative and collaborative.

The family unit will continue to change from nuclear to the single-parent and extended-family unit by choice and opportunity. Therefore, support structures must be adaptable and flexible.

The ethnic balance will change—families at risk will come from many socioeconomic and cultural backgrounds, with differences in educational levels, financial resources, and social support.

For integrated management systems to work, management of cultural factors must take a high priority. Cultural and subcultural differences must be recognized, understood, and taken into account during home care planning. Cultural conflicts will arise because of inherent differences in training, perspective, interest, and preferred approach among national and regional agencies; health-care and management disciplines; and providers, payors, and users of home-care products. Cultural differences have an enormous effect upon medical care and services. Finally, it
must be understood that the culture of home care represents a different set of assumptions, values, beliefs, and expected norms of behavior than that of hospital health care. This culture may not be one in which health care professionals are comfortable.

Trends in Health Care

Home respiratory care will provide opportunity for the respiratory care practitioner. The rationale comes from current hospital, home, and respiratory care trends.

Hospital Care Trends

Because of overcapacity, hospitals will continue to engage in new activities—a natural extension of the hospital is home care that requires respiratory care expertise.

Because of cost-containment concerns, hospitals will scrutinize all cost centers; respiratory care is no longer a profit center.

Hospitals want to eliminate all unnecessary treatments while maintaining quality control. Consequently, demand for hospital-based respiratory therapists will decrease and job responsibilities for respiratory care practitioners will change.

In an attempt to operate more efficiently, other professionals will assume tasks previously performed by respiratory therapists.

Home Care Trends

Increased interest in the home care option will be expressed by payors who are losing money due to prolonged institutionalization.

Financial support will increase because of increased interest in long-term and catastrophic care.

Consumer awareness of home care as a desirable option will increase.

All components of the home care industry will grow, and the growth of the respiratory care segment will depend upon competitive forces in the marketplace and funding policies of public and private sources.

Respiratory Care Trends

The need for respiratory care services in hospitals will decrease except in special units and specialized hospitals; future utilization of respiratory care practitioners and specialists will be justified by economic considerations.

The need for respiratory care services in the home will increase because of the increasing complexity of medical and technical requirements. Growth will be limited by reimbursement for services provided; respiratory care licensure will therefore be a big factor. It must be recognized that respiratory care practitioners play a unique role in the home and that they are cost-effective.

Scenarios of Home Respiratory Care

Present Scenario

Home care has been successful and the benefits of home care have been recognized, but are still not universally accepted or understood.

Past cost savings are being eroded by inefficient operations due to fragmentation of payment and provision of services and uncontrolled pricing in a partially regulated marketplace. Increased financial and tort-liability risk exists.

Those involved are dissatisfied with the way things are going without a system, but concerned about the constraints that a system would impose.

Desired Scenario of the Future

An integrated management system—responsive to the needs of all beneficiaries (payors, providers, and users)—should link all participants. Such a system should be flexible and adaptable and should meet the individual needs of each participant and group and maximize the utilization of all resources. Four goals should be realized: safety in the home, medical necessity or appropriateness, quality service, and cost-containment.

Conclusion

The challenge that confronts us is to assure the desired scenario. The question for us to ponder is, By what process will it be put into place?
During the transition state, I propose that we:
- identify all potential beneficiaries of the system,
- have the future participants define the needs,
- have all beneficiaries involved in the planning process,
- provide mechanisms for continued participation during implementation,
- design a feedback mechanism to evaluate outcomes, and
- build in strategies for adaptation and change.

The desired outcome is a living, dynamic, participative process attending to issues of safety, quality, and cost.

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The Quest for a Red Blood Cell Substitute

David H Ingbar MD

Introduction

For many years the potential utility of artificial substitutes for red blood cells has been appreciated. Over the course of the past 20 years, claims have been advanced about several substances that have been studied. However, some investigators are skeptical of the value of the currently available red blood cell substitutes. This paper will critically review our knowledge of red blood cell substitutes and suggest the possible directions of progress over the next decade.

Function of Red Blood Cells

Red blood cells (RBCs) have four major functions, among a number of lesser ones: loading oxygen (O₂) in the pulmonary capillaries and releasing it in the systemic capillaries; picking up carbon dioxide (CO₂) from the capillaries of peripheral tissues and carrying it to the lungs where it is unloaded for excretion; buffering acid present in blood; and, finally, providing intravascular volume. Researchers have sought the optimal method of expanding intravascular volume—RBCs vs crystalloid or colloid therapy—in a variety of clinical states, including hemorrhagic shock, septic shock, and the adult respiratory distress syndrome (ARDS); however, I will not discuss that further.

Respiratory Failure and Tissue Oxygen Supply

In some forms of respiratory failure, a diminished oxygen supply to the tissues can limit their metabolism. The oxygen delivered to the peripheral tissues can be calculated as the systemic oxygen transport (SOT):

\[
SOT = (C.O.)(C_\text{aO}_2),
\]

where C.O. = cardiac output, and CₐO₂ = arterial oxygen content, and

\[
C_{\text{aO}_2} = (\text{Hgb})(S_{\text{aO}_2}) + (P_{\text{aO}_2})(0.003),
\]

where Hgb = hemoglobin concentration in g/dL (ie, g%), SₐO₂ = oxygen saturation of arterial blood expressed as a decimal fraction, and 0.003 = solubility coefficient of oxygen in serum expressed as mL · dL⁻¹ · torr⁻¹ (volumes %, vol%).

When SOT drops below the so-called ‘critical point,’ tissue oxygen consumption (\(V_{O_2}\)) decreases linearly with any further decrease in oxygen delivery (ie, it becomes supply-limited). In normal human beings undergoing cardiac bypass surgery, the critical point is at an SOT of approximately 8-10 mL O₂ · kg⁻¹ · min⁻¹. Because the normal oxygen supply to the tissues is in the range of 20 mL O₂ · kg⁻¹ · min⁻¹, the reserve is usually twofold or more. However, in many illnesses (including respiratory failure), the critical point at which \(V_{O_2}\) becomes supply-limited occurs at a higher level of SOT. For ARDS and sepsis, the critical point often occurs at 20 mL O₂ ·
kg⁻¹ · min⁻¹. In addition, the tissue \( \dot{V}_O_2 \) itself often is increased in these same illnesses. Supply limitation has been demonstrated in septic shock, ARDS, non-ARDS respiratory failure, pulmonary hypertension, and, less convincingly, COPD.

Many critical care physicians believe that increasing oxygen supply to the peripheral tissues should permit higher tissue \( \dot{V}_O_2 \). In theory, this could provide a better clinical outcome for the patient. For example, it might decrease the likelihood of acute tubular necrosis and renal failure or hepatic dysfunction in patients with multisystem organ failure. To date, this theoretical reason for attempting to increase \( SOT \) in critically ill patients has not been rigorously shown to yield clinical benefit.

I know of little data on the efficacy of RBC transfusion in acute respiratory failure, although increasing the Hgb concentration is usually the simplest and most effective way to increase \( SOT \) in a critically ill patient. A potential benefit of volume expansion with RBCs is that most of the RBCs should remain intravascular. In patients with leaky capillaries—those with ARDS or sepsis—such transfusion can help lessen movement of fluid and protein into the third space.

One of the few studies of the efficacy of RBC transfusion in respiratory failure was done on 15 patients with hematocrits (Hct) < 35% and \( P_{aO_2} < 70 \) torr on inspired oxygen concentrations (F\(_{iO_2}\)) > 0.40 with at least 5-cm-H\(_2\)O positive end-expiratory pressure (PEEP). Patients were given 7 mL/kg of packed RBCs over a 2-hour period; their Hgb values increased from 10.9 to 12.5 g/dL \([109 \text{ to } 125 \text{ g/L}]\), and their Hct values increased from 34 to 40% \([0.34 \text{ to } 0.40]\). Although \( C_{aO_2} \) and mixed-venous oxygen content \( (C_{vO_2}) \) increased, no change occurred in cardiac index (CI), stroke index, pulmonary capillary wedge pressure (PCWP), right-atrial pressure, arterial-venous oxygen difference \( (C_{a-vO_2}) \), or tissue \( \dot{V}_O_2 \). No data were presented on mixed-venous \( P_O_2 \) \((P_{vO_2}) \) or oxygen extraction ratio values. The failure of this study to show the effectiveness of transfusion may be related to the relatively high Hct (34%) prior to transfusion and to the relatively small magnitude of the increase in Hct. In theory, a beneficial response to RBC transfusion would include one of the following: (1) increase in tissue \( \dot{V}_O_2 \), (2) decrease in cardiac work, (3) increased \( P_{vO_2} \), or (4) better clinical outcome.

### Abbreviations Used in this Paper

- ARDS = Adult respiratory distress syndrome
- \( C_{aO_2} \) = Arterial oxygen content
- \( C_{a-vO_2} \) = Arterial-venous oxygen difference
- CI = Cardiac index
- C.O. = Cardiac output
- \( C_{vO_2} \) = Mixed-venous oxygen content
- \( D_O_2 \) = Delivered oxygen
- FDA-20 = Fluosol DA-20
- \( F_{iO_2} \) = Fractional inspired oxygen concentration
- Hct = Hematocrit
- Hgb = Hemoglobin
- IHP = Inositol hexaphosphate
- \( P_{aO_2} \) = Arterial oxygen tension
- \( P_{CO_2} \) = Partial pressure of carbon dioxide
- PCWP = Pulmonary capillary wedge pressure
- PFC = Perfluorocarbon
- \( P_{50} \) = \( P_{aO_2} \) at which hemoglobin is 50% saturated with \( O_2 \)
- PFOB = Perfluorocetylbrimide
- \( P_O_2 \) = Partial pressure of oxygen
- P-SFH = Pyrioxylated SFH
- \( P_{vO_2} \) = Mixed-venous oxygen tension
- RBCs = Red blood cells
- \( S_O_2 \) = Per cent oxygen saturation of arterial blood
- SFH = Stromas-free hemoglobin
- SOT = Systemic oxygen transport
- \( S_{vO_2} \) = Mixed-venous oxygen saturation
- 2,3-DPG = 2,3-diphosphoglycerate
- Vol% = Volumes per cent
- \( \dot{V}_O_2 \) = Oxygen consumption

To my knowledge, the optimal Hct for patients in respiratory failure has not been defined. Most critically ill patients in intensive care units are maintained with Hct values near 30% by support with transfusions, a practice based largely on data for optimal coronary artery blood flow following cardiac bypass grafting. However, this practice may not translate to other conditions such as respiratory failure. Another neglected question in the population of critically ill patients is What is the optimal \( P_{50} \) of their hemoglobin (ie, at what oxygen tension should hemoglobin be 50% saturated)? Because the oxygenhemoglobin dissociation curve is not directly assessed in most critically ill patients, the \( P_{50} \) of the patient's red blood cells is not usually known. We do know that the \( P_{50} \) is shifted by changes in temperature, \( \text{pH} \), \( P_{aCO_2} \), and 2,3-diphosphoglycerate (2,3-DPG). For optimal oxygen loading, transport, and unloading of RBCs, the \( P_{50} \) should lie midway between the \( P_{aO_2} \) and the \( P_O_2 \) of blood leaving the
systemic vascular bed. (The conventionally acceptable $S_vO_2$ of 75% represents the summed average of the tensions of blood leaving capillary beds from different organs.) In addition, there should be a steep slope of the curve on both sides of the $P_{SO_2}$ so that the hemoglobin is fully loaded at $P_{aO_2}$ and fully unladen as it leaves the systemic capillary beds. Thus, for an individual patient, the optimal $P_{SO_2}$ is a function of the arterial and tissue capillary $P_{O_2}$.4

Blood Substitutes

Blood Substitutes—Why Consider Them?
Although RBC transfusion can be beneficial, Table 1 lists reasons for avoiding transfusion or not using

<table>
<thead>
<tr>
<th>Table 1. Reasons To Avoid Red Blood Cell Transfusion</th>
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<tbody>
<tr>
<td>Patient refuses (eg, Jehovah's Witnesses)</td>
</tr>
<tr>
<td>No crossmatched blood available</td>
</tr>
<tr>
<td>Blood difficult to crossmatch (eg, immune hemolytic anemia)</td>
</tr>
<tr>
<td>Cost and scarcity of blood</td>
</tr>
<tr>
<td>Possibility of complications</td>
</tr>
<tr>
<td>Transfusion reactions</td>
</tr>
<tr>
<td>Transmission of infectious diseases</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome (AIDS)</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>Babesiosis</td>
</tr>
<tr>
<td>Decreased hemoglobin-oxygen affinity</td>
</tr>
<tr>
<td>Volume overload</td>
</tr>
</tbody>
</table>

transfusion in a particular patient and provides support for considering blood substitutes. Many studies of blood substitutes have been done in patients—typically Jehovah’s Witnesses—who refused transfusion.

Uses and Types. Artificial blood substitutes have uses beyond treatment of anemia or blood loss, most of which are experimental. Blood substitutes have been used to preserve organs—including kidneys, hearts, and livers—for transplantation. They have also been used to treat organ ischemia based on their potential to better penetrate into the microvasculature than do the larger RBCs. They have been tested in myocardial ischemia and cerebrovascular disease and have potential for use in sickle cell anemia. Clinical trials of blood substitutes as sensitizers for chemo- or radiation therapy are currently under way. In theory they might increase oxygen delivery to local regions of anaerobic infection. Blood substitutes also could be used to deliver hormones, drugs, or enzymes. Testing of the currently available blood substitutes is still in its infancy, and most of these potential uses have not been explored in detail yet.

The desired qualities of a blood substitute are:

- Effectively takes up $O_2$ at normal $P_{aO_2}$ and $CO_2$ at normal systemic capillary $P_{aCO_2}$
- Releases $O_2$ at normal capillary $P_{O_2}$ and $CO_2$ at normal $P_{aO_2}$
- Contains or binds large volumes of $O_2$ and $CO_2$
- Supports circulatory dynamics
- Buffers tissue acidosis
- Is nontoxic
- Is stable over a range of temperatures
- Survives for a reasonable half-life, without auto-oxidation
- Does not need to be cross-matched

Not surprisingly, no current blood substitute meets all these criteria. As each of the current substitutes is reviewed, their function can be compared against this standard.

The blood substitutes being evaluated clinically and experimentally are listed in Table 2. Perfluorocarbons (PFCs) have received the most extensive testing. For the last 10 years, Hgb solutions have been gradually modified in the search for an optimal product. A newcomer among these blood substitutes is the

<table>
<thead>
<tr>
<th>Table 2. Types of Blood Substitutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorocarbons</td>
</tr>
<tr>
<td>FC43—Perfluorotributylamine</td>
</tr>
<tr>
<td>Fluosol DA-20%</td>
</tr>
<tr>
<td>Perfluorocetyl bromide</td>
</tr>
<tr>
<td>Hemoglobin solutions</td>
</tr>
<tr>
<td>Native stroma-free hemoglobin</td>
</tr>
<tr>
<td>Modified hemoglobins</td>
</tr>
<tr>
<td>Pyridoxylated</td>
</tr>
<tr>
<td>Polymerized pyridoxylated</td>
</tr>
<tr>
<td>Microencapsulated hemoglobin</td>
</tr>
<tr>
<td>Resealed RBCs</td>
</tr>
<tr>
<td>Liposomes (neohemocytes)</td>
</tr>
</tbody>
</table>
liposome, or resealed red blood cell enclosing hemoglobin.

Perfluorocarbons

Early Studies

Perfluorocarbons attracted attention as an oxygen carrier when Clark and Gollan published studies on the survival of mice immersed in preoxygenated PFCs for hours—a first demonstration of liquid ventilation. This work was carried further by Geyer and colleagues who demonstrated in 1968 that virtually bloodless rats could survive for 8 hours after complete exchange transfusion with the PFC FC43. Subsequently, Geyer’s group showed that these rats could survive, eat, drink, and grow after complete exchange transfusion, for as long as 7 days. In 1978, the first human volunteers received PFCs intravenously. Formal testing of PFCs began in Japan in 1979 on patients with brain death. After 10 normal Japanese volunteers safely received 20-500 mL of PFCs, clinical trials were begun in Japan for patients with hemorrhagic shock and a variety of other conditions. U.S. clinical trials were begun at the same time, but were restricted to Jehovah’s Witnesses with severe anemia who refused transfusion therapy.

Properties of Perfluorocarbons

PFCs have a high intrinsic solubility for oxygen, presumably related to the adjacent fluorine atoms. Most PFCs are fluorinated 8-10 carbon hydrocarbon chains. They are immiscible in water and hence must be dispersed for emulsification prior to use; otherwise they will occlude capillaries and decrease tissue oxygenation. This dispersion and emulsification limits the concentration of PFC that can be used in the bloodstream. PFCs are chemically inert and more than twice as dense as water. Because of their low vapor pressure, they are not rapidly excreted during passage through the lungs. O2 and CO2 are 20 times more soluble in PFCs than in water. When emulsified, PFCs form very small droplets of 0.1-0.2 μm diameter, approximately 1/50th the diameter of a RBC. Consequently, they have a very high surface area and a very low viscosity, even at low shear rates.

The amount of oxygen dissolved in PFCs—like the amount dissolved in plasma—is directly proportional to the P02. A solution of pure perfluorocarbon carries 20 times the oxygen content of plasma. However, because the PFC must be dispersed, the dissolved oxygen content is limited by the PFC % (the so-called fluorocrit), which can be measured in a manner similar to that used to determine hematocrit:

PFC O2 content = (fluorocrit)(PaO2)(0.00574),

where 0.00574 is the solubility coefficient for O2 in PFC.

Two problems combine to limit the utility of PFCs in vivo. The first problem is the maximum achievable fluorocrit. The second problem is achieving a very high PaO2 in order to dissolve as much oxygen as possible in the PFCs. With a 100% PFC solution at P02 of 760 torr and 37 °C, the oxygen content will be approximately 45 vol%. At a more realistically achievable P02 of 400 torr, the same solution would have an oxygen content of 24 vol%. For a fluorocrit of 42% and 400 torr oxygen, the total O2 content would be 10.6 vol% oxygen. In contrast, blood with a hematocrit of 42% at 400 torr PaO2 carries 20 vol% oxygen. This illustrates the impact of the achievable fluorocrit and PaO2 on the true ability of current PFCs to carry oxygen. A fluorocrit percentage point is half as effective as a hematocrit percentage point for carrying oxygen. A 1% fluorocrit represents 13 mg of PFC per mL. A 3-4% fluorocrit at 500 torr PO2 is roughly equivalent to 0.5 g/dL of hemoglobin. Typically, a 20 mL/kg infusion of Fluosol DA-20 (FDA-20) leads to a fluorocrit of only 3-4%.

Perfluorocarbons are removed by excretion through the lungs and some clearance by the reticuloendothelial system. In human beings, the intravascular half-life varies between 6 and 24 hours. The clearance rate is dose-dependent, with clearance slower following larger doses. Although most of the PFCs are excreted through the lungs, small amounts are excreted in urine and stool. Autopsy studies of Japanese patients indicate that residual PFCs can be measured in the liver for months after a single dose. Presumably, the Kupffer cells of the liver and macrophages in other parts of the body take up PFCs and then clear them very slowly. The PFCs may alter the hepatic cytochrome-P450 system and affect drug metabolism.

FDA-20 (Green Cross, Osaka, Japan, and Alpha Therapeutic Corp, Los Angeles CA) is the most commonly used PFC worldwide and the only one
Table 3. Concentration and Function of the Components in Fluosol DA-20%

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration (g/100 mL)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorodecalin</td>
<td>14.0</td>
<td>Oxygen carrier</td>
</tr>
<tr>
<td>Perfluorotripropylamine</td>
<td>6.0</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Pluronic F-68</td>
<td>2.7</td>
<td>Non-Ionic surfactant</td>
</tr>
<tr>
<td>Yolk phospholipids</td>
<td>0.4</td>
<td>Emulsifier</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.8</td>
<td>Preservative</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>3.0</td>
<td>Oncotic agent</td>
</tr>
<tr>
<td>Salts (NaCl, KCl, MgCl₂, Ca⁺⁺, HCO₃⁻)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

used clinically in the United States. Its components are shown in Table 3. The primary oxygen carrier is perfluorodecalin with some assistance from the stabilizer perfluorotripropylamine. The two agents involved in emulsifying the PFC are yolk phospholipids and the nonionic surfactant Pluronic F-68 (PF68). PF68 has been implicated in causing many of the reactions to FDA-20 that occur in some patients. Glycerol functions as a preservative while the hydroxyethyl starch increases the oncotic pressure of the FDA-20. FDA-20 is usually stored frozen and has a pH of 7.44.

**FDA-20 for Treatment of Anemia**

Results have been published on the use of FDA-20 for treatment of anemia in five different patient series (Table 4). In Mitsuno and Ohyanagi's series of 401 patients, 220 were given FDA-20 for acute blood loss. The series included patients with other indications for FDA-20 treatment, and the surgeon's desire to perform bloodless surgery was also a factor in patient selection. Given the heterogeneity of the patients treated and the lack of systematic data collection, I find it difficult to interpret the results. Oxygen delivery did increase, but no change in \( P_{V\text{O}_2} \) was observed. It is not clear whether consistent changes in C.O. or tissue \( V_{\text{O}_2} \) occurred.

The remainder of the reports have had very small numbers of patients and have been restricted to patients with severe anemia. The maximum dose of FDA-20 administered was 20 mL/kg and, as can be seen from Table 4, response was not uniform in each of the small number of patients that were carefully studied. Examining the most positive and most negative trials in detail is useful for understanding the potential benefits and problems of FDA-20.

None of the studies done in the United States or Canada were designed to test whether survival was improved by FDA-20 transfusion for severe anemia. In Tremper et al's study, the FDA-20 infusion led to increased mean values—PCWP from 5 to 14 torr; \( \dot{V}_{\text{O}_2} \) from 92 to 112 mL \( \text{O}_2 \cdot \text{min}^{-1} \cdot \text{m}^{-2} \), \( P_{\text{aO}_2} \) from 291 to 361 torr, \( C_{\text{aO}_2} \) from 7.1 to 8.6 vol%; and \( P_{\text{V}_2} \) from 44 to 70 torr. These results were obtained with a fluorocril of 2.9%, \( F_{\text{IO}_2} \) of 0.84, and a mean Hgb concentration of 5.4 g/dL. FDA-20 infusion also was accompanied by a fall in the CI from 5.3 to 4.6 L \cdot \text{min}^{-1} \cdot \text{m}^{-2} \. Tremper et al believe that FDA-20 is efficacious, but that its overall safety in large numbers of patients has not yet been proven. They are trying to separate the effects of volume expansion from those of the FDA-20 and oxygen.

Table 4. Clinical Trials of Fluosol DA-20% in Severe Anemia

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Patients No. &amp; Type</th>
<th>Dose mL/kg</th>
<th>Cardiac Output</th>
<th>( D_{\text{O}_2} )</th>
<th>( \dot{V}_{\text{O}_2} )</th>
<th>( P_{\text{V}_2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsuno</td>
<td>1985</td>
<td>220 Mixed</td>
<td>≥ 20</td>
<td>Increased</td>
<td>Increased</td>
<td>? Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Tremper</td>
<td>1982</td>
<td>7 Anemia</td>
<td>20</td>
<td>Stable</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Wassman</td>
<td>1984</td>
<td>6 Anemia (Hgb &lt; 7)</td>
<td>20</td>
<td>Stable</td>
<td>Increased</td>
<td>Increased</td>
<td>?</td>
</tr>
<tr>
<td>Stefaniozyn</td>
<td>1985</td>
<td>3 Anemia Prior to surgery</td>
<td>10-20</td>
<td>Varied</td>
<td>Increased</td>
<td>Varied</td>
<td>Increased</td>
</tr>
<tr>
<td>Gould</td>
<td>1986</td>
<td>8 Anemia</td>
<td>20</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Increased</td>
</tr>
</tbody>
</table>

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per se by studying anemic patients given FDA-20 after normalization of PCWP. These results have not been published yet.

Gould and colleagues evaluated 23 adults with anemia due to acute blood loss from surgically correctable lesions (Jehovah’s Witnesses who refused transfusion). To receive FDA-20, patients were required to have Hgb concentrations of <3.5 g/dL or oxygen extraction ratios above 50% on FiO2 of >0.60. Of the 23 patients evaluated, 8 received FDA-20: 5 had low Hgb levels, 2 had elevated oxygen extraction ratios, and 1 had both. The patients had a mean maximal fluorocrit of 5% and mean PaO2 of 430 torr on FiO2 of 1.00. CaO2 increased 17% with the fluorocarbon, accounting for 15% of the CaO2 and 28% of oxygen consumed. Both the plasma and FDA-20 unloaded more than 80% of their oxygen, in contrast to relatively inefficient unloading of oxygen from RBCs (19%). Utilization of oxygen dissolved in plasma accounted for 50% of the oxygen consumed, whereas the FDA-20 and RBC oxygen accounted for approximately 25% each. The physiologic effects of FDA-20 infusion included mean changes—decreased heart rate from 117 to 108 bpm, increased PaO2 from 356 to 430 torr, and increased P(O2) from 40 to 78 torr. However, FDA-20 had no effect on DO2, VO2, extraction ratio, CaO2, or Cl. The lack of an increase in CaO2 probably reflects the hemodilution of the remaining RBCs balanced by the increased oxygen carried in the FDA-20. The mean half-life of FDA-20 was 24 hours with a range of 12 to 37 hours. Six of the 8 patients died. The authors of this study concluded that FDA-20 loads oxygen poorly, but is a very effective unloader. Without continued doses, FDA-20 did not survive long enough for bone marrow erythropoiesis to produce RBCs. The authors summarized their experience, saying, “In acute blood loss, Fluosol-DA is unnecessary when anemia is moderate and ineffective when it is severe. When RBCs cannot be used, Fluosol-DA 20% appears to be an inadequate RBC substitute.”

In summary, considerable controversy exists about the clinical utility of FDA-20 for treatment of anemia. Its predominant use has been in patients who absolutely refuse transfusion and have severe anemia—patients with a very high underlying mortality. The clinical utility of FDA-20 is limited by (1) the need for very high FiO2 (approximately equal to 1.0), (2) the need for repeated doses or continuous infusion, (3) the low fluorocrits that can be obtained, and (4) its volume expanding and hemodiluting effect. If continuous infusion were possible or if repeated doses were proven to be safe, then the utility of FDA-20 for treating anemia probably would be significantly higher. However, after more than 3 days of use, the potential for oxygen toxicity in the lungs becomes important.

**FDA-20—Other Uses**

FDA-20 can be used in many ways. It may be beneficial for oxygenating regions of abnormal microvasculature. Because the droplets are 1/50th the size of an RBC, they can pass partially obstructed regions in small vessels and achieve distal oxygenation. Experimental studies of dogs with occlusion of their left anterior descending coronary artery have demonstrated reductions in myocardial infarct size. In human beings undergoing percutaneous transluminal coronary angioplasty, FDA-20 infusion can prevent the drop in left ventricular ejection fraction that occurs during balloon inflation. No human trials of systemic or coronary artery infusion of FDA-20 during myocardial ischemia or infarction have been published.

FDA-20 infusion may have benefits for cerebrovascular ischemia. In monkeys with ligation of their middle cerebral artery, FDA-20 decreases the histologic extent and severity of ischemic damage. One study demonstrated a 10% increase in cerebral blood flow after FDA-20 infusion in patients with strokes. However, results in larger clinical studies of human subjects with evolving strokes reportedly have been less promising, although these studies have not been published. Finally, it has been proposed on the basis of in-vitro studies that FDA-20 may be useful in treating sickle cell crisis. It can help reoxygenate sickled red blood cells and could have access to areas distal to regions of sickling that are inaccessible to normal RBCs.

Theoretical reasons why PFCs could be helpful in ischemic microcirculation include: (1) low viscosity of the fluid allows a higher flowrate at the same blood pressure, (2) the hemodilution that is created leads to increases in collateral blood flow as well, (3) the smaller size of PFC particles allows them to bypass obstructions in abnormal microcirculation.
(such as endothelial 'blubs' or sludged RBCs), (4) they may actually reoxygenate RBCs that have been sludged and thereby decrease the stiffness of the RBC membrane, (5) the small size and flow characteristics also may permit better distribution of tissue blood flow, and (6) as I will discuss, they can inhibit a variety of neutrophil functions including phagocytosis, chemotaxis, and production of oxidants. This may decrease damage to an already injured microcirculation.

Experimental and clinical studies have suggested that FDA-20 may be a beneficial preservative for organs to be transplanted. For example, use of FDA-20 to preserve hearts for transplantation can prevent weight gain and diminish the production of the cardiac isozyme of creatinine phosphokinase (CPK-MB), lactic acid, and the oxidant malondialdehyde. The CI of such a heart is also better preserved. Similar benefit has been suggested for livers and kidneys that are to be transplanted.

For cancer therapy, PFCs have been used experimentally and clinically as radiation and chemotherapy sensitzers. The rationale for their use in radiation therapy is that hypoxia protects cells against the cytotoxic effect of radiation. PFCs can increase the oxygen content of tumor cells but not of normal cells. In experimental studies, the combination of PFCs and high FIO2 with radiation therapy has increased the responsiveness of solid tumors. Trials are under way (1989-90) using FDA-20 and hyperbaric oxygen (3 atmospheres pressure) for central nervous system gliomas, head and neck carcinomas, and lung cancer. No major increase in toxicity from the radiation therapy has been reported except for slightly enhanced skin response to the radiation therapy. No definitive outcome data are available from these trials, but early results have suggested more rapid clearance of squamous cell carcinoma of the head and neck.

PFCs also can sensitize tumor cells to alkylating agents and various other chemotherapeutic compounds, with a consequent delay in tumor growth in animal models. For example, the combination of the antineoplastic agent carmustine (BCNU), 95% oxygen, and FDA-20 doubles the survival time of rats with tumor cells implanted into their brains. If any of the three elements are missing, the increase in survival is less significant. The use of the combination may have some cost in terms of increased complications, however. Bleomycin combined with FDA-20 and hyperoxia diminish the growth of fibrous sarcomas implanted into mice. However, lung inflammation is markedly increased, with increased cellularity seen on histologic examination and a fivefold increase in bronchoalveolar lavage cells in comparison to exposure to bleomycin and hyperoxia without FDA-20. Most of the increase in cell numbers is in neutrophils. This suggests there is potential for long-term lung damage from this combination of therapies.

Perfluorocarbons—Complications of Administration

The complications of PFC administration are shown in Table 5. In addition to increasing the circulating blood volume and diluting the hematocrit, PFC administration may cause a transient drop in circulating platelet and neutrophil counts. Complement activation has been attributed to Pluronic F-68, and PF68 also may be responsible for the cytotoxicity of artificial blood substitutes for cells in culture. A number of patients have been described with chest pressure and shortness of breath shortly

<table>
<thead>
<tr>
<th>Table 5. Complications Resulting from the Administration of Perfluorocarbons</th>
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</thead>
<tbody>
<tr>
<td><strong>Early/Immediate</strong></td>
</tr>
<tr>
<td>Transient decrease in platelet and neutrophil counts</td>
</tr>
<tr>
<td>Complement activation</td>
</tr>
<tr>
<td>Prolongation of bleeding time</td>
</tr>
<tr>
<td>Increased circulating blood volume</td>
</tr>
<tr>
<td>Fall in hematocrit</td>
</tr>
<tr>
<td>Chest pressure and shortness of breath</td>
</tr>
<tr>
<td>Hypotension, decreased systemic vascular resistance, normal C.O.</td>
</tr>
<tr>
<td>Bradycardia, decreased C.O., increased systemic vascular resistance, normal blood pressure</td>
</tr>
<tr>
<td><strong>Subacute/Late</strong></td>
</tr>
<tr>
<td>Fever, bilateral pulmonary infiltrates, fall in PaO2</td>
</tr>
<tr>
<td>Decreased platelet aggregation</td>
</tr>
<tr>
<td>Oxygen toxicity</td>
</tr>
<tr>
<td>Increased LFT* (SGOT &amp; SGPT)</td>
</tr>
<tr>
<td>Possible increased levels of antidiuretic hormone</td>
</tr>
<tr>
<td>Decreased host immune defenses</td>
</tr>
<tr>
<td>Possible increased infections</td>
</tr>
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</table>

*LFT = liver function transaminases.
after receiving infusion of PFCs—perhaps related to complement activation and neutrophil adhesion to the pulmonary capillary endothelium. For reasons that are unclear, the bleeding time often is prolonged after treatment with FDA-20. Finally, there are two patterns of immediate hemodynamic response. In the first, hypotension is accompanied by a normal cardiac output and decreased systemic vascular resistance. Two other patients have been reported who had a normotensive bradycardia with a fall in cardiac output balanced by an increase in systemic vascular resistance. These patients complained of mild vague chest and abdominal pressure within minutes of receiving a test dose of FDA-20. At present, the frequency of these immediate complications of PFC administration is not well established because of the small number of patients treated. Administration of steroids prior to FDA-20 infusion partially prevents both the drop in the number of circulating granulocytes and the fall in \( P_{aO_2} \).

Three patients with pulmonary reactions occurring several days after FDA-20 administration have been reported. Each patient had a diffusely abnormal chest x-ray, fever, an elevated white blood cell count, and worsening oxygenation. The mechanism of pulmonary complications could be related to: (1) ARDS due to the patient's underlying illness; (2) oxygen toxicity; (3) direct toxic effect of the PFC related to activation of complement, to initiation of intravascular coagulation by activation of plasminogen, or to damage to lung endothelial cells or microemboli of the fluorocarbon; (4) increased susceptibility to infection; or (5) volume overload. In some patients increased levels of liver transaminases (SGOT and SGPT) have been observed after PFC treatment. Increased levels of antidiuretic hormone also have been reported. A decrease in platelet aggregation may predispose to increased bleeding. Finally, it has been suggested that host immune defenses are diminished by FDA-20. Mice injected interperitoneally with \( Escherichia coli \) had increased mortality if they received either FDA-20 or Pluronic F-68 prior to the bacteria. The mechanism proposed for the decreased host resistance is related to decreased neutrophil migration and adherence. In addition, after PFC exposure neutrophils mount a delayed and diminished burst of oxygen radical production, and phagocytosis also may be diminished. In-vitro PFCs selectively kill macrophages and also diminish their stimulated oxidative burst. After phagocytosis of PFCs, the reticuloendothelial system may be blocked in a fashion similar to that seen after silica exposure. These interferences with the inflammatory cells that perform a primary role in host defenses may translate into an increased risk of infection. However, the clinical studies of FDA-20 in human beings have not directly addressed this issue and have not yet reported an increase in clinical infections.

**Perfluorochemicals—New Agents and Exotic Uses**

Several unusual uses have been suggested for PFCs. Because many PFCs are radio-opaque, they have been used as contrast agents for bronchography or computed tomography scans. For example, the new PFC perfluorocetyl bromide (PFOB) has been used in Europe as a contrast agent for bronchograms, blood pool studies, liver and spleen scans, and localization of inflammatory lesions. Like FDA-20, PFOB is taken up by macrophages and excreted by the lungs. However, it has a longer intravascular half-life of 14-43 hours. It can be prepared as a denser emulsion than FDA-20 and does not contain Pluronic F-68. However, little has been published about the oxygen-carrying properties of this agent. Other exotic uses of PFCs include their use with liquid membrane oxygenators or for cardioplegia and/or cardiopulmonary bypass. Although the technique is impractical, intraperitoneal injection of oxygenated PFCs can provide an extrapulmonary route of oxygen delivery. Finally, harkening back to Clark and Gollan's experiments in 1966, liquid ventilation with oxygenated PFCs for premature neonates with severe respiratory failure is being tested experimentally.

**Perfluorochemicals—Conclusions**

At present, oxygen transport by PFCs is limited by important physiologic factors: (1) requirement for a very high \( P_{aO_2} \); (2) the inability to achieve fluorocrits above 10%; (3) the short intravascular half-life; and (4) the relatively low oxygen-carrying capacity compared to RBCs. Although current agents may not be of great benefit for treatment of severe anemia, they may prove of greater benefit for acute use to supply oxygen to diseased microvascular beds. More studies are needed, but it is exciting to think that they may be useful in myocardial ischemia or sickle
cell crisis. Current clinical studies should help define their utility as sensitizers for radiation and chemotherapy of tumors. The microvascular and tumor therapy uses of these agents may avoid some of the oxygen toxicity caused by prolonged use of high inspired oxygen fractions. However, it is possible that PFCs augment toxicity and damage—such as in patients with ARDS or those undergoing chemotherapy. New PFCs are being tested to see if they can overcome the problems observed with FDA-20—PFOB, for example, has some potential advantages. Many other PFC compounds are probably being tested in the industrial sector. The lack of published information about other new PFCs may reflect proprietary concerns of the companies studying them.

Hemoglobin Solutions
Advantages and Characteristics

The infusion of stroma-free hemoglobin (SFH) has several advantages over the use of PFCs. First, the need for very high fractions of inspired oxygen is eliminated. Second, the viscosity of SFH is very low. Finally, SFH is easily shipped, stored, and handled. By eliminating the stromal component of RBCs, much of the toxicity caused by intravascular RBC lysis is avoided.

The use of hemoglobin solutions has a longer history than might be suspected. In 1934, Mulder et al replaced RBCs of dogs and cats with a hemoglobin solution with no measurable change of oxygen consumption. They argued that the animals were physiologically intact, because the cats retained their righting reflex. In 1976, Gould et al treated nine baboons with complete exchange transfusion using SFH. The baboons maintained their normal \( V_{\text{O}_2} \) but had markedly lower \( P_{5\text{O}_2} \) levels of approximately 20 torr. Although the affinity of hemoglobin for oxygen was markedly increased (reduced \( P_{50} \)), the major mechanism of the baboons' adaptation was to increase oxygen extraction, instead of increasing cardiac output. The cause of the increased hemoglobin-oxygen affinity was the loss of 2,3-DPG.

In order to normalize the \( P_{50} \) of the hemoglobin solution, the hemoglobin was pyridoxylated. As expected, baboons transfused with pyridoxylated SFH (P-SFH) had higher whole blood \( P_{50} \) levels and somewhat higher \( P_{5\text{O}_2} \) levels. Further analysis indicated that the cause of the higher \( P_{5\text{O}_2} \) was the use of relatively anemic hemoglobin solutions (7 g/dL). However, achieving a hemoglobin level of 15 g/dL, would increase onotic pressure above 60 torr, or more than three times normal.

In response to this problem, methods of polymerizing hemoglobin have been explored, with Hgb typically first being pyridoxylated and then polymerized with glutaraldehyde. Because the polymerization is not uniform, the molecular weights of polymerized pyridoxylated SFH range from 64,000 to above 600,000 kilodaltons. This solution has a normal oxygen-binding coefficient as well as normal hemoglobin concentration and osmotic pressure.

Efficacy studies have been carried out with exchange transfusions of polymerized P-SFH in both rats and baboons. In contrast to the short half-life of tetrameric SFH (2-4 hours), the half-life of polymerized P-SFH was markedly prolonged at 38 hours. The \( P_{50} \) for oxygen binding is 18-22 torr, comparable with that of banked blood. There is some loss of cooperativity between the hemoglobin chains, presumably due to the crosslinking of the four Hgb subunits. The polymerized Hgb solution can be stored in the cold (4-8°C) for several months with methemoglobin concentrations remaining below 5% and no increase in viscosity.

Recently a new crosslinked hemoglobin has been reported that prevents dissociation of the Hgb tetramer. The crosslinking agent used, bis-pyridoxyl tetraphosphate, creates a covalent linkage between the 2,3-DPG binding sites on each of the beta subunits. Consequently, it prevents dissociation of the tetramer to alpha-beta dimers. This prolongs intravascular half-life and reduces oxygen affinity (\( P_{50} \) 31 torr). This compound (bis-PL)P4 Hgb is now undergoing testing in rats and other animals.

The major advantage of hemoglobin solutions is their much greater oxygen-carrying capacity compared to that of PFCs at normal \( P_{\text{aO}_2} \) levels. Gould et al directly compared the use of FDA-20 with pyridoxylated SFH in 10 ventilated baboons who underwent exchange transfusions to hematocrits of 2%. All animals survived with either a final SFH concentration of 4.7 g% or a final fluorocrit of 12.9%. The P-SFH contributed more to oxygen delivery to the tissues than did FDA-20. It also contributed more of the consumed oxygen at very low hematocrit values than did FDA-20 (87% vs 61%). However, with both
QUEST FOR RBC SUBSTITUTE

solutions $V_{O_2}$, was maintained relatively constant. The baboons transfused with FDA-20 received $F_{O_2}$ of 1.0, whereas the animals receiving P-SFH were breathing room air. One can presume that polymerized P-SFH would have performed even better. The properties of the different forms of stroma-free hemoglobin are contrasted in Table 6. The major

Table 6. Properties of Stroma-Free Hemoglobins (SFH)

<table>
<thead>
<tr>
<th>Property</th>
<th>SFH</th>
<th>PyridoxalSFH</th>
<th>Polymer P-SFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin concentration (g/dL)</td>
<td>6-8</td>
<td>6-8</td>
<td>14-15</td>
</tr>
<tr>
<td>Methemoglobin (%)</td>
<td>?</td>
<td>3-5</td>
<td>5-8</td>
</tr>
<tr>
<td>$O_2$-carrying capacity (mL $O_2$/g Hgb)</td>
<td>1.32</td>
<td>1.32</td>
<td>1.30</td>
</tr>
<tr>
<td>Colloid osmotic pressure (torr)</td>
<td>20-25</td>
<td>20-25</td>
<td>20-22</td>
</tr>
<tr>
<td>$P_50$ (torr)</td>
<td>12-14</td>
<td>18-24</td>
<td>14-16</td>
</tr>
<tr>
<td>Intravascular half-life (hours)</td>
<td>2-4</td>
<td>2-4</td>
<td>38</td>
</tr>
</tbody>
</table>

advantages of polymerized P-SFH are its prolonged intravascular half-life and the higher concentrations that can be achieved. Toxicity studies have not yet been published.

Complications from the Use of Hemoglobin Solutions

Although Hgb solutions offer many exciting possibilities, they also carry a number of potential problems. One of the major concerns has been the potential for nephrotoxicity. Most of the nephrotoxicity resulting from intravascular hemolysis probably is due to RBC stromata rather than the Hgb because the stromata are toxic for renal tubular epithelial cells. However, a clinical safety trial of SFH in normal human volunteers in 1977 showed an early transient decrease in both urine volume and creatinine clearance.\(^{48}\) It is not clear whether this may have been related to (1) the SFH itself, (2) to some stromal contamination with phospholipid, or (3) the presence of a vasoactive substance in the hemoglobin solution. Given this concern and the current lack of human safety data, the use of polymerized hemoglobins or encapsulated hemoglobins is appealing because neither of these substances should be filtered at the glomerulus, nor should they contact the renal tubular epithelium.

Other problems with SFH solution infusion include the frequent occurrence of transient bradycardia and mild hypertension. Hemoglobin solutions may be immunogenic because fevers, chills, and shortness of breath have occasionally been observed. Finally, some immunosuppression may occur following infusion.

Conclusions

In summary, hemoglobin solutions appear to show greater promise than FDA-20 for treatment of severe anemia in situations where RBC transfusion cannot be used. However, the intravascular half-life of SFH solutions still is short in comparison with that of RBCs. In states of capillary leak, the Hgb, like albumin, may move into the extravascular space. This loss of intravascular protein would be decreased by the use of polymerized P-SFH. At present, little information on either efficacy or toxicity of polymerized P-SFH solution in humans is available. One hopes that this information will become available over the next several years. One exciting potential of the substances is their capacity for easy transportation, storage, and reconstitution.

Encapsulated Hemoglobins

Encapsulated hemoglobins have been explored much less than have the other two groups of blood substitutes. For a number of years, there has been an interest in salvaging red blood cells after they have become outdated. One approach has been to rejuvenate the cells in a solution containing pyruvate, glucose, phosphate, adenine, and inosine and to preserve the cells by freezing them in glycerol. These freeze-preserved RBCs have been infused into elderly anemic recipients with cardiopulmonary insufficiency.\(^{49}\) The infusions were well tolerated with no untoward effects observed in 15 transfusions of more than 4 units each of RBCs. More than three quarters of the cells still were present in the circulation 24 hours after infusion. The RBCs had increased 2,3-DPG levels and decreased affinity for oxygen, but no data on oxygen delivery or consumption was determined. For chronic anemia (such as occurs in beta-thalassemia) lysed, resealed RBCs have been
used to carry oxygen. Ropars and colleagues\textsuperscript{50} have loaded resealed RBCs with hemoglobin that has been modified by the allosteric regulator inositol hexaphosphate (IHP). IHP causes a large rightward shift of the hemoglobin oxygen dissociation curve, with consequent oxygen unloading. The in-vivo lifespan of these lysed and resealed RBCs is normal (33 days). They also can be loaded with desferrioxamine to chelate iron stores at sites of RBC destruction and, thus, avoid iron overload.

Hemoglobin has also been encapsulated within liposomes—small spheres (diameter 0.7 \( \mu \) m) made up of a lipid bilayer capsule of mixed lipids.\textsuperscript{51} A 50% solution of liposomes contains 7.5 g/dL of hemoglobin with a \( P_{50} \) of 24 torr. Less than 2% of the Hgb is methemoglobin. Rats regularly survive 50% exchange transfusions and sometimes survive 95% exchanges. In rats, the apparent half-life of these neohemocytes is approximately 6 hours, with no evidence of kidney or liver damage. Rats can be exchange transfused to hematocrits of 3% without any alteration in the oxygen extraction ratio or \( \dot{V}_{\text{O}_2} \).\textsuperscript{52} Because rodent studies have consistently shown that liposome-encapsulated hemoglobin transfusions are well tolerated, it will be interesting to determine whether they can be used safely in humans. Much work on these encapsulated hemoglobins lies ahead. For example, the optimal liposomal size and lipid mixture must be determined to optimize their half-life and minimize their toxicity.

Summary

Perfluorocarbons have been the most extensively tested class of artificial blood substitute compounds. Results of PFC use in the treatment of severe anemia in Jehovah’s Witnesses have been disappointing, but they may be occasionally useful. Their major utility may prove to be in conditions of abnormal microvascular circulation and in serving as chemo and radiation-sensitizers. The PFCs themselves may have significant direct toxic effects in addition to the potential toxicity of high levels of oxygen and oxygen radicals at sites of inflammation or disease.

Polymerized P-SFH solutions and encapsulated Hgb hold more promise than does FDA-20 for tissue oxygen delivery. However, few toxicity studies and no human clinical trials have been done using Hgb solutions or liposome-encapsulated hemoglobins. These methods may permit safe use of outdated hemoglobin that currently is wasted.

Investigations of all these substances have focused on their oxygen carrying and delivery properties. Future investigations must look at other RBC properties such as carbon dioxide transport and acid buffering. In addition, the efficacy of these blood substitutes must be tested when multiple stresses on the oxygen transport system are present. Unfortunately, combinations of anemia, cardiac dysfunction, and respiratory failure do occur in clinical situations.

The potential exists for the development of new PFCs with greater oxygen-carrying capacity and/or longer half-lives. These newer PFCs will hold even greater potential for use in ischemic diseases and in tumor therapy. Hemoglobin solutions may prove very useful in treating acute anemia, both in patients who refuse RBC transfusions and in outlying locations such as accident sites or on battlefields. Finally, the use of artificial blood substitutes to restore intravascular volume has the potential to provide two clinical benefits. The first benefit is the persistence of these substances in the circulation for longer periods than the half-lives of albumin or crystalloid. The second benefit is the additional oxygen transport.

It will be important to test the hypothesis that improvement in oxygen transport and oxygen consumption in critically ill patients leads to improved clinical outcomes. If this theory is given credence, then finding new blood substitutes that do not tax the already stressed national blood banking system will become even more important.

The habit of accepting a hematocrit of 30% in the ICU patient needs to be questioned. Further studies on the optimal hematocrit for patients with respiratory failure or multisystem organ failure need to be carried out.

Bartlett\textsuperscript{53} emphasized our lack of attention to oxygen transport by RBCs in his “Critical Carol,” an essay in which the ghost of the physiologist Ernest Starling visits a physician caring for Charles Cratchit, a typical ICU patient, on Christmas Eve. Starling comments to the physician on the “habit of using anemia as a treatment . . . you bleed poor Charlie every day and leave him with a hematocrit of 32. You are a modern day intensive care leech.” The physician’s response is “I resent being compared to a leech. This patient is not anemic . . . Charlie’s hematocrit is 32% . . . I mean it’s, it’s not anemic.
for a critically ill patient. Most of our critically ill patients have hematocrits in the 30s."

Although artificial blood substitutes may not immediately replace red blood cell transfusion, they focus our attention on oxygen delivery and oxygen consumption in critically ill patients. While artificial blood substitutes are being tested and perfected over the next decade, the utility of maintaining hematocrits of 35%, 40%, or even 45% in the critically ill patient should be rapidly determined.

ACKNOWLEDGMENTS

I thank Ms Elizabeth Brown for her expert assistance in the preparation of the Schering lecture and the manuscript.

REFERENCES


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**PRESCRIBING INFORMATION**

**WARNING:** RIBAVIRIN AEROLEG SHOULD NOT BE USED IN INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EFFILAGE MAY IMPAIR MUCUS CLEARANCE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still under development.

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Ribavirin is 5 beta-n-hydroxy-1,2,4-diazine-3-carboxamide with the following structural formula:

\[ \text{C}_{12}\text{H}_{17}\text{N}_{3}\text{O}_{4} \]

**CLINICAL PHARMACOLOGY:**

**Antiviral effects:** Ribavirin has antiviral activity in vitro against respiratory syncytial virus (RSV) and influenza type A and B viruses, but has no activity against adenovirus, cytomegalovirus, herpes simplex virus, varicella-zoster virus, or reovirus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats. In animal models, ribavirin is effective against influenza virus and smallpox virus. Ribavirin has been noted to cause fetal toxicity in rats and mice and to be excreted in the milk of rats and mice.

**Immunologic effects:** Ribavirin may cause immunosuppression in some animals. In vitro, ribavirin may inhibit the production of interferon and the expression of interferon in murine fibroblast cell cultures. Ribavirin may also reduce the number of natural killer cells in vitro.

**Toxicity and adverse reactions:** Ribavirin toxicity has been observed in rats, mice, and rabbits. In mice, ribavirin is highly toxic and is excreted in the milk of rats and mice.

**Type of drug:** Ribavirin is a synthetic nucleoside that is metabolized by the kidneys and excreted in the urine.

**Clinical trials:** Ribavirin has been evaluated in several clinical trials to determine its safety and efficacy in the treatment of respiratory viral infections. The results of these trials have been mixed, with some studies showing promising results and others revealing significant side effects.

**Contraindications:** Ribavirin is contraindicated in women of childbearing potential who are not using effective contraception and in patients with a history of hemoglobinuria. Ribavirin is also contraindicated in patients with a history of drug allergy or sensitivity to ribavirin.

**Indications and usage:** Ribavirin is indicated for the treatment of respiratory viral infections in children and adults. It is also used for the treatment of respiratory viral infections in newborns and infants.

**Dosage and administration:** The dosage and administration of ribavirin depend on the specific viral infection being treated. The drug is usually administered as an aerosol using a nebulizer.

**Precautions and cautions:** Patients who have a history of respiratory tract infection should be monitored closely during treatment with ribavirin. Patients who have a history of respiratory tract infection should be monitored closely during treatment with ribavirin.

Ribavirin should be administered cautiously to patients with renal impairment or liver disease, as ribavirin is primarily excreted by the kidneys and may accumulate in these patients.

**Drug interactions:** Ribavirin should be used with caution in patients taking other medications that may interact with ribavirin, such as diuretics or anticoagulants.

**Overdosage:** The use of ribavirin in overdose may lead to significant toxicity, including respiratory depression, hypoxia, and cardiac arrest. Treatment of ribavirin overdosage includes supportive care, such as oxygen administration and ventilation support. If ribavirin is an ingredient in a medication, the patient should be monitored closely for signs of toxicity.

**REFERENCES:**


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Asthma and Bronchitis: A Shift of Therapeutic Emphasis

Hugh S Mathewson MD

Asthma affects more than 5% of the population in developed countries; the figure is estimated to be between 5 and 7% in the United States. According to a recent report from the United Kingdom, the incidence of asthma is increasing. Other studies indicate a rise in asthma mortality. It is probable that the overall management of asthmatic patients can be improved.

Treatment of the chronic asthmatic patient has often tended to be directed primarily toward control of bronchoconstriction, while the underlying inflammatory mechanisms that cause bronchial hyperreactivity have been under-treated. Evidences of bronchial inflammation can be found even in mild asthmatics. Increased concentrations of inflammatory cells, particularly eosinophils and lymphocytes, are found in bronchoalveolar lavage fluid; and mucosal biopsy sections show these in abundance. Bronchial hyperreactivity is directly related to the degree of inflammation, although there is some variability between tissue changes and the severity of symptoms.

The central role of eosinophils is characteristic of the asthmatic condition, and the term chronic eosinophilic bronchitis has been suggested to indicate its inflammatory nature. Eosinophilic proteins are localized at sites of epithelial damage, suggesting that mucosal epithelial shedding may be attributable to their toxic effects. It has been shown that eosinophils are relatively unaffected by beta-adrenergic drugs and theophylline, whereas corticosteroids definitely inhibit their degranulation. The roles of lymphocytes and neutrophils in the asthmatic process are less well defined, although interleukin-5, a lymphokine elaborated by T-lymphocytes, may augment the activity of eosinophils.

The natural course of an asthma episode is characterized by two phases. The first is an acute allergic phase, in which there is mast cell degranulation and release of histamine, leukotrienes, and possibly other bronchoconstrictor substances. The second phase is inflammatory in nature, and involves the actions of mediators elaborated by eosinophils, neutrophils, macrophages, and lymphocytes. Beta-adrenergic drugs tend to inhibit mast cell degranulation, whereas corticosteroids do not. Conversely, beta agonists do not notably affect the membrane stability of eosinophils, neutrophils, macrophages, or T-lymphocytes, while corticosteroids play multiple roles in suppressing the formation and release of bronchoactive contents of such cells. These findings may account in part for the immediate therapeutic response to beta-adrenergic drugs, whereas corticosteroids, in contrast, require considerably more time, but eventually cause a reduction of inflammatory processes and a consequent decrease in bronchial irritability.

Reversal of bronchial hyperreactivity is most reasonably approached by the use of anti-inflammatory drugs. Of these, corticosteroids are the most widely applicable. They are most effective and have fewer side actions if administered by aerosol. Beclo-methasone dipropionate, triamcinolone acetonide, flunisolide, and budesonide are potent corticosteroids that are topicaly active. Given in proper dosage they can usually control asthma without producing adverse metabolic effects or adrenal suppression. Budesonide, which has the greatest topical activity, is not yet available in the United States. High-dose inhalers that deliver 4 to 5 times the dose per puff provided by conventional inhalers are likely to be released soon. These will materially aid in suppressing severe or refractory exacerbations. Advocates of control of inflammation as a primary goal in asthma therapy emphasize that corticosteroids represent first-line treatment, and should not be used only when beta agonists and theophylline prove inadequate.

Cromolyn sodium continues to be employed with good results in some patients, although it is less effective than are aerosolized steroids. It has been noted that inhaled cromolyn can
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markedly reduce cough, suggesting that it has a depressant effect on mucosal sensory nerve endings. A pharmacologically similar but more potent compound is nedocromil, which is available in Europe but not in the United States. Ketotifen is an antihistamine-like compound that has received a long clinical trial but has yet to be proven effective for asthma prevention.

Increased emphasis on control of airway inflammation has led to the use of anti-inflammatory drugs typically employed for other diseases—particularly chronic rheumatoid arthritis, which has some immunological features similar to chronic asthma. Methotrexate, a folic acid antagonist, has been found to be effective in reducing steroid requirements of refractory asthmatics. Because it has marked toxic side actions, it is given in low doses. Gold salts have been used in a similar manner, again in limited doses to minimize systemic toxicity. The immediate therapeutic need is reduction of steroid dosage, to prevent the development of osteopenia, myopathy, skin fragility, cataracts, hypertension, and diabetes—a formidable list of potential complications. Of these, osteopenia is the most urgent indication for steroid reduction because it is likely to be irreversible.

Troleandomycin, a macrolide antibiotic, can be used to reduce the dosage of methylprednisolone, probably by prolonging the half life of the steroid. It has also been shown that premenstrual exacerbations of asthma can be prevented to some degree by intramuscular dosage of progesterone.

Bronchodilator drugs will continue to be routinely employed for extended treatment of asthma. Both beta-adrenergic drugs and theophylline show damping effects on inflammation, especially on microvascular leakage. Beta-2 specificity has been optimized with albuterol and terbutaline; however, the duration of action of these compounds is less than 6 hours, which is not long enough to encompass the nocturnal sleeping hours. Two new agents, formoterol and salmeterol, are presently under clinical study. Formoterol, which is 10 times more potent than salbutamol, sustains bronchodilation for 8 hours. Salmeterol, a compound structurally akin to salbutamol, has maintained its effect for a 12-hour period, with no tachyphylaxis after 9 days of treatment.

The action of theophylline has been extended through the development of slow-release oral preparations. It is anticipated that reasonably steady plasma levels will soon be attainable with a single daily dose. Experimental efforts are now directed toward the synthesis of xanthine-like bronchodilator compounds that have minimal cardiovascular side actions. Although the therapeutic effect of theophylline is no longer considered to be due to phosphodiesterase (PDE) inhibition, work continues on PDE-inhibitor compounds, most of which are different from xanthines. Selective PDE inhibitors that are potent bronchodilators have been derived from the nucleoside, griseolic acid.

Anticholinergic drugs depress muscarinic receptors on both airway smooth muscle and mucosal and bronchial secretory cells. They are less effective than beta-adrenergic drugs in asthma management, and are usually used in combination with other bronchodilators. Ipratropium bromide is the most widely used aerosol compound; it is the N-isopropyl quaternary homologue of atropine. Experimental studies have not strayed far from well-known atropine-like structures. However, the identification of at least three types of muscarinic receptors (M1, M2, M3) has stimulated new research to find compounds that discriminate among them. Pirenzepine, an orally active specific M1 antagonist, reportedly dilates both large and small airways in asthmatic patients. Its primary clinical application thus far is for peptic ulcer therapy, and its use is still investigational.

Much research effort continues to be directed toward suppressing the mediators that trigger asthma attacks. Compounds can be designed that interfere with biosynthesis or release of the mediator. Other agents can block the receptor sites or prevent smooth muscle cell responses to the mediator. Drugs that blockade histamine receptors are relatively ineffective, and research interest has focused on compounds that can control lipid mediators such as leukotrienes, thromboxanes, and prostaglandins. Several leukotriene (LTD4) antagonists have been tested clinically. Inhibitors of 5-lipoxygenase, an enzyme essential to leukotriene biosynthesis, have also been prepared. A thromboxane (TXA2) antagonist was recently reported to decrease allergen-induced bronchoconstriction in man.

Platelet-activating factor (PAF) is a lipid substance that attracts and activates eosinophils. It can induce a state of bronchial hyperresponsiveness that lasts up to 4 weeks. Inhibitors of PAF have shown clinical promise, but their application in asthma therapy is yet to be established. Similarly, the release of certain neuropeptides (bradykinins, substance P) contribute to bronchial inflammation. Finding agents that control these compounds constitutes another line of therapeutic investigation.

A novel approach to bronchodilator drug development involves the study of potassium-ion (K+) channel openers. Several of these are known, but one in particular, chreokalamin has been reported to inhibit histamine-induced bronchoconstriction in man. Clinical trials of K+ channel openers will occur soon, although probably for conditions other than asthma. Because they relax vascular smooth muscle, they offer promise as antihypertensive agents.
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Gary Smith, the Associate Executive Director of the National Board for Respiratory Care (NBRC), has interwoven the contributions of five distinguished personalities in our profession with his own prose to produce a rather unusual book. These contributors are Steven K Bryant MBA, NBRC Executive Director; H Frederic Helmholz Jr MD, NBRC Trustee; Vincent D Kracum RRT, AARC Life Member and former AARC representative to the Joint Review Committee for Respiratory Therapy Education (JRCRTE); Robert M Lawrence MD, former NBRC Trustee; and James F Whitacre MS RRT, AARC Life Member, former JRCRTE Trustee, and former Secretary of the NBRC's predecessor organization the American Registry of Inhalation Therapists.

The author's stated intention is to develop and present a coherent history of the profession for the benefit of its students, potential students, educators, and current practitioners. To this end, the book's major chapters follow an outline that includes the chapter theme followed by commentary on clinical practice, educational developments, credentialing, and the “Association” (meaning the American Association for Respiratory Care [AARC]). The book's nine chapters are complemented by nine appendices, the most ambitious of which is Appendix I — Chronology of Respiratory Care Milestones. This 19-page appendix, which includes notes on technical developments, carries the reader forward from Hippocrates, 410 BC, to the 1989 NBRC decision to offer the perinatal-pediatric respiratory care specialty examinations in 1991.

Evolution of a Profession is the only book of its kind of which I am aware and should serve as a benchmark volume against which other books of its genre can be measured. Because of this, I feel that the author has served the profession well.

When I first read the book, cover-to-cover, I found the writing-style differences among Smith and his contributors to be somewhat disconcerting. The smooth, erudite sentence structures created by Dr Helmholz do not flow easily into the witty, humorous, and loquacious forms presented by Dr Lawrence. Too, I initially perceived as a structural flaw the fact that there was not a major contributor representing the insider viewpoint of the AARC. Mr Smith reserved that task for himself.

I read it again — this time for fun as Helmholz suggested — and found myself drawn into the high drama of the past. Nearly every page and nearly every name provoked a memory, not always a pleasant one but a memory nonetheless. As a case in point, I had never before fully appreciated what a tremendous impact a single lawsuit could have on an entire profession even though I was an active participant early on. The implications and far-reaching ramifications of the class-action, antitrust complaint known as Veizaga et al vs NBRT et al are succinctly described.

Happily, the book has some of the elements of a good mystery tale — elements that readily lend themselves to the folklore of the profession. Who assaulted Bill Morrison in Anaheim, California, in 1975? Who was the AAIT representative who helped incorporate the ‘wrong’ Board of Schools in 1967? What transpired over lunch in early 1982 to alter the AARC's reportedly turbulent posture on sponsor representation of the NBRC?

Finally, the flaw that I had seen became a strength! The author has presented the refreshing viewpoint of a member interested in his association—not that of a biased direct participant in those political events that have shaped the AARC.

This book could well have profited from the assistance and guidance of a professional editor. The reading audience, having spent hard-earned money, is entitled to a finished product. Yet, as early in the book as Page 5, we find reference to Dr Comroe's "lab" when it would have been more appropriate to discuss the good Doctor's laboratory. On Page 20, we find that Norton treated pulmonary “edema” and that the NBRC resorted to legal “horsepower” rather than high-level legal council between 1976 and 1979 (Page 108). It is most probable that “sometimes” in 1961 Mr Whitacre convinced Dr Lawrence to become his medical director rather than “someplace,” as reported on Page 126. Also, the author permitted Mr Bryant to write about "this” data rather than these data on Page 179.

A typeface that has diacritical marks should have been used. I consider it discourteous not to use these marks when writing proper names such as Mörch or Dräger.

Be that as it may, I feel that the soft-cover edition of Respiratory Care: Evolution of a Profession is well worth the money I spent for it. I felt this to be particularly true when I learned that the author is contributing
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Respiratory care for infants and children is a unique discipline devoted to a population that cannot be considered to consist of little adults. Because neonatal and pediatric respiratory care is a specialty, those who don't work with this age group on a regular basis and even those who do may benefit from a 'luggable' handbook that is no farther away than one's lab coat pocket. Neonatal/Pediatric Respiratory Care: A Critical Care Pocket Guide is a book that fits this bill. In a world of increasing numbers of respiratory care handbooks, this is the only handbook to my knowledge completely devoted to respiratory care of neonatal and pediatric patients. The author is a seasoned therapist-educator with more than 11 years of teaching experience.

The handbook can be utilized not only by respiratory therapists but by physicians and nurses as well. It covers a wide range of subject matter related to respiratory care and is exhaustive in the information presented. I found more information than I would ever have need for as a pediatric respiratory therapist. The author states in the preface that a basic knowledge of neonatal and pediatric respiratory care is required when using this book. This is probably because its intended audience is assumed to be using the handbook at a critical care level. The handbook measures 4.5" × 6.5" × 1.5" and offers the user varying charts, tables, illustrations, and algorithms. The book is bound with a 6-ring binder, making it convenient to add or delete pages. The 6-page index makes it easy to locate desired subjects in the book, although for the subject matter presented an even more complete index would have been appreciated. I was unable to locate Ribavirin or Alupent, two commonly aerosolized medications, in the index.

The table of contents consists of 17 sections. Six of the first eight deal exclusively with assessment, the other two with CPR and perinatal transport. It would probably flow better with these two in a different part of the table of contents so that the assessment group could be together. There is a chapter perhaps mistitled named General Nursing Care that adequately covers several aspects of thermal regulation and half a page of infection control information. This is somewhat misleading and should have been titled Thermal Regulation. I found only one error in the page numbers (the omission of Page 40 in Section 17 of the Diseases/Disorders chapter).

With any handbook, the user must expect to encounter smaller sized print. This is also true with this book. I had no problem at all reading the type and only experienced moderate hindrance in reading a few charts; the appendix conversion of pounds and ounces to grams can be interpreted, but in the situation where the user may find himself in a poorly lit area, much difficulty may be experienced. The only other item that was somewhat hard to read was the postural drainage photographs for infants, which looked to be copies of black and white photography of poor resolution.

The chapter titled Epiglottitis has a helpful chart and algorithm that provide a logical progression through the diagnosis and the initial treatment of croup and epiglottitis; however, the three croup scoring diagrams in the chapter Croup left me somewhat confused. Different degrees of a cough were assigned different scores in the diagrams. On one chart, a barking cough is assigned a 1 and on the other a 2. The author's attempt to provide a lot of information, led to some confusion on my part. Perhaps one diagram would suffice. Nevertheless, I do appreciate the wealth of information regarding croup and epiglottitis.

The mechanical ventilation chapter is comprehensive. It was helpful to see a classification of positive pressure ventilators broken down into the four phases of a mechanical breath and the peculiarities associated with the different types of ventilators compared. The four phases of the mechanical breath are inspiratory phase, switch from inspiration to expiration, expiratory phase, and switch from expiration to inspiration. He also covers in detail the specific settings associated with mechanical ventilation. The initial settings and ventilator management seem well thought out.

Overall, I believe that this book provides a needed service not only to respiratory care practitioners but also to physicians and nurses who provide neonatal and pediatric care. I agree with Dr Field's statement in the Foreword "this book may serve the respiratory therapist, nurse, or physician as well as the Harriet Lane Manual has served the pediatric house officer for general care." Neonatal/Pediatric Respiratory Care: A Critical Care Pocket Guide is a handbook that I would not hesitate to refer to daily.
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AARC & AFFILIATES

March 15-16 in Newport, Rhode Island. The Rhode Island Society for Respiratory Care presents its 6th annual Respiratory Care Symposium, "The Newport Challenge—Sails On." Contact Jayne Matoian RRT, PO Box 9051, Providence RI 02940-9051. (401) 723-8496.

April 3-5 in Fargo, North Dakota. The North Dakota Society for Respiratory Care presents its annual meeting. Airway mechanics (pediatric PFTs), oxygen consumption, and HFJV ventilation are among the topics presented. Featured speakers include Neil MacIntyre MD, Richard Branson RRT, and Evan Richards RRT. Contact Mike Leier or Gary Brown, St Luke's Hospitals, 720 4th Street N, Fargo ND 58122. (701) 234-5191.

April 4-6 in Baton Rouge, Louisiana. The Louisiana Society for Respiratory Care holds its 20th Annual Educational Meeting at the Embassy Suites. Contact Jim Lamoha RRT, (504) 387-7080.

April 10-13 in Southfield, Michigan. The Michigan Society for Respiratory Care presents its 32nd Annual Respiratory Care Symposium, "1990: Now What?" Noted speakers include Neil MacIntyre, John Goodman, and Sam Giordano. Contact MSCR, PO Box 950, East Lansing MI 48826, or call Caroline Kimmeld, (517) 337-1351.

April 11-13 in Nashville, Tennessee. The Tennessee Society for Respiratory Care presents its annual educational seminar and exhibition, "1990—A New Frontier," at the Vanderbilt Plaza Hotel in Nashville. Contact Colleen Schubacker, Cardiopulmonary Dept, Jesse Holman Jones Hospital, 509 Brown St, Springfield TN 37172, or call (615) 384-1569. For exhibitor information, contact Candace Partee, (615) 449-0500.

April 17-19 in Philadelphia, Pennsylvania. The Pennsylvania Society for Respiratory Care presents its annual conference and exhibition at the Adam's Mark Hotel. This year's theme is "Putting on the Ritz for Our 25th!" Respiratory care and cardiovascular technology will be highlighted. Contact Jill Bucholtz, (215) 526-3341; or Wendy Janor, (215) 456-8049.

April 18-20 in Rancho Mirage, California. The California Society for Respiratory Care, Chapters 1, 2, 3, and 4, co-host their 9th annual "Bright Horizons in Respiratory Care Symposium" at the Annenberg Center for Health Sciences on the Eisenhower Medical Center campus. Speakers include David Pierson MD, John Bach MD, Dean R Hess MD, RRT, Bud Spearman BS RRT, Michael Gurevich MD RRT. Topics include pressure ventilation, updates on barotrauma and auto-PEEP, MDRs vs SVN in ventilator therapy, ventilator-trigger sensitivity and WOB, noninvasive mask ventilation, neonatology, pediatrics, and oxygen transport and assessment. For more information, call (800) 321-3690, In California (800) 621-7322. FAX (619) 773-4513.

April 18-20 in Des Moines, Iowa. The Iowa Society for Respiratory Care presents its 1990 Iowa Lung Conference at the Hotel Jort Des Moines. Contact Mike Wheeler, (515) 283-6207.

April 18-20 in Osage Beach, Missouri. The Missouri Society for Respiratory Care presents its annual meeting, "Come Cruise With Us" at the Tan-Tar-A resort, Lake of the Ozarks. Keynote speakers are Jerome Sullivan RRT, Joel Cooper MD, and Robert Kacmanek RRT. Contact Jack Dale, (816) 836-8100.

April 25-27 in Sioux Falls, South Dakota. The South Dakota Society for Respiratory Care hosts its annual meeting, "The New Decade—A Survival Kit of the '90s" at the Howard Johnson. Contact Mary Reineisch, (605) 333-6477.

May 8-10 in Fontana, Wisconsin. The Wisconsin Society for Respiratory Care presents its annual meeting, "Celebrating 20 years," at the Abbey on Lake Geneva. Contact Tami Hansen RRT, (608) 263-7050.

May 16-18 in Myrtle Beach, South Carolina. Georgia/South Carolina Region VI presents its 14th Annual Conference and Assembly at the Landmark Hotel. Contact Mike Payne, Georgia/South Carolina Region VI, 730 S Pleasantburg Dr, Suite 525, Greenville SC 29607. (803) 879-0200.

June 13-15 in St Charles, Illinois. The Illinois Society for Respiratory Care presents its annual convention, "Westward Ho: Golden Opportunities in Respiratory Care," at Pheasant Run. Contact Trudy Watson RRT, Black Hawk College, 6600 34th Ave, Moline IL 61265, (309) 796-1311, ext 3303; or Vince Madama RRT, Rock Valley College, 3301 N Mulford Dr, Rockford IL 61103, (815) 654-4413 or (815) 654-4410.


August 24-26 in Marco Island, Florida. The Florida Society for Respiratory Care presents the Southernmost Sandcastle Seminar at the Marco Beach Hilton Resort. Seminar fees cover all Saturday meals including a sunset buffet beach party. Bring your own musical instruments to join our sing-along or win a prize for the Best Sandcastle on the Beach. Ample time is planned for exhibits. Deadline for reservations is July 12. Contact Dave Robbins RRT, Coral Gables Hospital, 3100 Douglas Rd, Coral Gables FL 33133. (305) 441-6819.

OTHER MEETINGS

March 23 in Dayton, Ohio. The Ohio Association of Air Medical Services, hosted by Care Flight Air Ambulance Service and co-hosted by Miami Valley Hospital, meets at the Daytonian Hilton. Contact Margie Mahle, (513) 220-2094.

April 5-6 in Cleveland, Ohio. Saint Vincent Charity Hospital and Health Center presents its 11th annual Respiratory Care Seminar. Contact Gene Andrews, Pulmonary Services Dept, St Vincent Charity Hospital and Health Center, 2351 E 22nd St, Cleveland OH 44115. (216) 363-2576.

April 20-22 from Miami to Nassau. Another "floating seminar" on sleep-related disorders. Three-day, two-night cruise. Deadline for reservations is March 16. Contact Dave Robbins, (305) 441-6819.

April 23-24 in Chapel Hill, North Carolina. The Respiratory Care Department of UNC Hospitals and the UNC Department of Pediatrics co-sponsor the 4th annual "Current Concepts in Pediatric and Neonatal Respiratory Care" at the Kenan Center on the University of North Carolina campus. Contact Susan Hardisty RRT, (919) 966-1336.


August 30-September 8, Hawaiian cruise aboard the SS Constitution. Dream Cruises' 4th Annual Cruise for Continuing Education presents "Each One, Teach One." Fly to Oahu for two days in Waikiki before boarding ship to four other ports and the islands of Hawaii, Maui, and Kauai. Prices start at $1,215 plus airfare from your gateway city. Write Dream Cruises, 10882 La Dona Ave, Garden Grove CA 92640. 800-462-3628. California residents call (714) 636-2566.
A 60-year-old male with multiple injuries from an automobile accident was admitted to the ICU via the OR after having a tracheostomy tube placed. The patient also had a flail chest that required ventilation with positive end expiratory pressure (PEEP).

Clinical Status

1 hour after admission to the ICU—The capnogram was noted to have an irregular alveolar plateau and a low end-tidal CO$_2$ value. During the expiratory phase it was also noted that the PEEP level was erratic. ABG: Pa$_O_2$ = 96 mmHg, Pa$_C_0_2$ = 41 mmHg, pH = 7.32.

Upon careful assessment, a leak around the tracheostomy tube cuff was found. Manipulation of the tube did not improve the alveolar plateau. It was determined that the tracheostomy tube should be changed.

5 minutes later—The tracheostomy tube was changed and there was no longer a leak. The capnogram returned to normal with a good alveolar plateau.

Monitored Variables

| BP  | 112/68 |
| HR  | 92 BPM |
| RR  | 12/min |
| EtCO$_2$ | 30 mmHg |

Discussion

Tracheostomy cuff leaks should not be present when patients require high levels of PEEP. In this patient, the N-1000 capnographic waveform fell in the middle of the alveolar plateau phase as a result of the demand valve of the ventilator opening to maintain a PEEP of 10. During expiration, the PEEP level dropped as gas escaped around the cuff. The N-1000 capnogram was the first indication that there was a tracheal tube leak. Changing the tracheal tube maintained the optimal end expiratory pressure and ventilatory support.

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Specifications
Please Read Carefully

An abstract may report (1) an original study, (2) the evaluation of a method or device, or (3) a case or case series. Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, health occupations education, or management of personnel and health-care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal.

The abstract will be the only evidence by which the reviewers will decide whether the abstract should be presented at the Open Forum. Therefore, the abstract must provide all important data, findings, and conclusions. Give specific information. Do not write such general statements as “Results will be presented” or “Significance will be discussed.”

Essential Content Elements

An original study abstract must include (1) Introduction: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results.

A method/device evaluation abstract must include (1) Introduction: identification of the method or device and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author’s practical experience or a notation of lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate.

A case report abstract must report a case that is uncommon or of exceptional teaching/learning value and must include: (1) case summary and (2) significance of case. Content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

Abstract Format and Typing Instructions

An optical scanner will be used to process abstracts. Do not use a dot-matrix printer. First line of abstract should be the title. Title should explain content. Type the abstract double-spaced on plain white bond paper; on one page only (copier bond is excellent). Do not underline or boldface and insert only one letter space between sentences. Provide a 1-inch margin top and bottom, a 1/2 inch left margin, and an approximate 1/2 inch ragged right margin.

No identification of authors or institutions is to appear on the abstract sheet or in the abstract itself. Make the abstract all one paragraph. Data may be submitted in table form provided the table width is limited to 60 letter spaces (ie, letters or numbers plus necessary blank spaces = 60). No figures or illustrations are to be attached to the abstract.

Type all information required to complete the author information form on the other side of this page. A photocopy of good quality may be used.

Standard abbreviations may be employed without explanation. A new or infrequently used abbreviation should be preceded by the spelled-out term the first time it is used. Any recurring phrase or expression may be abbreviated if it is first explained.

Check the abstract for (1) errors in spelling, grammar, facts and figures; (2) clarity of language; (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed.

Questions about abstract preparation may be telephoned to the editorial staff of RESPIRATORY CARE at (214) 243-2272.

Deadlines

The mandatory Final Deadline is June 9 (postmark). Authors will be notified of acceptance or rejection by letter only—to be mailed by August 15.

Authors may choose to submit abstracts early. Abstracts received by March 26 will be reviewed and the authors notified by May 1. Rejected abstracts will be accompanied by a written critique that should in many cases enable authors to revise their abstracts and resubmit them by the final deadline (June 9).

Mailing Instructions

Mail 1 copy of the abstract, 1 author information sheet, and a stamped, self-addressed postcard (for notice of receipt) to:

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Instructions for Authors and Typists

These Instructions are meant to guide authors and typists, including veterans in those roles, in the production of quality manuscripts. Perfection is not expected, but the well-prepared manuscript has the best chance for prompt review and early publication.

General Requirements

Submissions should (1) be related to respiratory care, (2) be planned for one of the publication categories below, and (3) be prepared as indicated in these Instructions. A letter accompanying the manuscript must specify the intended publication category, be signed by all the authors, and, when there are two or more authors, state that “We, the undersigned, have all participated in the work reported, read the accompanying manuscript, and approved its submission for publication.”

Publication Categories

Research Article (Study): A report of an original investigation.
Evaluation of a Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification.
Case Report: A report of a clinical case that is uncommon or of exceptional teaching value. The author(s) must have been associated with the case. A case-managing physician must be one of the authors or, if not an author, must supply a letter approving the manuscript.
Case Series: Like a Case Report but including a number of cases.
Review Article: A comprehensive, critical review of the literature and state of the art of a pertinent topic that has been the subject of 40 or more published research papers.
Overview: A critical review of a pertinent topic about which not enough research has been published to merit a Review Article.
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Case Report or Case Series: Title page, abstract page, continuous text (Introduction, Case Summary, Discussion), Acknowledgments page, references, tables, figure legends. Also see “How To Write a Better Case Report,” Respir Care 1983;27:29 (Jan 1983).

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