State of the Art

Noninvasive Ventilation

SANGEETA MEHTA and NICHOLAS S. HILL

Divisions of Pulmonary and Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada and Brown University School of Medicine, Providence, Rhode Island

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Correspondence and requests for reprints should be addressed to Nicholas S. Hill, M.D., Pulmonary Division, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903.

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Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway. During the first half of the 20th century, negative pressure types of noninvasive ventilation were the main means of providing mechanical ventilatory assistance outside of the anesthesia suite. By the 1960s, however, invasive (i.e. via an endotracheal tube) positive pressure ventilation superceded negative pressure ventilation, primarily because of better airway protection. The past decade has seen a resurgence in the use of noninvasive ventilation, largely because of the development of nasal ventilation, which has the potential of providing ventilatory assistance with greater convenience, comfort, safety, and less cost than invasive ventilation. The following will explore these trends in the use of noninvasive ventilation and then provide a current perspective on applications in patients with acute and chronic respiratory failure. The discussion will consider the rationale for use, currently available techniques and equipment, evidence for efficacy, selection of appropriate patients, and general guidelines for application, monitoring, and avoidance of complications.

This review is based on an evaluation of the literature using a multimethod approach. A computerized MEDLINE search from 1966 through June 2000 was undertaken using search terms including *mechanical ventilation*, *intermittent positive pressure ventilation*, *negative pressure ventilation*, *respiratory insufficiency/failure*, *lung disease/obstructive*, and *lung disease/restrictive.* Bibliographies of articles were also searched for relevant articles. Review articles and consensus statements were also examined and recommendations synthesized into general guidelines.

TRENDS IN THE USE OF NONINVASIVE VENTILATION

The Age of Body Ventilators

The earliest noninvasive ventilators were the "body" ventilators, so-called because they assist ventilation by applying negative or positive pressure to various regions of the body. The earliest description of a body ventilator was that of a tank-type negative pressure device by the Scottish physician John Dalziel in 1838 (1). It consisted of an airtight box in which the patient was seated with the head protruding through a neck seal. A manually powered bellows generated the negative pressure. Numerous other prototypes of this device were described during the 1800s (2), but they did not achieve widespread use until the 1900s when electricity became readily available and a large demand was created by the polio epidemics (3). The first electrically powered body ventilator used widely was the iron lung, developed in 1928 by Philip Drinker,

a Boston engineer (4). It consisted of a one ton metal cylinder encasing the patient who lay supine on a mattress with his or her head protruding through an air-tight rubber neck seal. In 1931, J. H. Emerson, of Cambridge, Massachusetts, constructed a simpler, quieter, lighter and less expensive version of the iron lung that could be manually operated in the event of power failure. Drinker unsuccessfully sued Emerson for patent infringement, and the Emerson lung became the predominant version for ventilator support of patients with respiratory paralysis caused by poliomyelitis, with thousands manufactured between 1930 and 1960 (5).

The bulk and lack of portability of early tank ventilators stimulated the development of more portable negative pressure devices, including the chest cuirass or "shell" ventilator and raincoat (or wrap) ventilator (3). The first cuirass, developed in 1876 by Ignez von Hauke of Austria (2), consisted of an iron shell covering the anterior part of the thorax, with an air-filled rubber edge that created a tight seal. In 1927, R. Eisenmenger patented the first mechanical chest shell, the Biomotor, which was used from 1935 onward to treat respiratory paralysis (6). The first mass-produced chest shells, the Fairchild-Huxley chest respirator and the Monaghan Portable Respirator, were introduced in 1949. Shortly thereafter, the prototype wrap-style ventilator, the Tunnicliffe breathing jacket, was described (7). These devices saw widespread use for chronic support of polio patients with respiratory paralysis.

The polio epidemics stimulated the development of other approaches to noninvasive ventilation, including the rocking bed and the intermittent abdominal pressure ventilator, commonly referred to as the "pneumobelt." The technique of rocking to assist ventilation was described by F. C. Eve in 1932 (8) and was subsequently used by the British Navy until the early 1960s as a technique to resuscitate drowning victims (9). Wright introduced the first rocking bed during the late 1940s as a modification of a bed designed to improve circulation (10). This device became popular during the 1950s as a means of facilitating weaning from the iron lung. Some postpolio patients subsequently used it for chronic ventilatory support, sometimes for decades (11).

Sir William Bragg, a Nobel-Prize-winning physicist, invented the "pneumobelt" during the 1930s. He fashioned a pneumatic belt from a rubber football bladder for a friend with muscular dystrophy. The bladder was strapped around the abdomen and lower thorax and was inflated by a small air pump, compressing the abdominal viscera during expiration. Robert Paul improved the belt, and it was subsequently called the Bragg-Paul Pulsator. The device gained popularity during the late 1950s because of enhanced convenience and portability for chronic ventilator users, just as the polio epidemics were drawing to a close (12).

Proliferation of Invasive Positive Pressure Ventilation

Prior to 1960, invasive positive pressure ventilation was used mainly for administration of anesthesia. Although tracheostomy tubes were often placed to manage airway secretions in patients with bulbar polio, ventilatory support was still usually provided by iron lungs. A turning point occurred during a large outbreak of polio in Copenhagen, Denmark, in 1952 (13). The few available negative pressure ventilators were overwhelmed by the hundreds of afflicted patients. A massive effort was mobilized to provide round-the-clock ventilation to these patients using invasive positive pressure resuscitators borrowed from anesthesia suites and powered manually by medical students, nurses, and other volunteers. Survival rates using positive pressure ventilation were much better than those seen during use of negative pressure ventilation early during the epidemic, an improvement thought to be related to better airway protection from aspiration of secretions (5).

Partly as a consequence of this experience, there was a gradual transition to invasive positive pressure ventilation that was accelerated during the 1960s by the development of intensive care units and the introduction of simple to operate, relatively inexpensive positive pressure ventilators. Administration of positive pressure ventilation via translaryngeal endotracheal tubes became standard practice for the support of patients with acute respiratory failure.

Reemergence of Noninvasive Ventilation

Although rarely used in the United States after the 1960s for patients with acute respiratory failure, body ventilators continued to be used for patients with chronic respiratory failure through the mid-1980s, particularly for those with neuromuscular disease or kyphoscoliosis (14, 15). However, because of a number of disadvantages relative to noninvasive positive pressure ventilation, including patient discomfort, restrictions on positioning, problems with correct fitting, time-consuming application, lack of portability, and a tendency to potentiate obstructive sleep apneas, body ventilators have seen diminishing use since the mid-1980s (16).

The noninvasive application of positive pressure dates back to the 1930s, when the pioneering studies of Alvan Barach demonstrated that continuous positive airway pressure could be useful in the treatment of acute pulmonary edema (17). First described in 1947 (18), intermittent positive pressure breathing (IPPB) administered via a mouthpiece was used widely until the early 1980s in acute care hospitals in the United States. Although it was used mainly as a means of delivering aerosolized bronchodilators to patients with chronic obstructive pulmonary disease (COPD) and asthma, several studies evaluated this modality as a means of noninvasive ventilatory support. Fraimow and colleagues (19) observed that IPPB reversed the increase in Pa_{CO_2} occurring in patients with emphysema receiving oxygen. On the other hand, two studies in which IPPB was administered to patients with COPD at home for periods of 22 mo and 4 yr, respectively, found no benefit in FEV_1 or arterial blood gases and reduced survival in comparison with nonrandomized control subjects (20, 21). After publication of these studies and the randomized, prospective trial sponsored by the National Institutes of Health that showed no benefit of IPPB over nebulizer treatments in patients with COPD (22), use of IPPB declined drastically. Perhaps the main reason for the failure of IPPB as a means of ventilatory support, though, was that it was used primarily to deliver aerosol treatments for only 10 to 15 min three or four times daily; too brief to substantially assist breathing.

Noninvasive positive pressure ventilation (NPPV), administered nocturnally and as needed during the daytime, was used successfully to treat patients with neuromuscular disease at centers such as the Goldwater Rehabilitation Center in New York dating back to the early 1960s (23). However, these centers used mainly mouthpiece interfaces that failed to gain wide acceptance elsewhere. Face masks were also available, but these likewise failed to gain wide acceptance for the chronic administration of noninvasive ventilation, largely because of poor patient tolerance. The signal change that led to the recent proliferation of noninvasive ventilation came in the early 1980s with the introduction of the nasal continuous positive airway pressure (CPAP) mask for the treatment of obstructive sleep apnea (24). Rideau and colleagues (25) of France proposed in 1984 that such masks should be used with positive pressure ventilators to achieve nocturnal respiratory muscle rest in patients with Duchenne muscular dystrophy (DMD), so that disease progression could thereby be slowed. Soon there-

after, the success of nocturnal nasal ventilation was reported in ameliorating gas exchange disturbances and symptoms in patients with chronic respiratory failure caused by a variety of neuromuscular diseases and chest wall deformities (26–28). Subsequent studies have confirmed the favorable findings of these earlier studies, establishing an important role for NPPV in the management of chronic respiratory failure. More recent work has begun defining the role in the management of patients with acute respiratory failure. Subsequent sections will critically review this recent work and provide guidelines on current indications for NPPV in both acute and chronic settings.

Why the Interest in Noninvasive Ventilation?

A major driving force behind the increasing use of noninvasive ventilation has been the desire to avoid the complications of invasive ventilation. Although invasive mechanical ventilation is highly effective and reliable in supporting alveolar ventilation, endotracheal intubation carries well-known risks of complications that have been described elsewhere in detail (29). These fall into three main categories: complications directly related to the process of intubation and mechanical ventilation, those caused by the loss of airway defense mechanisms, and those that occur after removal of the endotracheal tube.

The first category includes aspiration of gastric contents, trauma to the teeth, hypopharynx, esophagus, larynx, and trachea, arrhythmias, hypotension, and barotrauma that may occur during placement of a translaryngeal tube (30–32). With tracheostomy placement, risks include hemorrhage, stomal infection, intubation of a false lumen, mediastinitis, and acute injury to the trachea and surrounding structures, including the esophagus and blood vessels (32). In the second category, endotracheal tubes provide a direct conduit to the lower airways for microorganisms and other foreign materials, permitting chronic bacterial colonization, inflammation, and impairment of airway ciliary function. These factors facilitate the occurrence of nosocomial pneumonia, seen in as much as 21% of mechanically ventilated intensive care unit (ICU) patients (33), and sinusitis, that occurs in 5 to 25% of nasally intubated patients, related to blockade of the sinus ostia and accumulation of infected secretions in the paranasal sinuses (34). The chronic aspiration and irritation associated with endotracheal intubation also necessitate endotracheal suctioning that further irritates lower airway mucosa, causing discomfort, further inflammation, edema, and increased mucus production. In the third category, hoarseness, sore throat, cough, sputum production, hemoptysis, upper airway obstruction caused by vocal cord dysfunction or laryngeal swelling, and tracheal stenosis may follow extubation (35).

From the point of view of the patient, perhaps the most troubling aspects of translaryngeal intubation are tube-associated discomfort and the compromised ability to eat and communicate that contributes to feelings of powerlessness, isolation, and anxiety (36). This may increase the need for sedation, delaying weaning, adding to the costs of care, and potentiating the risks of further complications. Placement of a tracheostomy does little to simplify care. Sophisticated equipment, including suctioning paraphernalia and a high level of technical expertise among caregivers, is required, adding substantially to costs (37). In addition, tracheostomies lead to upper airway colonization with gram-negative bacteria, increasing the risk of pneumonias (35). Further, long-term tracheostomies are complicated by tracheomalacia, endotracheal granulation tissue formation, and tracheal stenoses that sometimes contribute to airway obstruction, chronic pain, and tracheoesophageal or even tracheoarterial fistulas (35). These considerations and potential complications may limit the options for chronic care placement and may even preclude home discharge in patients with limited personnel and financial resources who would otherwise be candidates for home placement.

By averting airway intubation, noninvasive ventilation has the potential of avoiding these problems if candidates are carefully selected using established guidelines which will be discussed in detail in later sections. In contrast to invasive ventilation, noninvasive ventilation leaves the upper airway intact, preserves airway defense mechanisms, and allows patients to eat, drink, verbalize, and expectorate secretions. Several recent studies indicate that NPPV reduces infectious complications of mechanical ventilation, including nosocomial pneumonia and sinusitis (38–40). Noninvasive ventilation may enhance comfort, convenience, and portability at no greater (41) or even less cost than endotracheal intubation (37). Furthermore, noninvasive ventilation may be administered outside of the intensive care setting, as long as adequate nursing and respiratory therapy support can be provided, allowing caregivers to more rationally utilize acute-care beds, and it greatly simplifies care for patients with chronic respiratory failure in the home.

EQUIPMENT AND TECHNIQUES FOR NONINVASIVE VENTILATION

The following will describe equipment currently available for administration of noninvasive ventilation including NPPV and body ventilators. Mechanisms of action and principles of application of body ventilators will also be considered. Because of its current popularity, NPPV will be emphasized and its mechanisms of action and applications will be discussed in more detail later. CPAP as opposed to intermittent positive pressure ventilation may be used for some forms of respiratory failure, so equipment required for the noninvasive administration of CPAP will also be discussed. Finally, brief descrip-

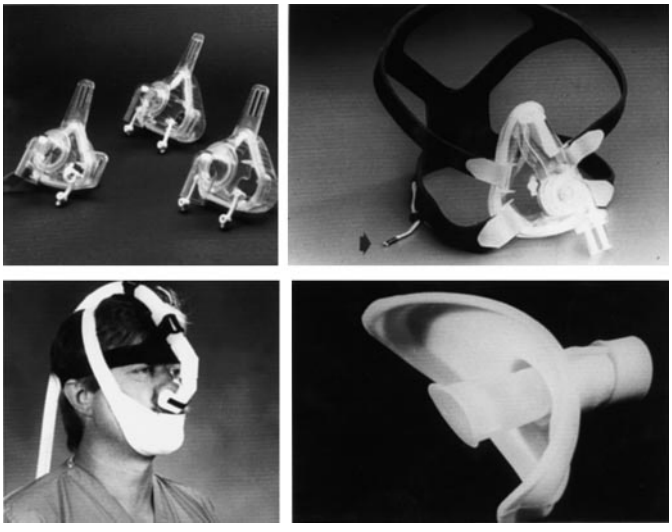

Figure 1. Examples of different types of interfaces. *Upper left* panel shows different sizes of typical disposable nasal masks (Respironics, Murrysville, PA) used for continuous positive airway pressure (CPAP) or noninvasive positive pressure ventilation (NPPV). *Lower left panel* shows nasal "pillows" (Mallinkrodt, Minneapolis, MN) with a chin strap used to reduce air leaks through the mouth. *Upper right panel* shows oronasal mask with four strap headgear system (Resmed, San Diego, CA). *Arrow* shows "quick release" strap to be used if rapid removal (such as with vomiting) is desired. *Lower right panel* shows mouthpiece with lipseal (Mallinkrodt).

tions of other ventilatory aids and cough-enhancing techniques will also be included.

Noninvasive Positive Pressure Ventilation

Positive pressure ventilators, whether invasive or noninvasive, assist ventilation by delivering pressurized gas to the airways, increasing transpulmonary pressure, and inflating the lungs. Exhalation then occurs by means of elastic recoil of the lungs and any active force exerted by the expiratory muscles. The major difference between invasive and NPPV is that with the latter, gas is delivered to the airway via a mask or "interface" rather than via an invasive conduit. The open breathing circuit of NPPV permits air leaks around the mask or through the mouth, rendering the success of NPPV critically dependent on ventilator systems designed to deal effectively with air leaks and to optimize patient comfort and acceptance.

Interfaces for the delivery of NPPV or CPAP. Interfaces are devices that connect ventilator tubing to the face, facilitating the entry of pressurized gas into the upper airway during NPPV. Currently available interfaces include nasal and oronasal masks and mouthpieces.

Nasal masks. The nasal mask is widely used for administration of CPAP or NPPV, particularly for chronic applications. The standard nasal mask is a triangular or cone-shaped clear plastic device that fits over the nose and utilizes a soft cuff to form an air seal over the skin (Figure 1). Nasal masks are available from many manufacturers in multiple sizes (pediatric and adult small, medium, large, wide, and narrow, and so on) and shapes, largely because of the demand for such devices in the treatment of obstructive sleep apnea. The standard nasal mask exerts pressure over the bridge of the nose in order to achieve an adequate air seal, often causing skin irritation and redness, and occasionally ulceration. Various modifications are available to minimize this complication such as use of forehead spacers or the addition of a thin plastic flap that permits air sealing with less mask pressure on the nose. Recently, several manufacturers have introduced nasal masks with gel seals that may enhance comfort. In addition, newer "mini-masks" have been developed that minimize the bulk of the mask, reducing feelings of claustrophobia and permitting patients to wear glasses while the ventilator is in use. For occasional patients who have difficulty tolerating commercially available masks, custom-molded, individualized masks that can be made to conform to unique facial contours are also available.

Straps that hold the mask in place are also important for patient comfort, and many types of strap assemblies are available. Most manufacturers provide straps that are designed for use with a particular mask. Straps that attach at two or as many as five points on the mask have been used, depending on the interface. More points of attachment add to stability. Strap systems with Velcro fasteners are popular, and elastic caps that help to keep the straps from tangling or sliding have been well received by patients.

An alternative type of nasal interface, nasal "pillows" or "seals," consist of soft rubber or silicone pledgets that are inserted directly into the nostrils (Figure 1). Because they exert no pressure over the bridge of the nose, nasal pillows are useful in patients who develop redness or ulceration on the nasal bridge while using standard nasal masks. Also, some patients, particularly those with claustrophobia, prefer nasal pillows because they seem less bulky than standard nasal masks.

Oronasal masks. Oronasal or full-face masks cover both the nose and the mouth (Figure 1). They have been used mainly on patients with acute respiratory failure but may also be useful for chronic applications. Oronasal masks have been used in approximately half of the studies evaluating NPPV for acute respiratory failure. During chronic use, patients may object to having both the nose and the mouth covered, and asphyxiation may be a concern in patients who are unable to remove the mask in the event of ventilator malfunction or power failure. Furthermore, interference with speech, eating, and expectoration, the likelihood of claustrophobic reactions, and the theoretical risks of aspiration and rebreathing are greater with oronasal than with nasal masks. On the other hand, oronasal masks may be preferred for patients with copious air leaking through the mouth during nasal mask ventilation. Also, recent improvements in oronasal masks, such as more comfortable seals, improved air-sealing capabilities, and incorporation of quick-release straps and antiasphyxia valves to prevent rebreathing in the event of ventilator failure, have increased acceptability of these interfaces for chronic applications. One recently commercially available interface that holds promise is the "total" face mask (42), which resembles a hockey goalie's mask. Made of clear plastic, it uses a soft cuff that seals around the perimeter of the face, avoiding direct pressure on facial structures.

The efficacy of nasal and oronasal masks has recently been compared in a controlled trial of 26 patients with stable hypercapnia caused by COPD or restrictive thoracic disease. The nasal mask was better tolerated than either nasal pillow or an oronasal mask but was less effective at lowering Pa_{CO_2}, perhaps because of greater air leaking (43). This supports the commonly held belief that in the acute setting, oronasal masks are preferable to nasal masks, because dyspneic patients are mouth breathers, predisposing to greater air leakage and reduced effectiveness during nasal mask ventilation. However, efficacy of the mask types has been similar when compared among published reports that have used one mask or the other. Also, a recent preliminary report from a controlled trial comparing nasal and oronasal masks found that Pa_{CO_2} and respiratory rate fell at equal rates when the masks were used for patients with acute respiratory distress (44).

Mouthpieces. Mouthpieces held in place by lipseals have been used since the 1960s to provide NPPV for as long as 24 h a day to patients with chronic respiratory failure (Figure 1) (45). The mouthpiece has the advantages of being simple and inexpensive. Custom-fitted mouthpieces, that may increase comfort and efficacy are also available at some centers (23). Success using these devices has been reported in a large number of patients with neuromuscular disease, some with little or no vital capacity (46). During the daytime, patients receive ventilatory assistance via a mouthpiece attached to their wheelchair controls or held by a gooseneck clamp. During sleep, some patients use strapless custom mouthpieces, and others use strapped-on lipseals. Nasal air leaking may compromise efficacy, but this can be managed by increasing ventilator tidal volume or occluding the nostrils with cotton pledgets or noseclips. The use of mouthpieces has allowed some tetraplegic patients to be successfully converted from tracheostomies to NPPV (47).

Ventilators for NPPV

Delivery of CPAP. Although not a true ventilator mode because it does not actively assist inspiration, CPAP is used for certain forms of acute respiratory failure. By delivering a constant pressure during both inspiration and expiration, CPAP increases functional residual capacity and opens collapsed or underventilated alveoli, thus decreasing right to left intrapulmonary shunt and improving oxygenation. The increase in functional residual capacity may also improve lung compliance, decreasing the work of breathing (48). In addition, by

lowering left ventricular transmural pressure, CPAP may reduce afterload and increase cardiac output (49, 50), making it an attractive modality for therapy of acute pulmonary edema. Further, by counterbalancing the inspiratory threshold load imposed by intrinsic positive end-expiratory pressure (PEEPi), CPAP may reduce the work of breathing in patients with COPD (51, 52). A few uncontrolled trials have observed improved vital signs and gas exchange in patients with acute exacerbations of COPD treated with CPAP alone (53–55), suggesting that this modality may offer benefit to these patients.

Pressures commonly used to deliver CPAP to patients with acute respiratory distress range from 5 to 12.5 cm H_2O. Such pressures can be applied using a wide variety of devices including CPAP valves connected to a compressed gas source, small portable units used for home therapy of obstructive sleep apnea, and ventilators designed for use in critical care units (critical care ventilators). Depending on the critical care ventilator selected, CPAP may be administered using "demand," "flow-by," or "continuous flow" techniques, with imposed work differing slightly between them (56). The main considerations for selection of an appropriate device include provision of an adequate air flow rate so that a continuous positive pressure is maintained, even in patients with acute respiratory failure, who may breathe at high flow rates, and the perceived need for alarms, convenience, or portability. Although not appropriate for the acute care setting where high flow rates may be needed, simple, small, inexpensive portable units are usually adequate for home applications.

Pressure-limited ventilators. Pressure-limited modes are available on most ventilators designed for use on intubated patients in critical care units. Most such "critical care ventilators" provide pressure support ventilation (PSV) that delivers a preset inspiratory pressure to assist spontaneous breathing efforts and has attained popularity in recent years as a weaning mode (57). Many also offer pressure control ventilation (PCV) that delivers time-cycled preset inspiratory and expiratory pressures with adjustable inpiratory:expiratory ratios at a controlled rate. Most such modes also permit patient-triggering with selection of a backup rate. Nomenclature for these modes varies between manufacturers, causing confusion. For the pressure support mode, some ventilators require selection of a pressure support level that is the amount of inspiratory assistance added to the preset expiratory pressure and is not affected by adjustments in PEEP. Others require selection of peak inspiratory and expiratory positive airway pressures (IPAP and EPAP), the difference between the two determining the level of pressure support. It is important to recall that with the latter configuration, alterations in EPAP without parallel changes in IPAP will alter the pressure support level.

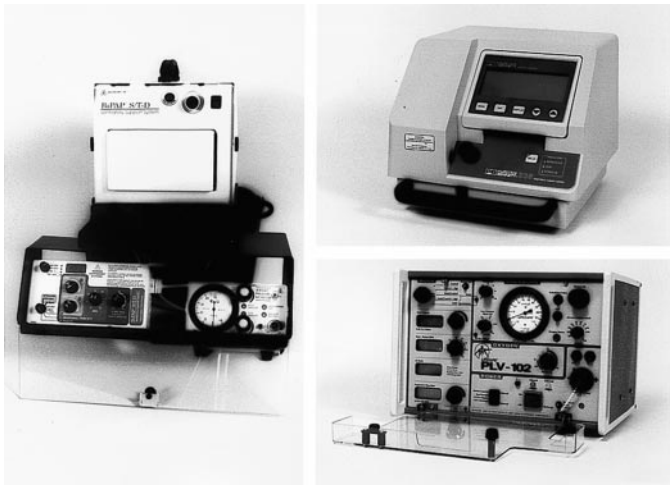

Figure 2. Several examples of portable positive ventilators. On *left* is prototype "bilevel" ventilator with a remote control panel (BiPAP, Respironics). On *upper right* is Knightstar 335 (Mallinkrodt), a bilevel ventilator that incorporates adjustible inspiratory and expiratory trigger sensitivities. These devices provide CPAP, pressure support with positive end-expiratory pressure (PEEP), or pressure-assist ventilation. *Bottom right panel* shows example of volume-limited portable ventilator (PLV-102; Respironics). Unlike bilevel ventilators, this ventilator has a built-in battery backup, an oxygen blender, high pressure-generating capability, and a sophisticated alarm system.

What distinguishes PSV from other currently available ventilator modes is the ability to vary inspiratory time breath by breath, permitting close matching with the patient's spontaneous breathing pattern. A sensitive patient-initiated trigger signals the delivery of inspiratory pressure support, and a reduction in inspiratory flow causes the ventilator to cycle into expiration. In this way, PSV allows the patient to control not only breathing rate but also inspiratory duration. As shown in patients undergoing weaning from invasive mechanical ventilation (58), PSV offers the potential of excellent patient-ventilator synchrony, reduced diaphragmatic work, and improved patient comfort. However, PSV may also contribute to patient-ventilator asynchrony, particularly in patients with COPD. High levels of pressure support and the resulting large tidal volumes may contribute to inadequate inspiratory efforts on subsequent breaths, leading to failure to trigger (59). Also, brief rapid inhalations that may be seen in patients with COPD may not permit adequate time for the PSV mode to cycle into expiration, so that the patient's expiratory effort begins while the ventilator is still delivering inspiratory pressure (60). The patient must exert expiratory force to cycle the ventilator, and this may contribute to breathing discomfort. During noninvasive ventilation, these forms of asynchrony are exacerbated in the presence of air leaks.

Although noninvasive PSV is often administered using standard critical care ventilators, portable devices that deliver pressure-limited ventilation (Figure 2) have also seen increasing use for both acute and chronic applications. These devices, sometimes referred to as "bilevel" devices because they cycle between two different positive pressures, are lighter (5 to 10 kg) and more compact (< 1 ft^3) than critical care ventilators, offering greater portability at lower expense (61). Some offer not only a spontaneously triggered pressure support mode but also pressure-limited, time-cycled, and assist modes. Some also offer adjustable trigger sensitivities (62), "rise time" (the time required to reach peak pressure), and inspiratory duration, all features that may enhance patient-ventilator synchrony and comfort. Further, the performance characteristics of these ventilators compare favorably with those of critical care ventilators (63).

On the other hand, unlike the critical care ventilators, the bilevel devices have limited pressure-generating capabilities (20 to 35 cm H_2O, depending on the ventilator) and most lack oxygen blenders or sophisticated alarm or battery backup systems. Therefore, they are not currently recommended for patients who require high oxygen concentrations or inflation pressures, or are dependent on continuous mechanical ventilation unless appropriate alarm and monitoring systems can be added. Recently, however, new versions of bilevel ventilators have been introduced that have more sophisticated alarm and monitoring capabilities, graphic displays, and oxygen blenders and are quite suitable for use in the acute care setting.

Because of their portability, convenience, and low cost, the bilevel devices have proven ideal for home use in patients with

chronic respiratory failure requiring only nocturnal ventilatory assistance. In addition, unlike volume-limited ventilators, they are able to vary and sustain inspiratory airflow to compensate for air leaks, thereby potentially providing better support of gas exchange during leaking (64). However, in addition to limited alarm capabilities, other concerns have been raised about bilevel ventilators. Because they use a single tube with a passive exhalation valve, rebreathing may occur (65). This concern is discussed further in the section on applications of NPPV.

Volume-limited ventilators. Most critical care ventilators offer both pressure- and volume-limited modes, either of which can be used for administration of noninvasive ventilation. If volume-limited ventilation is desired for chronic applications, portable volume-limited ventilators (Figure 2) are usually chosen because of their greater convenience and lower cost. These are applied just as for invasive ventilation, using standard tubing and exhalation valves, with oxygen supplementation and humidification as necessary. Compared with the portable pressure-limited ventilators described above, the volume-limited portable ventilators are more expensive and heavier. However, they also have more sophisticated alarm systems, the capability to generate higher positive pressures, and built-in backup batteries that power the ventilator for at least a few hours in the event of power failure. These ventilators are usually set in the assist/control mode to allow for spontaneous patient triggering, and backup rate is usually set at slightly below the spontaneous patient breathing rate. The only important difference relative to invasive ventilation is that tidal volume is usually set higher (10 to 15 ml/kg) to compensate for air leaking. Currently available volume-limited ventilators are well suited for patients in need of continuous ventilatory support or those with severe chest wall deformity or obesity who need high inflation pressures.

Newer noninvasive ventilator modes. Because patient comfort and compliance with the therapy are so critical to the success of noninvasive ventilation, newer modes that are capable of closely mirroring the patient's desired breathing pattern are of great interest. One such new ventilator mode is proportional assist ventilation (PAV), which targets patient effort rather than pressure or volume (66). By instantaneously tracking patient inspiratory flow and its integral (volume) using an in-line pneumotachograph, this mode has the capability of responding rapidly to the patient's ventilatory effort. By adjusting the gain on the flow and volume signals, the operator is able to select the proportion of breathing work that is to be assisted. This ventilator mode is not yet commercially available in the United States, but preliminary reports on noninvasive applications are promising (67, 68). Ventilators designed specifically for the administration of noninvasive ventilation are being introduced by a number of ventilator manufacturers. These offer a variety of pressure-limited modes and include proportional assist ventilation or similar modes except in the United States, where the Food and Drug Administration has yet to approve these latter modes.

Negative Pressure Ventilation

Although negative pressure ventilators are used much less often now than they were in the past, knowledge of their characteristics and applications is useful because they may be used for patients who fail to adapt to NPPV. Negative pressure ventilators work by intermittently applying a subatmospheric pressure to the chest wall and abdomen, increasing transpulmonary pressure and causing atmospheric pressure at the mouth to inflate the lungs. Expiration occurs passively by elastic recoil of the lungs and chest wall as pressure within the device rises to atmospheric levels.

The efficiency of negative pressure ventilation (tidal volume generated for a given negative pressure) is determined by the compliance of the chest wall and abdomen and the surface area over which the negative pressure is applied. The tank ventilator is the most efficient by virtue of its application of negative pressure over the entire chest wall and abdomen. The cuirass is least efficient, because it applies negative pressure only to a portion of the anterior chest and abdomen (69). Although the wrap ventilator is usually more efficient than the shell ventilator, collapse of the jacket onto the upper chest wall and lower abdomen during use may compromise its efficiency. Problems with air leaking may also reduce efficiency of the wrap and chest shell ventilators and, to a lesser extent, the iron lung, which only has to seal around the neck.

The tank ventilator is reliable and relatively comfortable, but it is bulky (3 m long) and heavy (300 kg), virtually precluding portability. It is also intolerable to claustrophobic patients and interferes with nursing care, although it does have portholes on the sides to facilitate access. A more portable fiberglas tank ventilator is available, but it weighs approximately 50 kg and requires two persons for portage. The chest shell and wrap are lightweight, but the negative pressure generators necessary to power them still weigh 15 to 30 kg. Also, the tank and wrap ventilators restrict patients to the supine position, often inducing musculoskeletal back and shoulder pain. The chest shell may be used in the sitting position, but it can induce discomfort and pressure sores at points of skin contact, particularly if fit is suboptimal. Patients with chest wall deformities can be managed with custom-fit cuirasses, but efficiency of these may be poor.

These limitations of negative pressure ventilation interfere with patient tolerance, but most can be overcome with fitting adjustments or nonsteroidal anti-inflammatory drugs (16). However, the tendency for negative pressure ventilators to induce obstructive sleep apnea, even in normal subjects (70), may affect safety. Obstructive apneas associated with severe oxygen desaturations occur commonly during negative pressure ventilation in patients with restrictive thoracic disorders and may necessitate a switch to positive pressure ventilation (71–73). This problem is related to the lack of preinspiratory contraction of pharyngeal muscles that prevents collapse of upper airway structures during a normal patient-initiated breath (74). Traditional negative pressure ventilators, lacking patient-triggered modes, render the upper airway susceptible to collapse during ventilator-triggered breaths that are out of synchrony with the patient's spontaneous breaths. It remains to be seen whether newer patient-triggered negative pressure ventilators, such as the NEV-100 or Emerson NPV, will alleviate this problem.

External high frequency ventilation offers an alternative to standard negative pressure ventilation (75, 76). Consisting of a chest and abdominal cuirass connected to an oscillator, this device is capable of delivering pressures ranging from -70 to $+70$ cm H_2O at frequencies as great as 60/min for ventilation and 999/min for secretion removal. I:E ratios can be from 6:1 to 1:6. The Food and Drug Administration in the United States has approved this device for frequencies only as great as 1 Hz. The chest wall oscillator has been proposed as a means of enhancing secretion clearance by applying frequencies of 1 to 1.5 Hz and inverting the I:E ratio. Although the device has been shown to augment minute volumes in normal subjects (75) and patients with COPD (76), it has not been adequately tested on patients with respiratory failure, and it should be considered investigational for this application.

Abdominal Displacement Ventilators

The rocking bed (77) and pneumobelt (12) both rely on displacement of the abdominal viscera to assist diaphragm motion and, hence, ventilation. The rocking bed consists of a mattress on a motorized platform that rocks in an arc of approximately 40 degrees on a fulcrum at hip level. The patient lies supine with the head and knees raised slightly to prevent sliding. When the head rocks down, the abdominal viscera and diaphragm slide cephalad, assisting exhalation. As the head rocks up, the viscera and diaphragm slide caudad, assisting inhalation. The rocking rate is between 12 and 24/min, adjusted to optimize patient comfort and minute volume, as measured with a handheld spirometer or magnetometer. The chief advantages of the rocking bed are ease of operation, lack of encumbrances, and patient comfort, although bulkiness, noisiness, and lack of portability limit its appeal.

The pneumobelt consists of a corsetlike device that wraps around the patient's midsection and holds an inflatable rubber bladder firmly against the anterior abdomen (12). The rubber bladder is connected to a positive pressure ventilator that intermittently inflates the bladder. When the patient is sitting, bladder inflation compresses the abdominal contents, forcing the diaphragm upward and actively assisting exhalation. With bladder deflation, gravity returns the diaphragm to its original position, assisting inhalation. Raising bladder inflation pressure increases tidal volume; typical pressures are between 35 and 50 cm H_2O. Desired minute volume can then be attained by adjusting ventilator rate, usually between 12 and 22/min. The pneumobelt is highly portable, easily hidden under clothing with the ventilator mounted on a wheelchair to facilitate mobility, and leaves the hands and face unencumbered. Because it requires gravity to pull the diaphragm down during bladder deflation, it is ineffective unless patients sit at angles of at least 30 degrees. Hence, nocturnal use is limited to patients who can learn to sleep while sitting (78, 79). However, it may be valuable as a daytime adjunct in appropriate patients who are using other forms of noninvasive ventilation nocturnally (80).

Both the rocking bed and pneumobelt are especially well-suited for use in patients with bilateral diaphragmatic paralysis because their main action is to assist diaphragm motion (81, 82). However, they are both relatively ineffective ventilators and are of limited value in patients with acute respiratory deteriorations. Furthermore, efficacy of both depends on abdominal and chest wall compliance, so that patients with severe kyphoscoliosis, excessive thinness, or obesity may not be adequately ventilated.

Other Modes of Noninvasive Ventilatory Assistance

Diaphragm pacing and glossopharyngeal breathing are ventilatory methods used in selected patients to increase independence from more cumbersome modes. Diaphragm pacing consists of a radio-frequency transmitter and antenna that signal a receiver and electrode that are surgically implanted, usually in the subclavicular area (83). The receiver and electrode stimulate the phrenic nerve, causing diaphragmatic contraction. Use of diaphragm pacing is limited to patients with central hypoventilation or high spinal cord lesions who have an intact diaphragm and phrenic nerve, or a phrenic nerve that can be repaired (84). However, recent advances in NPPV have virtually eliminated the need for diaphragm pacing in patients with central hypoventilation (85).

Diaphragm pacing has a number of limitations, including high cost and the tendency to produce upper airway obstruction by the same mechanism as negative pressure ventilators, necessitating continuation of tracheostomy in as much as 90% of users (85). In addition, there are no controlled studies that demonstrate long-term efficacy. On the other hand, diaphragm pacers are very easy to use, highly portable, and free patients from the need to be connected to positive pressure ventilators. Thus, some patients with high cord lesions still prefer diaphragm pacing to other types of ventilatory assistance. Its chief application at the present time is in children with high spinal cord lesions who have difficulty adapting to noninvasive forms of ventilation (86).

Glossopharyngeal or "frog" breathing utilizes intermittent motions of the tongue and pharyngeal muscles to inject (or gulp) air into the trachea (87). When gulping, the patient lowers and then raises the tongue against the palate in a pistonlike fashion, forcing air into the trachea. With practice, each gulp injects 50 to 150 ml of air in about 0.5 s. The patient then closes the glottis to prevent escape of air and rapidly repeats the gulping until a tidal volume of approximately 500 or 600 ml is achieved. The air is then exhaled, and the maneuver is repeated eight to 10 times per minute, so that a normal minute volume can be attained. The technique can be used instead of mechanical ventilation for periods of several hours, even in patients with severely weakened lower respiratory muscles. It can also be used to augment individual breaths in patients with low tidal volumes or to achieve inhaled volumes of 2 to 2.5 L to assist in coughing. The obvious advantage of the technique is that it requires no mechanical appliance. However, use is limited to patients who have intact upper airway musculature, more or less normal lungs, and who are capable of learning the technique. Good candidates include those with high spinal cord injuries, postpolio syndrome, and selected patients with other neuromuscular diseases (88).

Techniques to Assist Cough

The techniques to assist ventilation described above serve mainly as aids to inspiration. However, when weak expiratory muscles are combined with a markedly reduced vital capacity, as occurs in end-stage neuromuscular diseases, the cough mechanism is severely impaired. The inability to cough effectively is tolerable for patients who have minimal airway secretions and an intact swallowing mechanism, but an episode of acute bronchitis or aspiration of oral secretions can precipitate a life-threatening crisis. When this occurs, strategies to assist cough and expectoration may be lifesaving.

An effective cough depends on the ability to generate adequate expiratory airflow, estimated at > 160 L/min (89). Expiratory airflow is determined by lung and chest wall elasticity, airway conductance, and, at least at higher lung volumes, expiratory muscle force. By generating an adequate vital capacity (> 2.5 L) to take advantage of respiratory system elasticity, inspiratory muscle function also contributes to cough adequacy. In addition, an effective cough requires intact glottic function, so that explosive release of intrathoracic pressure can generate high peak expiratory cough flows (90). Considering that many patients with severe neuromuscular disease are too weak to take advantage of many of these mechanisms and have insufficient cough flows, techniques to assist cough should be applied.

The simplest maneuver to augment cough flow is manually assisted or "quad" coughing. This consists of firm, quick thrusts applied to the abdomen using the palms of the hands, timed to coincide with the patient's cough effort. The technique should be taught to caregivers of patients with severe respiratory muscle weakness with instructions to use it whenever the patient encounters difficulty expectorating secretions. With practice, the technique can be applied effectively and frequently, with

minimal discomfort to the patient. Peak expiratory flows can be increased severalfold when manually assisted coughing is applied successfully (91). To minimize the risk of regurgitation and aspiration of gastric contents, the patient should be semiupright when manually assisted coughing is applied, and the technique should be used cautiously after meals.

Although manually assisted coughing may enhance expiratory force, it does not augment inspired volume. Patients with severely restricted volumes, therefore, may still achieve insufficient cough flows, even when assisted by skilled caregivers. To overcome this problem, the inhaled volume should be augmented (92). One approach is to "stack" breaths using glossopharyngeal breathing or volume-limited ventilation and then to cough using manual assistance. Another is to use a mechanical insufflator-exsufflator, a device that was developed during the polio epidemics to aid in airway secretion removal. This device delivers a positive inspiratory pressure of 30 to 40 cm H_2O via a face mask and then rapidly switches to an equal negative pressure (91). The positive pressure assures delivery of an adequate tidal volume, and the negative pressure has the effect of simulating the rapid expiratory flows generated by a cough. Use of the insufflator-exsufflator has been combined with manually assisted coughing in an effort to further augment cough flows.

Although no controlled trials have evaluated the efficacy of the cough insufflator-exsufflator, anecdotal evidence suggests that it enhances removal of secretions in patients with impaired cough (92, 93). It has been particularly useful in patients' homes to treat episodes of acute bronchitis, permitting avoidance of hospitalization (94). Other devices that aid expectoration such as the percussive ventilator and Hayek oscillator have theoretical advantages over some of the other techniques for assisting secretion removal (92). Their use of high frequency vibrations (as much as 10 to 15 Hertz) may facilitate mobilization of airway secretions. Unfortunately, even anecdotal evidence to support their use is lacking.

Clinicians caring for patients with severe cough impairment should be familiar with the various techniques available to assist expectoration. These are particularly important with noninvasive ventilation, because there is no direct access to the airway, and secretion retention is a frequent complication and common cause for failure. Although controlled data are lacking, these techniques appear to be helpful in maintaining airway patency in patients with cough impairment during use of noninvasive ventilation in both acute and chronic settings.

NONINVASIVE VENTILATION TO TREAT RESPIRATORY FAILURE

Noninvasive Ventilation in the Acute Care Setting

Until recently, endotracheal intubation has been the preferred mode for the ventilatory management of acute respiratory failure. The recent increase in use of noninvasive ventilation in the acute care setting has been fueled by the desire to reduce complications of invasive ventilation and to improve resource utilization, as discussed previously. Noninvasive ventilation for acute respiratory failure has the potential of reducing hospital morbidity, facilitating the weaning process from mechanical ventilation, shortening length of hospitalization and thereby costs, and improving patient comfort. However, patients must be selected carefully because the risk of complications could be increased if noninvasive ventilation is used inappropriately. Evidence for efficacy, selection guidelines and concerns about time demands on medical personnel are discussed in detail below.

Evidence for Efficacy

Continuous positive airway pressure. Although not a form of mechanical ventilatory assistance per se, CPAP is commonly used for the therapy of certain forms of respiratory failure. The use of CPAP to treat acute pulmonary edema was first described in 1938 (17). In more recent years, four randomized prospective trials and one large prospective series (95–99) have demonstrated significant improvements in vital signs and gas exchange as well as drastic reductions in intubation rates attributable to the use of CPAP (10 to 12.5 cm H_2O) administered via a face mask (Table 1). The evidence for CPAP's ability to improve oxygenation and avoid intubation in these studies is very strong, with average intubation rates dropping to 19% from 47% in control subjects. However, with the exception of ICU length of stay in one study (98), improvements in other outcome variables such as complication rates, lengths of hospital stays, or mortality have not been demonstrated.

CPAP has also been tried in patients with various other causes of respiratory failure, both hypoxemic and hypercapnic. In a number of uncontrolled studies on mainly postoperative and trauma patients, application of CPAP by face mask was associated with an abrupt improvement in oxygenation and little need for intubation (100–103). However, entry criteria permitted inclusion of patients with mild to moderate respiratory distress, and, in the absence of controls, it is unclear

TABLE 1

STUDIES ON THE EFFICACY OF CONTINUOUS POSITIVE AIRWAY PRESSURE IN ACUTE PULMONARY EDEMA

Author	Yr	Reference No.	Technique*	Positive Pressure (*cm H_2O*)	Patients† (*n*) CPAP	Patients† (*n*) Control		Pa_{CO_2} (*mm Hg*) B	Pa_{CO_2} (*mm Hg*) A	Pa_{O_2} (*mm Hg*) B	Pa_{O_2} (*mm Hg*) A
Rasanen	1985	95	CPAP	10	20 (7)	20 (13)		41	39	52	60
Viasanen	1987	96	CPAP	10	40 (7)			36	35	55	79
Lin	1991	97	CPAP	12.5	25 (7)	30 (18)		30	32	326	416
Bersten	1991	98	CPAP	10	19 (0)	20 (7)		58	46	138‡	206‡
Lin	1995	99	CPAP	12.5	50 (8)	50 (18)					
Totals					154 (29)	120 (56)	Means	41	38		
Success rate					81%	53%					

Definition of abbreviations: A = 10 min to 3 h after initiation of noninvasive positive pressure ventilation; B = baseline; CPAP = continuous positive airway pressure.

* In all studies, CPAP was administered via oronasal mask.

† Numbers in parentheses are numbers of failures, i.e., those who were intubated or who failed to tolerate the mask.

‡ Pa_{O_2}/FI_{O_2} ratios.

that CPAP was more successful than oxygen supplementation alone would have been. CPAP has also been tried in patients with acute exacerbations of COPD (104, 105) and deteriorations of obstructive sleep apnea (106). In these studies, use of nasal CPAP (5 to 9.3 cm H_2O) was associated with improvements in Pa_{CO_2} and Pa_{O_2}, with few patients requiring intubation. In COPD, relatively low levels of CPAP (5 cm H_2O) appear to be beneficial, perhaps by counterbalancing the effects of auto-PEEP (107). However, the lack of controls renders these studies inconclusive, and further studies comparing CPAP to conventional therapy or NPPV are needed.

Negative pressure ventilation. In recent years, a few reports of negative pressure ventilation used to treat acute respiratory failure have come from Spain and Italy. In patients with COPD exacerbations, Montserrat and colleagues (108) compared a 6-h period of wrap ventilation with a 6-h control period on consecutive days, observing lower Pa_{CO_2} values and improvements in oxygenation and dyspnea during ventilator use. In an uncontrolled study also using wrap ventilation for patients with COPD exacerbations, Sauret and colleagues (109) showed reductions in Pa_{CO_2} and improved oxygenation during ventilator use. Subsequently, Corrado and colleagues (110) reported a 16-yr experience using the tank ventilator to treat 2,011 patients, mainly with acute COPD exacerbations and some with restrictive thoracic disorders. Arterial blood gas values improved substantially during tank use (Pa_{CO_2} fell from 80 mm Hg on admission to 50 mm Hg on discharge) and hospital mortality rate was only 10%. Even patients who were initially in coma had a mortality rate of only 23%. However, the study was retrospective, and selection criteria were not given.

More recently, Corrado and colleagues (111) compared the outcomes of 26 patients with COPD and acute respiratory failure treated with negative pressure ventilation to those of 26 matched patients ventilated with invasive positive pressure ventilation, but the patients were treated in different units. The investigators found similar mortality rates (23 versus 27%, negative pressure versus invasive) and hospital lengths of stay (12 d for both), but negative pressure ventilation was used for only 16 h on average, whereas invasive mechanical ventilation was used for 96 h ($p < 0.05$). Thus, available evidence suggests that negative pressure ventilation can improve alveolar ventilation, tolerance of O_2 supplementation, and the sensation of dyspnea in acutely ill patients with COPD. However, the lack of randomized controls or well-defined selection criteria among the available studies makes it difficult to draw firm conclusions or offer general recommendations.

Noninvasive positive pressure ventilation. The recent enthusiasm for treating acute respiratory failure with noninvasive ventilation has been directed at NPPV. The demonstration that NPPV reduces esophageal pressure swings and the diaphragmatic electromyogram (EMG) sum signal in patients with respiratory disease (112, 113) led investigators to hypothesize that NPPV would be useful for supporting ventilation in patients with acute respiratory decompensations who were at risk for respiratory muscle fatigue. After the signal studies of Meduri and colleagues (114), Brochard and colleagues (113), and Elliott and colleagues (115), numerous other uncontrolled studies examining this hypothesis were reported (116–125). These uncontrolled studies will not be examined in detail; rather, the following discussion will focus on randomized controlled trials while reviewing the available evidence on the efficacy of NPPV for various applications in the acute care setting.

Obstructive Diseases

Chronic obstructive pulmonary disease (COPD). Patients with exacerbations of COPD constitute the largest single diagnostic category among reported recipients of NPPV. Among the numerous uncontrolled studies, success rates in avoiding intubation have ranged from 58 to 93%. In an early study using historically matched control subjects, Brochard and colleagues (113) reported that only 1 of 13 patients with acute exacerbations of COPD treated with face mask NPPV required endotracheal intubation, compared with 11 of 13 control subjects. In addition, patients treated with NPPV were weaned from the ventilator faster and spent less time in the intensive care unit than did the control subjects. A larger, more recent historically controlled trial has yielded similar results (126). However, historically-matched control subjects may bias studies in favor of the treatment group (127), so these studies are unable to provide definitive evidence.

Subsequently, five randomized controlled trials have been published (128–132) (Table 2) that lend support to the earlier observations of Brochard and colleagues (113). Bott and colleagues (128) randomized 60 patients with acute exacerbations of COPD to receive nasal NPPV or conventional therapy. Within the first hour of therapy, mean Pa_{CO_2} fell from 65

TABLE 2

SUMMARY OF RANDOMIZED CONTROLLED STUDIES USING NPPV IN ACUTE RESPIRATORY FAILURE CAUSED BY COPD

Author	Yr	Reference No.	Technique/Mask	Insp/Exp Pressure (*cm H_2O*)	Patients* (*n*)		Diagnosis		Pa_{CO_2} (*mm Hg*)		Pa_{O_2} (*mm Hg*)	
					NPPV	Control			B	A	B	A
Bott	1993	128	Volume/nasal		30 (3)	30 (9)	COPD		65	55		
Kramer	1995	129	BiPAP/nasal	8/2	16 (5)	15 (11)	COPD†		74	67	67	92
Brochard	1995	130	PSV/oronasal	20	43 (11)	42 (31)	COPD		70	68	41	66
Angus	1996	131	PSV/nasal	14/18	9 (0)	8 (3)	COPD		76	65		
Celikel	1998	132	PSV/oronasal	15/5	15 (1)	15 (6)	COPD		69	64	55	85
Plant	2000	134	VPAP/nasal/oronasal		118 (18)	118 (32)	COPD		66	61	52	56
Barbe	1996	135	BiPAP/nasal	14.8/5	14 (4)	10 (0)	COPD		59		45	
Totals					245 (42)	238 (29)		Means	68	60	54	67
Success rate					83%	61%						

Definition of abbreviations: A = 45 min to 3 h after initiation of NPPV; B = baseline; COPD = chronic obstructive pulmonary disease; Insp/Exp = inspiratory/expiratory; NPPV = noninvasive positive pressure ventilation; PSV = pressure support ventilation; VPAP = volume positive pressure;

* Numbers in parentheses are numbers of failures, i.e., those who were intubated, failed to tolerate the mask, or died.

† Included some patients without COPD.

to 55 mm Hg, and dyspnea scores improved among treated patients, whereas no significant changes occurred among control subjects. In addition, mortality rate fell from 30% among control patients to 10% among NPPV-treated patients, although this reduction became statistically significant only after exclusion of four patients who were randomized to the NPPV group but never actually received it. Kramer and colleagues (129) randomized 31 patients with various etiologies for respiratory failure, 21 of whom had COPD, to receive NPPV or conventional therapy. Among patients with COPD who received NPPV in their study, respiratory rates and Pa_{CO_2} values fell more rapidly during the first hour of therapy than among control patients, and intubation rates were reduced to 9% compared with 67% in control patients. Hospital lengths of stay and mortality rates tended to be less among the COPD subgroup of patients treated with NPPV, but differences were not statistically significant, perhaps because the number of patients was small.

Subsequently, a multicenter European trial randomized 85 patients with COPD to receive face mask PSV or conventional therapy (130). Respiratory rate but not Pa_{CO_2} fell significantly during the first hour, and intubation rates were lowered from 74% among control patients to 26% among NPPV patients. In addition, complication rates were reduced from 48 to 16%, mortality rates from 29 to 9%, and hospital lengths of stay from 35 to 23 d, respectively, among controls versus NPPV patients (all $p < 0.05$). Questions have been raised about the adequacy of standard therapy, the high complication and mortality rates and lengths of stay among control patients, and the generalizability of this study, considering that it was performed in ICUs and only 31% of patients admitted with COPD exacerbations were enrolled (133). On the other hand, its size and prospective randomized design are important strengths, and careful patient selection is clearly important to the success of NPPV.

An additional controlled trial compared the effects of NPPV with those of doxapram over 4 h in patients with acute exacerbations of COPD, finding that although doxapram transiently improved Pa_{O_2}, it had no effect on Pa_{CO_2} (131). After three deaths in the doxapram group, the protocol was amended so that patients who deteriorated while receiving doxapram could be offered NPPV. This occurred in two patients, who were treated successfully and discharged home. NPPV was deemed to be more effective than doxapram, because it brought about sustained improvements in both Pa_{CO_2} and Pa_{O_2}. Another randomized controlled trial on patients with COPD compared the efficacy of standard medical therapy with that of NPPV in 30 patients with acute hypercapnic respiratory failure caused by exacerbations, pneumonia, or congestive heart failure (132). Those randomized to NPPV had greater improvements in pH and respiratory rate within 6 h, a higher success rate (93 versus 60%, $p < 0.05$), and a shorter hospital length of stay (11.7 versus 14.6 d, $p < 0.05$) than control subjects.

The most recent and largest randomized controlled trial was performed on 236 patients with COPD exacerbations and pH values between 7.25 and 7.35 treated on general respiratory wards at 14 United Kingdom hospitals (134). Patients treated with NPPV, as opposed to control subjects, had a reduced need for intubation (15 versus 27%, $p = 0.02$), and more rapid improvements in pH and respiratory rate. The investigators noted that patients with a pH < 7.30 had a higher mortality rate than did those with a higher pH and suggested that a higher dependency unit might be preferable (if available) for this sicker subgroup. They also acknowledged that differences in ICU availability between countries might limit the generalizability of the results.

Among the numerous controlled and uncontrolled studies examining the efficacy of NPPV in acute respiratory failure due to COPD, only two have obtained negative results. Foglio and colleagues (135) used nasal NPPV to treat 49 consecutive patients with COPD and acute exacerbations. Twenty-four failed to tolerate the mask and served as the control group for the 25 who tolerated the mask. Blood gas determinations in both groups improved at similar rates, and no differences in outcome were apparent between the two groups. More recently, Barbe and colleagues (136) randomized 24 patients with acute COPD exacerbations to receive nasal NPPV or standard therapy. Patients in both groups had similar improvements in blood gas determinations and hospital lengths of stay, and no differences in breathing pattern or indices of respiratory muscle strength were apparent. Both Foglio and colleagues (135) and Barbe and colleagues (136) concluded that NPPV is ineffective in treating exacerbations of COPD.

However, both studies (135, 136) enrolled patients with average pH values (7.33 and 7.34, respectively) that were higher than those of patients in the favorable studies, and baseline Pa_{CO_2} in the Barbe study was lower (Table 2). This suggests that these patients had milder exacerbations than did those entered in most of the other studies. Furthermore, none of the control patients in the Barbe study required intubation, whereas almost three quarters of the control patients in the studies by Kramer and colleagues (129) and by Brochard and colleagues (130) were intubated. This supports the contention that patients in the two studies with negative findings were less acutely ill than those in the favorable studies and argues that NPPV should be reserved for patients with COPD who are at risk of requiring intubation. In fact, Foglio and her colleagues have subsequently reported favorable results with NPPV in a study on patients with COPD and more severe exacerbations (137). This latter study also used pressure- as opposed to volume-limited ventilation and full face masks instead of nasal masks, other factors that may have contributed to the more favorable results. Further studies have also found that survival rates are better and the need for rehospitalization less for patients treated with NPPV as opposed to those treated with conventional therapy, even for as long as a year after the acute episode (138, 139). Although these latter studies were not randomized so that less ill patients may have been treated noninvasively, it is also possible that NPPV avoids late complications of invasive ventilation such as sustained muscle weakness or swallowing dysfunction (140).

In summary, the available evidence establishes that NPPV improves vital signs and dyspnea scores and avoids intubation in patients with severe COPD exacerbations. Also, based on statistically significant differences or trends in the controlled studies, evidence suggests that NPPV reduces morbidity and mortality rates and intensive care unit or hospital lengths of stay. In a recent meta-analysis, Keenan and colleagues (141) concluded that the evidence from the combined controlled studies supports the use of NPPV in the therapy of COPD exacerbations. Although some investigators have questioned the strength of the evidence related to improvements in morbidity and mortality associated with NPPV use (133), these reported benefits pose ethical concerns if further confirmatory studies are to be performed. It should also be borne in mind that NPPV in the above studies was used to avoid intubation, but not to replace it. Thus, although NPPV may be viewed as the ventilatory therapy of first choice for selected patients with COPD (*see* section on patient selection), invasive ventilation remains the method of choice for COPD patients with contraindications to NPPV.

Asthma. No randomized controlled trials have been pub-

lished on the use of NPPV to treat acute asthma. Most studies have included two or fewer patients with asthma, but among five patients with acute asthma included in a study of 158 patients with acute respiratory failure treated with face mask NPPV (average initial Pa_{CO_2} 67 mm Hg), only one required intubation, and there were no mortalities (125). In a larger subsequent study (142), 17 patients with asthma and an average initial pH of 7.25 and Pa_{CO_2} of 65 mm Hg were treated with face mask PSV. Only two required intubation (for increasing Pa_{CO_2}), average duration of ventilation was 16 h, and no complications occurred. The investigators concluded that NPPV appears to be highly effective in correcting gas exchange abnormalities and avoiding intubation in patients with acute severe asthma exacerbations. However, medical therapy alone may be highly effective (143), and in the absence of controls or well-defined selection criteria, no conclusions can be drawn regarding the relative effectiveness of NPPV versus conventional therapy in asthma exacerbations.

Cystic fibrosis. Hodson and colleagues (144) described the use of NPPV to treat patients with end-stage cystic fibrosis with FEV_1 values ranging from 350 to 800 ml and severe acute on chronic CO_2 retention (initial Pa_{CO_2} values ranging from 63 to 112 mm Hg). Six patients were supported for periods ranging from 3 to 36 d, four of whom survived until a heart-lung transplant could be performed. This study illustrates the potential utility of NPPV as a rescue therapy in supporting patients with acutely deteriorating cystic fibrosis and in providing a "bridge to transplantation," but given the lack of any controlled trials, the efficacy of this approach remains unproven.

Restrictive diseases. The use of NPPV in patients with chronic respiratory failure caused by restrictive thoracic diseases is well accepted. However, controlled studies on the management of acute respiratory failure in these patients have not been done, perhaps because they make up only a small portion of patients presenting with acute respiratory failure. In a study that used NPPV to treat all eligible patients admitted to an intensive care unit during a 2-yr period, only five of 158 patients had restrictive lung disease (125). On the other hand, some uncontrolled series have reported success using NPPV to alleviate gas exchange abnormalities and avoid intubation in neuromuscular disease (145) and kyphoscoliosis (146) patients with acute respiratory failure.

Bach and colleagues (94) recently described a regimen for managing acute deteriorations in patients with chronic respiratory failure caused by neuromuscular disease. The patients receive 24-h noninvasive ventilation during the exacerbation. Pulse oximetry is monitored continuously and when oxygen saturation falls below 90%, secretion removal is aggressively assisted using manually assisted coughing and mechanical aids such as the cough insufflator-exsufflator until oxygen saturation returns to the 90% range. Although no controlled studies have established the efficacy of this approach, Bach and colleagues (94) reported that its use during acute exacerbations permitted management in the home, with a dramatic reduction in the need for hospitalization.

No information is available on NPPV therapy of acutely deteriorating restrictive lung diseases such as interstitial fibrosis. However, this application would not be recommended unless an acute reversible superimposed condition was thought to be responsible for the deterioration.

Acute Cardiogenic Pulmonary Edema

As discussed previously, CPAP has been shown to be effective in avoiding intubation in patients with acute pulmonary edema (Table 1). Considering that inspiratory assistance combined with expiratory pressure could reduce breathing work and alleviate respiratory distress more effectively than CPAP alone, patients with acute pulmonary edema have been included in a number of uncontrolled reports on the use of NPPV for acute respiratory failure. In their initial study, Meduri and colleagues (114) reported that one of two patients with acute pulmonary edema had an "excellent" response to NPPV. The same investigators have also described eight patients with acute pulmonary edema treated with face mask PSV, four of whom avoided intubation (125). Others (147) have reported small case series of patients with acute pulmonary edema successfully treated with NPPV.

More recently, two prospective but uncontrolled studies have evaluated face mask PSV administered to patients with acute pulmonary edema (148, 149). In the first (148), pulse oximetry, pH, and Pa_{CO_2} all improved within 30 minutes of initiation of NPPV in 29 patients, only one of whom required intubation. The second study (149) observed similar effects on gas exchange, but five of 26 patients required intubation, and successfully treated patients had higher Pa_{CO_2} values (54 versus 32 mm Hg) and lower creatine phosphokinases (176 versus 1,282 IU) (both $p < 0.05$) than failures. Further, four patients died in the first study and five in the second, three and four with myocardial infarctions, respectively. The investigators concluded that NPPV is a "highly effective technique," but an accompanying editorial advised caution when applying NPPV to patients with acute myocardial infarction (150). In addition, a retrospective survey of the emergency management of acute pulmonary edema (151) found that use of NPPV was associated with a 2-d shorter length of ICU stay than invasive ventilation.

In the only controlled trial yet published comparing CPAP with NPPV (using bilevel positive airway pressure), Mehta and colleagues (152) found that patients treated with NPPV had more rapid reductions in Pa_{CO_2} than did those in the CPAP group. However, the myocardial infarction rate was higher (71% in the NPPV group versus 31% in the CPAP group, $p = 0.05$), leading to premature termination of the study by the investigators. Rates of intubation, morbidity, and mortality were similar between the two groups. More patients in the NPPV groups than in the CPAP group had chest pain upon entry into the study (10 versus four, $p = 0.06$), raising concerns about the adequacy of patient randomization. The investigators concluded that most patients can be managed successfully with CPAP alone, but because it lowers Pa_{CO_2} more rapidly than CPAP, NPPV may have advantages in patients with CO_2 retention on presentation. They also advised caution when using NPPV in patients with acute myocardial infarctions and further evaluation of the hemodynamic effects of NPPV. In a meta-analysis of studies on the noninvasive therapy of acute pulmonary edema, Pang and colleagues (153) came to the same conclusion regarding CPAP, but they considered the evidence on NPPV too scanty to support any conclusions. Thus, pending the publication of more studies comparing CPAP and NPPV, CPAP (10 to 12.5 cm H_2O) should be considered the initial therapy of choice for acute pulmonary edema, with inspiratory pressure added in patients with hypercapnia or persisting dyspnea after initiation of CPAP.

Community-acquired pneumonia. Controlled trials examining the effect of NPPV in acute pneumonia have appeared only recently. Earlier large series included patients with pneumonia, but were unable to establish efficacy of NPPV (125). In fact, the presence of pneumonia has been associated with a poor outcome of NPPV in some studies (154). Recently, however, Confalonieri and colleagues (155) randomized 56 patients with severe community-acquired pneumonia to receive NPPV plus conventional therapy or conventional therapy

alone. Patients treated with NPPV had reduced intubation rates (21 versus 50%, $p < 0.03$) and a shorter duration of ICU stay (1.8 versus 6 d, $p < 0.04$) than did control subjects, although hospital lengths of stay and hospital mortality rates were similar. In addition, a subgroup analysis revealed that significant benefits were attributable only to patients with underlying COPD, who also had lower 2-mo mortality rates if treated initially with NPPV (11 versus 63%, $p = 0.05$). Although these results are promising, routine use of NPPV for community-acquired pneumonia in patients without COPD cannot be advocated until more studies clarify selection criteria and demonstrate benefit in this subgroup.

Hypoxemic Respiratory Failure

Studies on the use of NPPV for patients with hypoxemic respiratory failure (defined as those with a Pa_{O_2}/FI_{O_2} ratio of < 200, respiratory rate > 35/min, and diagnoses including acute pneumonia, acute pulmonary edema, ARDS, and trauma) (125) have yielded conflicting results. In their original study, Meduri and colleagues (114) included four patients with hypoxemic respiratory failure, two with acute pulmonary edema, and two with acute pneumonia. All were treated successfully with NPPV. Subsequently, Wysocki and colleagues (156) found that seven of eight patients in their trial with Pa_{CO_2} values $<$ 45 mm Hg failed NPPV, whereas seven of nine with initial Pa_{CO_2} values > 45 mm Hg were successfully treated. In a follow-up randomized trial on patients with a variety of causes for their acute respiratory failure (157), the same investigators found no benefit of NPPV over conventional therapy among all entered patients. When patients with a $Pa_{CO_2} < 45$ mm Hg (90% of whom required intubation) were excluded in a post hoc analysis, NPPV significantly reduced intubation rate, length of ICU stay, and ICU mortality among the remaining hypercapnic patients. The implication of these findings is that hypoxemic respiratory failure without CO_2 retention responds poorly to NPPV.

However, more recent uncontrolled studies suggest that some patients with hypoxemic respiratory failure may respond favorably to NPPV. Patrick and colleagues (67) reported the successful use of noninvasively administered proportional assist ventilation in eight of 11 patients with de novo respiratory failure who were in need of immediate intubation. These eight patients, four of whom were severely hypoxemic without CO_2 retention, had rapid improvements in dyspnea scores and avoided intubation while the cause of their respiratory failure was treated. In the larger series of Meduri and colleagues (125), 41 of 158 patients had hypoxemic respiratory failure. These patients had multiple causes for their respiratory failure including COPD, pneumonia, ARDS, pulmonary edema, and restrictive lung disease. Despite having average initial Pa_{O_2}/FI_{O_2} ratios of 110 mm Hg, these hypoxemic patients treated with NPPV required intubation in only 34% of cases. In addition, mortality was 22% compared with a predicted mortality (using the APACHE II score) of 40%. Among patients with ARDS, Rocker and colleagues (158) reported that NPPV successfully avoided intubation in six of 12 episodes among 10 patients with an average initial Pa_{O_2}/FI_{O_2} of 102. Beltrame and colleagues (159) examined trauma patients and found rapid improvements in gas exchange and a 72% success rate in 46 patients with respiratory insufficiency treated with NPPV, although those with burns did poorly. Despite the generally promising results, the retrospective and uncontrolled design of the above studies limits any conclusions that can be drawn.

In a recent controlled trial of 64 patients with hypoxemic respiratory failure randomized to receive NPPV or intubation (38), only 31% of the NPPV-treated patients required intubation. Improvements in oxygenation were comparable in the two groups, and NPPV-treated patients had significantly fewer septic complications such as pneumonia or sinusitis (3% versus 31%). In addition, there was a trend toward decreased mortality and length of ICU stay (27 versus 45% and 9 versus 15 d, respectively) in NPPV-treated patients versus control subjects. Another recent randomized controlled trial of 61 patients with various forms of acute respiratory failure found a significantly reduced intubation rate when patients with acute hypoxemic respiratory failure were treated with NPPV as opposed to conventional therapy (7.5 versus 22.6 intubations per 100 ICU d), although mortality rates were not significantly different (160).

In contrast to these favorable results, another controlled trial on NPPV use in the emergency department for acute respiratory failure of diverse etiologies found no reduction in the intubation rate (161). Also, this trial found a trend toward increased mortality in the NPPV-treated group (25% versus none for the control group), thought to be related to an inappropriate delay in the use of endotracheal intubation. This study had small numbers, patients were unevenly distributed in treatment and control groups despite randomization, and APACHE scores tended to be higher in the NPPV group. Nonetheless, this study points out that the use of NPPV may not be successful in all hands; experience may differ from one institution to another. Although evidence on the use of NPPV in patients with hypoxemic respiratory failure is for the most part favorable, further study is needed to establish efficacy and better define ways of identifying which subgroups within this very broad diagnostic category are most likely to benefit.

Immunocompromised Patients

A subcategory of patients that overlaps with the pneumonia and hypoxemic respiratory failure groups and has received considerable attention recently is that of immunocompromised patients. The use of NPPV to avoid endotracheal intubation in immunocompromised patients has considerable appeal because, by assisting ventilation without the need to invade and traumatize the upper airway, it should reduce infectious and hemorrhagic complications. Earlier uncontrolled trials have shown encouraging results. Meduri and colleagues (125) reported a 70% NPPV success rate in 11 patients with AIDS and *Pneumocystis caranii* pneumonia, and Ambrosino and colleagues (162) avoided intubation in two of three patients who developed pneumonia after lung transplantation. One of these patients failed to tolerate a face mask but was successfully managed using a poncho-wrap ventilator. Subsequently, Conti and colleagues (163) used NPPV to avoid intubation in 15 of 16 patients with acute respiratory failure complicating hematologic malignancies, although patients were excluded if they had more than two organ system failures or who were responding poorly to antineoplastic therapy.

More recently, Antonelli and colleagues (164) randomized 40 patients with acute respiratory failure of various etiologies after solid organ transplantation to receive NPPV or standard therapy. Compared with control patients, NPPV-treated patients had a reduced need for intubation and a lower ICU mortality rate (both 20 versus 50%, $p < 0.05$), but total hospital mortality was similar. There was also a trend toward fewer ventilator-associated pneumonias and a significant reduction in the rate of severe sepsis and septic shock among NPPV-treated patients. This reduction in infectious complications among NPPV-treated patients compared with intubated patients was also apparent in two recent prospective surveys (165, 166) that observed roughly a 4-fold reduction in the risk of nosocomial pneumonia, even after controlling for severity of illness. Thus, use of NPPV as first-line therapy for immuno-

compromised patients with acute respiratory failure who are otherwise good candidates is advisable as long as patients are watched closely and intubated without delay if needed.

Other Applications of NPPV in Acute Respiratory Failure

Although controlled data are lacking, anecdotal reports have appeared describing the use of NPPV in a number of other forms of acute respiratory failure. Sturani and colleagues (167) described the successful use of nasal NPPV administered with the BiPAP device (18 cm H_2O inspiratory and 6 cm H_2O expiratory pressures) in five morbidly obese patients (mean BMI, 50 mg/m^2) with severe sleep apnea presenting with confusion or obtundation and an average Pa_{CO_2} of 77 mm Hg. Meduri and colleagues (125) included several patients successfully treated for upper airway obstruction in their study of 158 patients. NPPV has also been described as a means of assisting ventilation during fiberoptic bronchoscopy in immunocompromised patients at high risk of respiratory failure in whom avoidance of intubation is desirable (167a).

Do-Not-Intubate Patients

Several reports have examined responses to NPPV of patients who have declined or are reluctant to undergo intubation. Benhamou and colleagues (121) studied 30 patients, most elderly (mean age, 76 yr) and with COPD, in whom endotracheal intubation was "contraindicated or postponed." Despite severe respiratory failure (mean Pa_{O_2}, 43 mm Hg and Pa_{CO_2}, 75 mm Hg), NPPV was initially successful in 60% of cases. In another uncontrolled series, Meduri and colleagues (168) observed a similar response to NPPV among 26 patients with acute hypercapnic and hypoxemic respiratory failure who refused intubation. In their randomized controlled trial on acute exacerbations in patients with COPD, Bott and colleagues (128) used invasive mechanical ventilation in only one of the nine control patients who died. Thus, the survival advantage they observed among NPPV-treated patients was, in effect, in comparison with do-not-intubate patients. In a follow-up retrospective study on mechanical ventilation in elderly patients, Benhamou and colleagues (169) considered NPPV to be preferable to endotracheal intubation, because short-term prognosis was better and the modality appeared to be more comfortable with fewer complications.

On the basis of these findings, the use of NPPV for patients who are not to receive invasive ventilation is justifiable as long as the patient understands that NPPV is being used as a form of life support, albeit noninvasive, and there is some prospect for reversal of the acute process. One could argue that there is little to lose by using NPPV in almost any terminal patient. In this context, NPPV could be used to lessen dyspnea, preserve patient autonomy, and permit verbal communication with loved ones (167a). However, this application is controversial, with some arguing that this could merely prolong the dying process and lead to inappropriate resource utilization (170).

Postoperative Patients

Some investigators have studied the utility of NPPV in postoperative patients who develop respiratory distress or failure. Pennock and colleagues (116) found that nasal ventilation using the BiPAP device avoided reintubation in 73% of 22 patients who had respiratory deteriorations at least 36 h after various types of surgery. In a follow-up study (171) on a larger number of patients, they found that this success rate was sustained, even when NPPV was administered as a "usual care" procedure rather than as a special research technique. Subsequently, Gust and colleagues (172) found that either CPAP or bilevel ventilation reduces extravascular lung water after cardiac surgery, and Matte and colleagues (173) found that NPPV was more effective than CPAP or chest physiotherapy in improving lung mechanics and oxygenation after coronary artery bypass surgery. Aguilo and colleagues (174) randomized 19 patients to receive nasal ventilation or routine care soon after they were extubated after lung resection. During a 1-h trial, oxygenation was improved in the NPPV group compared with that in the control group, and no adverse side effects were encountered. Also, Joris and colleagues (175) found that use of BiPAP via face mask at inspiratory pressures of 12 cm H_2O and expiratory pressures of 4 cm H_2O significantly reduced the pulmonary dysfunction that follows gastroplasty in comparison with O_2 supplementation alone among morbidly obese patients. These studies demonstrate that NPPV can be used to improve gas exchange and pulmonary function in postoperative patients, but further controlled trials are needed to establish whether this benefit translates into other improved outcomes such as reduced intubation, morbidity or mortality rates, or costs.

Pediatric Applications

Fewer reports of pediatric than of adult applications of NPPV for acute respiratory failure have appeared in the literature, and there have been no controlled trials. Case series of acute pediatric applications of NPPV began appearing in 1993, when Akingbola and colleagues (176) reported the successful use of nasal ventilation in two 12-yr-old boys with atelectasis and pulmonary edema. In a more recent retrospective series, Fortenberry and colleagues (177) described the use of nasal bilevel NPPV in 28 pediatric patients with hypoxemic respiratory failure, ranging in age from 4 mo to 16 yr, most of whom had acute pneumonias. After initiation of NPPV, respiratory rate, Pa_{CO_2} and oxygenation promptly improved, and only three patients required intubation. Padman and colleagues (178) subsequently reported similar results in a prospective series of 34 pediatric patients with respiratory insufficiency that was due to a variety of causes, including both hypoxemic and hypoventilatory, with again only three patients requiring intubation.

These favorable findings are not surprising considering that many patients in these series were older children suffering from conditions previously reported to be successfully managed by NPPV in adults. Concerns have been raised, however, about treating very young children with NPPV because of increased nasal resistance (179) and inability to cooperate (179). Nonetheless, success was reported among the 10 children younger than 5 yr of age in Fortenberry's series of 28 patients. The lack of controlled trials makes it impossible to formulate firm selection guidelines for NPPV in children, although reported success rates appear to be comparable to those in adults, and tentative guidelines have been proposed (180) that are based on those used for adults.

Facilitation of Weaning and Extubation

Udwadia and colleagues (181) were the first to report that patients who could not be weaned from invasive mechanical ventilation were weaned rapidly and entirely from mechanical ventilation after extubation and a brief period of support with NPPV. Most of these patients and those in a subsequent uncontrolled series (182) had tracheostomies, rendering the transition to NPPV safer because invasive ventilation could be easily resumed if patients were tolerant of NPPV. Restrick and colleagues (183), who reported successful application of NPPV in 13 of 14 weaning patients, expanded this experience to patients not only with tracheostomies but also with translaryngeal tubes, some of whom had extubation failure. In a prospective observational study, Gregoretti and colleagues (184) found

that of 22 trauma patients extubated to NPPV before they met standard extubation criteria, 13 (59%) were weaned to spontaneous breathing without requiring reintubation. In another uncontrolled study, Munshi and colleagues (185) examined the economic impact of eliminating routine oxygen supplementation in 451 postextubation trauma patients, 72 of whom became hypoxemic (O_2sat $< 88\%$) within 24 h and were given NPPV instead. Although this approach was successful in avoiding reintubation in 72% of the hypoxemic patients and saved an estimated $50,000, it is unclear how many of the hypoxemic patients would have improved with oxygen therapy alone. Further, the cost calculations did not allow for therapist, nurse, or physician time attributable to the administration of NPPV. In a study examining acute physiologic outcomes, Kilger and colleagues (186) extubated 15 patients with non-COPD causes of acute respiratory insufficiency before they met standard extubation criteria. After extubation, both CPAP (5 cm H_2O) alone and NPPV, using pressure support (15 cm H_2O), improved gas exchange, respiratory rate, shunt faction, and indexes of work of breathing, with a trend toward greater improvements during use of pressure support ventilation.

The above reports raise the possibility that patients with acute respiratory failure who require intubation initially could be successfully extubated and treated with NPPV before they meet standard extubation criteria. Further, the shortened duration of invasive ventilation would be anticipated to lower the occurrence of complications associated with invasive ventilation. Nava and colleagues (39) tested this hypothesis in a recent randomized, controlled trial of 50 patients intubated for acute respiratory failure because of COPD. Patients were randomized to undergo early extubation followed by face mask PSV or to remain intubated and undergo routine weaning when they failed a T-piece weaning trial after 48 h of invasive mechanical ventilation. Patients receiving NPPV had higher overall weaning rates (88 versus 68%), shorter durations of mechanical ventilation (10.2 versus 16.6 d), briefer stays in the intensive care unit (15.1 versus 24 d), and improved 60-d survival rates (92 versus 72%) (NPPV-treated versus controls, all $p < 0.05$). In addition, no NPPV-treated patients had nosocomial pneumonia, compared with seven of the control patients. In a similar trial, Girault and colleagues (187) randomized 33 patients with acute on chronic respiratory failure, mainly because of COPD, to continued intubation or immediate extubation and NPPV after failure of a 2-h T-piece trial. The NPPV group had a shorter duration of endotracheal intubation (4.6 versus 7.7 d, $p = 0.004$); however, weaning guidelines were not well defined, and the total duration of mechanical ventilation was longer in the NPPV group. Further, weaning and mortality rates and ICU and hospital lengths of stay were similar, although there was a trend toward fewer complications in the NPPV group.

These studies support the use of NPPV to expedite extubation in selected patients with COPD after intubation for acute respiratory failure, although the Girault study is less compelling than the Nava study, arguing that, rather than improving outcomes, early extubation shortens the duration of invasive ventilation without worsening outcomes. However, further studies are needed to confirm these promising results, to determine whether patients without COPD may benefit, and to better define patient selection criteria. If this approach is used, patients should be selected carefully with attention to cooperativeness and ability to clear secretions, patients who are difficult to intubate should be excluded, and possible ethical and medicolegal ramifications should be considered.

Another related potential application of NPPV in the weaning process is to avoid reintubation in patients who fail extubation. Epstein and colleagues (188) have observed that such patients have much higher morbidity and mortality rates than do those who are extubated successfully. No randomized controlled trials have yet examined this application of NPPV, but several case series have reported success (117, 125, 183). Meduri and colleagues (125) included 39 patients with postextubation respiratory failure in their series, 65% of whom avoided reintubation. Restrick and colleagues (183) included several cases of premature self-extubation treated successfully with NPPV in their series of 14 patients. Hilbert and colleagues (189) found that 30 patients with COPD and postextubation hypercapnic respiratory insufficiency required reintubation less often (20 versus 67%) and had a shorter intensive care unit length of stay than historically matched control subjects. Jiang and colleagues (190) randomized nonselected extubated patients to receive NPPV or conventional therapy and found a trend for a higher reintubation rate in the NPPV group, suggesting that indiscriminate use of this approach for patients who are likely to do well without ventilatory assistance is fruitless.

The above findings are, for the most part, supportive of the use of NPPV to treat extubation failure, and it is being used routinely for this application at some centers. During the postextubation period, patients with COPD exacerbations, acute pulmonary edema, and possibly increased upper airway resistance because of glottic swelling appear to be good candidates. However, it is important that controlled trials be performed to confirm that NPPV can improve outcomes in this subpopulation of patients with acute respiratory failure, particularly with regard to planned versus unplanned extubations.

Time Demands on Medical Personnel

Although NPPV has significant advantages over invasive PPV for therapy of acute respiratory failure in selected patients, widespread use of the technique will be limited if time demands on medical personnel are excessive. Chevrolet and colleagues (119) first drew attention to this potential drawback, noting that NPPV consumed large amounts of nursing time. However, Bott and colleagues (128) found that nurses rated NPPV as no more demanding to administer than conventional therapy. In addition, several subsequent studies have confirmed that nurses spend no more time at the bedsides of patients receiving NPPV than at the bedsides of control subjects (41, 129, 155). On the other hand, Kramer and colleagues (129) found that, compared with control subjects, NPPV patients tended to require more time from respiratory therapists during the first 8 h of use, an amount that fell significantly during the second 8 h. Nava and colleagues (41) also found that respiratory therapists spent more time during the first 48 h caring for NPPV than for invasively ventilated patients. These findings suggest that NPPV initially requires more time to administer than conventional therapy, for interface fitting and

TABLE 3

PREDICTORS OF SUCCESS DURING ACUTE APPLICATIONS OF NPPV

Younger age
Lower acuity of illness (APACHE score)
Able to cooperate; better neurologic score
Able to coordinate breathing with ventilator
Less air leaking, intact dentition
Hypercarbia, but not too severe ($Pa_{CO_2} > 45$ mm Hg, < 92 mm Hg)
Acidemia, but not too severe (pH < 7.35, > 7.10)
Improvements in gas exchange and heart and respiratory rates within first 2 h

initial ventilator adjustment. The individual spending this time may be a nurse in some countries or a respiratory therapist in others. However, as patients and medical practitioners become familiar with the technique, time demands rapidly diminish and are no greater than for conventional therapy after the initial period.

Selection of Patients for NPPV in the Acute Setting

Determinants of success. Soo Hoo and colleagues (191) retrospectively reviewed their experience with nasal NPPV and found that younger age, lower acuity of illness score (as determined by APACHE or SAPS), presence of teeth (that enhances airtight sealing of the interface), less air leaking through the mouth, and ability to coordinate breathing with the device correlated with successful outcome. These investigators also observed that patients with hypercapnia at baseline fared better than did those with hypoxemia alone and that prompt improvements in gas exchange and reductions in heart and respiratory rates within an hour or two of initiation are reliable indicators of success. Ambrosino and colleagues (154) reported similar predictors of success, and, in addition, found that patients with COPD and superimposed acute pneumonia fared less well than did those without pneumonia. They also noted that Pa_{CO_2} values were lower (79 versus 98 mm Hg) and pH values higher (7.28 versus 7.22) at baseline among successfully treated patients compared with failures. They concluded that NPPV "should be instituted early in every patient before a severe acidosis ensues" (154). As have others (117, 191), Poponick and colleagues (192) observed that early improvements in pH and Pa_{CO_2} (within the first 2 h) were predictive of NPPV success. A synopsis of determinants of success extracted from the above studies is presented in Table 3. Taken together, these studies suggest that initiation of NPPV may be viewed as taking advantage of a "window of opportunity." The window opens when acute respiratory distress occurs and shuts with the development of a severe deterioration necessitating immediate intubation. In this context, it should be emphasized that NPPV is used as a way of preventing intubation, not replacing it.

Selection guidelines. Based partly on the above indicators of success and entry criteria used for enrollment of patients into the many studies, consensus groups have outlined criteria for selecting appropriate patients to receive NPPV for acute respiratory failure (193). As presented in Table 4, the criteria may be seen as utilizing a two-step process. The first step is to identify patients at risk of needing intubation and who stand to benefit from ventilatory assistance. Patients with mild distress who are likely to do well without ventilatory assistance should not be considered. The criteria include clinical indicators of acute respiratory distress, such as moderate to severe dyspnea, tachypnea, accessory muscle use, and paradoxical abdominal breathing. In addition, blood gas criteria are used to identify those with acute or acute superimposed on chronic CO_2 retention. These criteria are most applicable to patients with COPD, but they can be used to screen those with other forms of expiratory failure, although some modifications are advisable. For example, studies on NPPV in acute pulmonary edema and acute hypoxemic respiratory failure have used higher respiratory rates as enrollment criteria ($>$ 30 to 35/min instead of $>$ 24/min), as well as a Pa_{O_2}/FI_{O_2} of $<$ 200 (38, 125, 152, 164).

Having identified patients in need of ventilatory assistance, the second step is to exclude those in whom use of NPPV would be unsafe (Table 4). Patients with frank or imminent respiratory arrest should be promptly intubated, because successful initiation of noninvasive ventilation requires some time for adaptation. Patients who have instability of nonrespiratory organs such as hypotensive shock, uncontrolled upper gastrointestinal bleeding, or life-threatening cardiac ischemia or arrhythmias are better managed with invasive PPV. In addition, those unable to fit a mask, adequately protect their upper airway, clear secretions, or cooperate should be excluded as candidates for NPPV. On the other hand, patients need not be alert to respond successfully. In one report (124), nearly half of patients were initially obtunded or somnolent, yet most were successfully managed with NPPV.

The underlying etiology and potential reversibility of the acute respiratory deterioration are also important considerations in patient selection. As discussed above, the strongest evidence from controlled trials is available only for patients with exacerbations of COPD. Weaker evidence supports the use of NPPV in respiratory failure of numerous other etiologies. These are listed in Table 5. If selection guidelines are observed and there is the potential for reversal of the acute precipitating factors of the respiratory failure within days, use of NPPV for these other etiologies may be justifiable. In this regard, NPPV may be viewed as a "crutch" that assists the patient through a critical interval, allowing time for other therapies such as bronchodilators, steroids, or diuretics to act. More severe, less easily reversed, forms of respiratory failure that will require prolonged periods of ventilatory support such as status asthmaticus requiring controlled hypoventilation, compli-

TABLE 4

SELECTION GUIDELINES: NONINVASIVE VENTILATION FOR PATIENTS WITH COPD AND ACUTE RESPIRATORY FAILURE

Step 1. Identify patients in need of ventilatory assistance:
- A. Symptoms and signs of acute respiratory distress:
  - a. Moderate to severe dyspnea, increased over usual and,
  - b. RR $>$ 24, accessory muscle use, paradoxical breathing
- B. Gas exchange abnormalities:
  - a. $Pa_{CO_2} > 45$ mm Hg, pH < 7.35 or
  - b. $Pa_{O_2}/FI_{O_2} < 200$

Step 2. Exclude those at increased risk with noninvasive ventilation:
- A. Respiratory arrest
- B. Medically unstable (hypotensive shock, uncontrolled cardiac ischemia or arrhythmias)
- C. Unable to protect airway (impaired cough or swallowing mechanism)
- D. Excessive secretions
- E. Agitated or uncooperative
- F. Facial trauma, burns, or surgery, or anatomic abnormalities interfering with mask fit

TABLE 5

TYPES OF ARF TREATED WITH NONINVASIVE VENTILATION

- Diagnosis for ARF
  - Obstructive
    - COPD
    - Asthma
    - Cystic fibrosis
    - Upper airway obstruction
  - Restrictive
    - Chest wall deformity
    - Neuromuscular diseases
    - Obesity hypoventilation
  - Parenchymal
    - AIDS-related pneumonia
    - ARDS
    - Infectious pneumonia
  - Cardiogenic
    - Acute pulmonary edema*

* CPAP currently considered initial ventilatory mode of choice.

cated pneumonias, or ARDS, should be managed using invasive PPV. Marginal patients might be considered for a trial of NPPV, but they should be watched closely for further deterioration so that needed intubation is not unduly delayed. It should be recalled that these recommendations are based on consensus opinion (193), they have not been validated in prospective studies, and clinical judgment should be exercised when applying them.

NONINVASIVE VENTILATION FOR CHRONIC RESPIRATORY FAILURE

Decades of experience during the polio epidemics (194, 195) and subsequently (14, 15) established that long-term nocturnal noninvasive ventilation stabilizes gas exchange and improves symptoms in patients with chronic respiratory failure. These beneficial effects can be achieved with the use of individual noninvasive ventilators or combinations of ventilators. For home mechanical ventilation, noninvasive ventilation has a number of advantages over invasive mechanical ventilation, including greater ease of administration, reduced need for skilled caregivers, elimination of tracheostomy-related complications, enhanced patient comfort, and lower cost (37). However, as is the case in the acute setting, not all patients with chronic respiratory failure are good candidates for noninvasive ventilation. The following discusses evidence for efficacy of noninvasive ventilation in chronic respiratory failure and patient selection guidelines to optimize the likelihood of success.

Evidence for Efficacy

"Body" Ventilators

Restrictive thoracic diseases. Numerous uncontrolled studies have examined the efficacy of body ventilators in patients with restrictive thoracic diseases, i.e., neuromuscular diseases and chest wall deformities. Many of the studies have included patients with either diagnosis, so both are considered in this section. Negative pressure ventilation was the mainstay of ventilatory support during the polio epidemics (5, 194, 195) and, more recently, has been used to provide intermittent ventilatory assistance to patients with symptomatic chronic respiratory failure caused by slowly progressive neuromuscular diseases, chest wall deformities, or central hypoventilation. Garay and colleagues (14) observed sustained reversal of abnormal gas exchange, cor pulmonale, and symptoms of CO_2 narcosis in four patients with neuromuscular disease and four with kyphoscoliosis treated with nocturnal negative pressure ventilation for as long as 10 yr. Curran and Colbert (15) reported similar findings in nine patients with DMD treated nocturnally with tank or cuirass respirators. Average daytime Pa_{CO_2} values fell from 60.8 to 45.5 mm Hg, and the improvement was sustained for as long as 4 yr. Splaingard and colleagues (196) reported 20 yr of experience in 40 patients with chronic respiratory failure caused by a variety of neuromuscular diseases, including muscular dystrophy (55%), spinal cord lesions (15%), spinal muscular atrophy (13%), and miscellaneous (17%). All patients experienced reductions in Pa_{CO_2} and were discharged home. Five- and 10-yr survivals were 76 and 61%, respectively. Goldstein and colleagues (197) subsequently reported that nocturnal negative pressure ventilation prevented alveolar hypoventilation during sleep in patients with neuromuscular disease or chest wall deformity. Although upper airway obstructions still occurred, particularly during REM sleep, these were easily managed using tricyclic medication or nasal CPAP. Nocturnal negative pressure ventilation has also been reported to be effective in reversing hypoventilation in patients with a variety of other neuromuscular diseases, including acid maltase deficiency (198).

Long-term follow-up studies of patients with DMD and postpolio syndrome treated with body ventilators (199, 200), have demonstrated that although the underlying illness steadily progresses, survival rates are favorable. Among patients treated mainly with negative pressure ventilators, Curran and Colbert (200) reported no deaths in six patients with postpolio syndrome followed for 56 mo, and six deaths among 23 patients with DMD followed for an average of 6.3 yr after the onset of respiratory failure. The underlying disease continued to progress in these latter patients, however, with a need to add 0.95 h of ventilatory assistance/24 h/yr to maintain ventilatory stability as pulmonary function gradually deteriorated.

The rocking bed may also be effective in supporting ventilation in patients with neuromuscular disease, particularly those with weakened or paralyzed diaphragms (81). These patients are severely dyspneic in the supine position, have great difficulty sleeping, necessitating the use of recliners, and frequently complain of restless sleep. The rocking bed facilitates sleep and prevents nocturnal hypoventilation in these patients. Abd and colleagues (82) used the rocking bed to assist ventilation in 10 patients who developed bilateral diaphragm paralysis after open heart surgery. They were supported nocturnally until diaphragm function returned, between 4 and 27 mo later. The rocking bed may also be effective in other neuromuscular diseases characterized by diaphragm involvement, as long as body habitus remains relatively normal. Chalmers and colleagues (201) used the rocking bed to assist ventilation in 53 patients, most with postpolio ventilatory insufficiency, but some with muscular dystrophies, motor neuron disease, or acid maltase deficiency. The vast majority had diaphragm weakness, and some had bulbar dysfunction. These investigators reported a drop in daytime Pa_{CO_2} after initiation of nocturnal rocking bed use, and 43 of the patients were treated successfully at home for an average of 16 yr. Others (202) have noted improvements in sleep quality during rocking bed use among neuromuscular patients.

The pneumobelt is used mainly as a daytime ventilatory aid that frees the hands and face in patients with severe respiratory muscle weakness who use other ventilators at night (12). It has also been used as the sole means of respiratory support in occasional patients with muscular dystrophies or quadriplegia caused by high cord lesions who can sleep while sitting (81, 203, 204). Like the rocking bed, it is particularly useful in patients with diaphragm dysfunction. In recent years, it has seen less use but is still applied as a daytime aid in some patients with high cervical cord lesions who use either invasive or noninvasive positive pressure ventilation at night (205).

Among studies examining the use of body ventilators in patients with chest wall deformities, Weirs and colleagues (206) described four patients with respiratory failure caused by severe kyphoscoliosis, three because of poliomyelitis. These patients were successfully treated for as long as 10 yr using cuirass ventilation, but because of their distorted anatomy, custom-fitted cuirasses were necessary. Subsequently, Kinnear and colleagues (207) evaluated the acute physiologic effects of cuirass ventilation in 25 patients with chest wall deformities, including kyphoscoliosis and thoracoplasty. Vital capacity was consistently augmented in proportion to the negative pressure, with wrap ventilators performing slightly more efficiently than cuirasses. Cardiac output was unaffected, and Pa_{CO_2} was reduced by 5 mm Hg, an effect that was sustained for at least a year by intermittent negative pressure ventilation, as established in a subsequent follow-up study (208).

Although no controlled trials have ever been performed,

these studies strongly support the contention that nocturnal noninvasive ventilatory assistance using body ventilators effectively reverses hypoventilation and ameliorates symptoms in chronic respiratory failure caused by a wide variety of restrictive thoracic diseases, including neuromuscular and chest wall disorders. In addition, noninvasive ventilation using body ventilators appears to prolong life in patients with restrictive thoracic processes, as evidenced by studies such as that by Curran and Colbert (200). Survival in this study averaged 6 yr and ranged to as long as 12 yr beyond the onset of respiratory failure in patients with DMD. Nonetheless, use of body ventilators to treat these conditions has largely been supplanted by NPPV for reasons discussed below.

Chronic obstructive lung diseases. The most controversial application of negative pressure ventilation has been its use in resting respiratory muscles in patients with severe stable COPD. The beneficial effect of negative pressure ventilation on gas exchange in patients with COPD was first investigated in 1951 (209). McClement and colleagues (210) subsequently reviewed the potential mechanisms for this benefit, including improved ventilation/perfusion relationships, reduced oxygen consumption, and mobilization of secretions. During the early 1980s, the theory that respiratory muscles are chronically fatigued and will benefit from intermittent rest was proposed (211, 212). Braun and Marino (213) treated 16 patients with severe COPD with wrap negative pressure ventilation for 5 h daily for 5 mo and observed improvements in vital capacity, maximal inspiratory and expiratory pressures, and daytime Pa_{CO_2} during spontaneous breathing. Although these results were interpreted as supporting the "muscle resting" hypothesis, controls were lacking, and other aspects of rehabilitation or passage of time alone could have been responsible for the improvements.

Three subsequent controlled studies yielded similar favorable findings (214–216). These studies documented respiratory muscle rest by showing significant reductions in the diaphragmatic EMG signal. After daily 3- to 6-h rest periods for 3 to 7 d, maximal inspiratory and expiratory pressure and daytime Pa_{CO_2} improved. In addition, one uncontrolled trial (217) that provided 8 h of wrap ventilation once weekly for 4 m to patients with severe COPD observed the same benefits as the other studies as well as significant improvements in the 12-min walking distance. Notably, initial Pa_{CO_2} values in these favorable studies using negative pressure ventilation for severe, stable COPD were quite elevated, averaging approximately 57 mm Hg.

Despite these early promising results, later longer-term controlled trials failed to substantiate the earlier findings. Celli and colleagues (218) studied 16 inpatients randomized to receive daily wrap ventilation plus rehabilitation or rehabilitation alone for 3 wk. Equivalent improvements were noted in cycling endurance in both groups, but no difference between groups was apparent. In a 3- to 6-mo crossover trial comparing wrap ventilation with standard therapy, Zibrak and colleagues (219) found no improvements in pulmonary function, respiratory muscle strength, blood gas determinations, or treadmill endurance time. In addition, patients tolerated the wrap ventilator poorly, with 11 of 20 patients withdrawing because of ventilator intolerance. Even those who completed the trial used the ventilators for less time than recommended, and no patient was able to sleep using the device.

Levine and colleagues (220) used 4-h daily wrap ventilation in patients with severe COPD for 4 wk. Although maximum sustainable ventilation improved slightly, no other improvements were noted, patients had marked worsening of dyspnea after ventilator use, and the investigators surmised that negative pressure ventilation lacked efficacy as a therapy for COPD. In the largest trial (221), 184 patients were randomly assigned to wrap or sham ventilation. Despite at least a 50% reduction in the diaphragmatic EMG signal to document respiratory muscle rest during ventilator use, no improvements in gas exchange, muscle function, or exercise capacity were detected after 3 mo of daily use for 4 to 5 h. As in the Zibrak study, wrap ventilators were poorly tolerated, with patients dropping out or using the ventilator for less time than recommended.

Notably, baseline Pa_{CO_2} values among these latter unfavorable trials was approximately 47 mm Hg, substantially lower than in the favorable studies. This raises the possibility that respiratory muscles in patients with severe CO_2 retention are more likely to benefit from intermittent negative pressure ventilation than are patients with little or no CO_2 retention,

TABLE 6

STUDIES ON THE USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION IN CHRONIC RESPIRATORY FAILURE*

						Arterial Blood Gas Determinations				
						Baseline		After Trial		
Author	Yr	Reference No.	Type of Masks/ Ventilator	Diagnosis RTD†	Symptom Relief	P_{CO_2}	P_{O_2}	P_{CO_2}	P_{O_2}	Duration (*mo*)
Kerby	1987	27	Nasal/Vol	5	Yes	58.8	63.0	44.3	77.8	> 3
Bach	1987	26	Nasal/Vol	5	Yes					
Ellis	1987	28	Nasal/Vol	5	Yes	70.0	61.0	46.0	83	3–12
Carroll	1988	224	Nasal/Vol	6	Yes	61.5	45.8	51.0	60.8	3–18
Leger	1989	225	Nasal/Vol	29 (5)	Yes	52.3	58.0	41.0	71.0	12
Bach	1990	226	Nasal/Vol	52	Yes	68.0†	46.0†			19.8
Heckmatt	1990	227	Nasal/Vol	14 (4)	Yes	61.5	50.3			18
Gay	1991	228	Nasal/Vol	22 (4)	Yes	64.0	52.0	51.0	68	5.8
Goldstein	1991	229	Nasal/Vol	6	Yes	60.3	43.5	51.6	54.2	14
Mean						61.7	53.5	47.7	69.8	
Total				144 (13)						
Percentage success				92						

Definition of abbreviations: RTD = restrictive thoracic disease; Vol = volume ventilator.

* From Meyer TJ, Hill NS. Noninvasive positive pressure ventilation to treat respiratory failure. *Ann Intern Med* 1994;120:760–770; with permission.

† Number of patients (number of failures).

‡ End-tidal Pa_{CO_2} data from 10 patients studied overnight.

perhaps because of relief of the unfavorable effect of hypercarbia on respiratory muscle function (222). The muscle resting hypothesis is in doubt, however, because patients with minimal or no CO_2 retention derive little benefit from muscle resting despite severe mechanical dysfunction. Consistent with this view, Similowski and colleagues (223) demonstrated that when corrected for shortened length, the diaphragm is no weaker in patients with severe COPD than in normal subjects, suggesting that chronic fatigue is not an important factor in respiratory muscle dysfunction, at least in normocapnic resting patients.

In summary, intermittent daytime negative pressure ventilation does not substantially improve respiratory muscle function in patients with severe COPD with minimal or no CO_2 retention. Although some evidence suggests that short-term rest periods may improve respiratory muscle function in patients with severe CO_2 retention, poor patient tolerance of the ventilators greatly limits clinical utility. Although some uncontrolled series have reported favorable outcomes after long-term use of intermittent negative pressure ventilation in severe COPD, controlled trials have failed to confirm these findings, and this application of noninvasive ventilation cannot be recommended.

Noninvasive Positive Pressure Ventilation

Restrictive thoracic diseases. Noninvasive positive pressure ventilation has been available for the therapy of restrictive thoracic diseases for decades. Bach and colleagues (46) summarized their decades-long experience with 257 patients with chronic respiratory failure, mainly with neuromuscular diseases, who were treated with mouthpiece NPPV for an average of 9.6 yr. These patients could swallow and talk, but they were otherwise severely compromised. One hundred forty-four of these patients required 20 to 24 h of ventilatory support daily and had vital capacities of only 10.5% predicted. Nonetheless, 67 were successfully switched from tracheostomies to NPPV, and only 38 died during the follow-up interval, which covered 37 yr. Although the study was uncontrolled, the investigators concluded that mouthpiece NPPV prolonged survival and enhanced convenience and communication in these severely compromised patients.

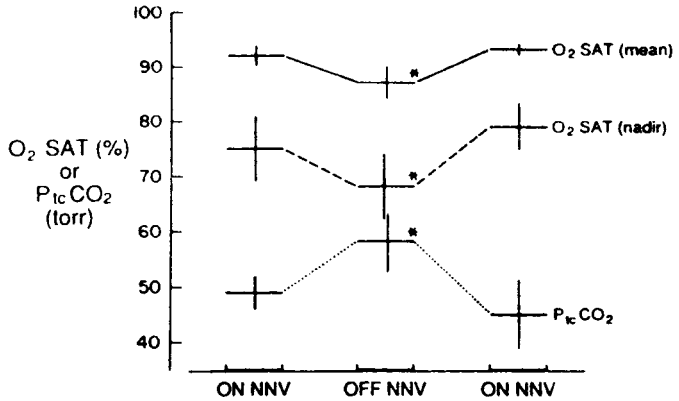

Figure 3. Effect of withdrawal of nocturnal nasal ventilation (NNV) on mean and nadir O_2 saturations and mean $P_{TC_{CO_2}}$ levels obtained during nocturnal monitoring. Values on the *left* labeled "on NNV" were obtained during NNV use on the night prior to NNV withdrawal, values in the middle were obtained on the last night of the NNV withdrawal period, and values on the *right* labeled "on NNV" were obtained a week after NNV was resumed. Data are mean ± SE. *Asterisk* indicates $p < 0.05$ compared with "on NNV" values ($n = 6$). From Reference 224, with permission.

Effects on gas exchange and symptoms. Since nasal ventilation was first proposed as a way to slow the progression of respiratory muscle weakness in patients with muscular dystrophy (25), numerous studies on the efficacy of nasal NPPV in various neuromuscular and chest wall diseases have been published (26–28, 71, 224–229) (Table 6). The first case series appeared in 1987 (26–28), showing improvements in daytime gas exchange and symptoms of fatigue, daytime hypersomnolence and morning headaches after a few weeks of nocturnal nasal ventilation in small groups of patients with respiratory failure caused mainly by neuromuscular diseases. In addition, NPPV eliminated the intermittent obstructive apneas and severe oxygen desaturations that occur during negative pressure ventilation, particularly during REM sleep (28). Soon thereafter, Ellis and colleagues (71) reported that nasal NPPV reversed chronic hypoventilation in five patients with severe kyphoscoliosis who had failed to improve with nasal CPAP alone.

Subsequent studies have consistently supported these initial favorable findings, extending the findings to patients with respiratory failure caused by a wide variety of restrictive thoracic disorders. Although Bach and Alba (226) noted improved tolerance of nasal compared with mouthpiece ventilation in some patients, no studies have directly compared nasal and mouthpiece NPPV. Either may be effective, even in patients with minimal pulmonary reserve, and both may be used in the same patient; nasal ventilation during sleep at night, for example, with mouthpiece ventilation used as needed during the daytime (45, 46).

Withdrawal studies: effects on nocturnal gas exchange and sleep. Although the uncontrolled case series listed in Table 6 are uniform in showing favorable responses of patients with chronic respiratory failure to nocturnal NPPV, firm proof of efficacy from randomized, controlled trials is lacking. Investigators have been stymied in performing such trials by the ethical concern that randomly withholding what is almost certainly effective therapy from patients in respiratory failure could cause morbidity or even mortality. Alternatively, investigators have evaluated efficacy using temporary withdrawal of nocturnal nasal NPPV from long-term users with restrictive thoracic diseases who had been improved by prior ventilator use (230, 231). The investigators hypothesized that if NPPV is efficacious, then temporary NPPV withdrawal would lead to clinical deterioration that would reverse with resumption. The hypothesis was confirmed; withdrawal caused a deterioration of nocturnal oxygenation and ventilation (Figure 3) as well as sleep quality, and symptoms of hypersomnolence and morning

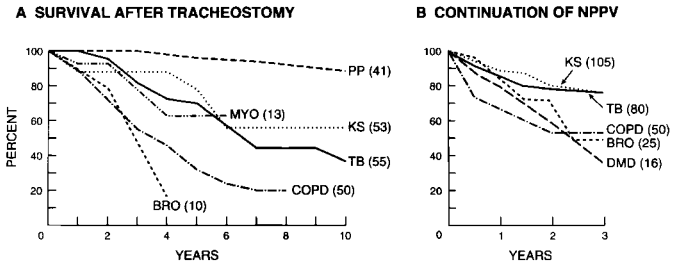

Figure 4. (*A*) Survival after tracheostomy in 222 patients with chronic respiratory failure of various etiologies followed for as long as 10 yr (redrawn from Reference 239 with permission). (*B*) Likelihood of continuing noninvasive positive pressure ventilation (NPPV) in 276 patients with chronic respiratory failure followed for as long as 3 yr (redrawn from Reference 236, with permission). BRO = bronchiectasis; COPD = chronic obstructive pulmonary disease; DMD = Duchenne muscular dystrophy; KS = kyphoscoliosis; MYO = myopathy; PP = postpolio syndrome; TB = history of tuberculosis.

headache recurred. All of these changes were promptly reversed upon resumption of NPPV.

These observations in combination with the favorable findings from uncontrolled studies lend strong support to the notion that NPPV is effective in treating certain forms of chronic respiratory failure. Consensus conferences (193, 232) agree that the evidence is sufficiently strong to consider NPPV the ventilatory mode of first choice in patients with chronic respiratory failure caused by restrictive thoracic diseases who can adequately protect their upper airway.

Effects on quality of life. Studies that have examined quality of life among patients with restrictive thoracic diseases using NPPV have found high levels of satisfaction. Bach (233) surveyed NPPV users who had switched from tracheostomy positive pressure ventilation. NPPV was rated as preferable to ventilation via a tracheostomy with regard to comfort, convenience, portability, and overall acceptability, but tracheostomy received higher scores for quality of sleep and providing a sense of security. The vast majority of these patients preferred NPPV. Another survey of 35 ventilator users, 29 using NPPV and six using tracheostomies, found satisfactory levels of psychosocial functioning and mental well-being as determined by standard questionnaires (234). The ratings compared favorably to those of a general population, and NPPV and tracheostomy ventilation received similar scores. In a survey of 75 ventilator users with amyotrophic lateral sclerosis, all 25 NPPV users were satisfied with their quality of life, compared with only 72% of 50 tracheostomy patients (235).

Effect on hospital days and survival. In their long-term follow-up study, Leger and colleagues (236) observed significant reductions in hospital days/patient/year from 34, 31, and 18 d for the year before starting NPPV to 6, 10, and 7 d for the year after for kyphoscoliosis, sequelae of tuberculosis and DMD, respectively. These findings suggest that NPPV may be useful to conserve health care resource utilization in these patients, with the potential for substantial cost savings.

Randomized trials that demonstrate a survival benefit of NPPV in patients with respiratory failure caused by restrictive thoracic diseases are lacking. Nonetheless, long-term follow-up series provide strong evidence that survival is prolonged in comparison with unventilated patients. In a small, uncontrolled series, Vianello and colleagues (237) found that five patients with end-stage DMD who accepted treatment with nasal NPPV were alive after 2 yr, whereas four of five similar patients who declined therapy had died. In addition, follow-up studies from France (236) and England (238) have reported on several hundred patients with chronic respiratory failure of various etiologies treated with nasal NPPV for periods as long as 5 yr (Figure 4). Rather than survival rates, these studies used the rate for continuation of NPPV, thought to correspond closely to survival for most diagnoses.

The studies found very favorable continuation rates for postpolio patients and those with kyphoscoliosis (approximately 100 and 80%, respectively, after 5 yr). Patients with sequelae of old tuberculosis had higher continuation rates in the British study compared with the French study (94 versus 60%, respectively), perhaps reflecting the greater morbidity of the French patients at the time of enrollment. Also, patients with DMD in the French study had lower continuation rates (47%) than did those with other neuromuscular diseases, with 28% undergoing tracheostomy and the remaining 25% dying. This was thought to reflect the more progressive nature of DMD than, for example, postpolio syndrome, and the difficulties patients with DMD have with airway protection once the cough mechanism has become severely impaired (236). Overall, the continuation rates from these long-term follow-up studies compare favorably with those observed for similar patients treated with invasive mechanical ventilation reported earlier by the French group (239) (Figure 4). A more recent study (240) from the English group found much better survival rates for patients with DMD than those previously reported by the French group; 85% for 1 yr and 73% for 5 yr. The disparity may reflect differences in the severity of illness when patients began NPPV, how cough impairment was managed, or practices with regard to switching to tracheostomy. Nevertheless, there can be little doubt that survival is prolonged by NPPV in a disease, which is characterized by death soon after the onset of respiratory failure in untreated patients.

Survival has also been examined in patients with amyotrophic lateral sclerosis (ALS). In a prospective but nonrandomized trial, Pinto and colleagues (241) treated the first 10 patients with medical therapy alone and the next 10 with NPPV. After 2 yr, 50% of the NPPV patients were alive, whereas all of the medical therapy patients had died. More recently, Aboussouan and colleagues (242) compared the survival of 31 patients with ALS who continued NPPV with that of 21 patients who were intolerant and discontinued NPPV. Those who were intolerant of NPPV had a significantly greater risk of dying during the 3-yr study period than did those who continued use (relative risk, 3.1). As might be anticipated, patients with bulbar involvement were more likely to be intolerant of NPPV, but even these patients had a survival advantage if they were able to tolerate NPPV. Although uncontrolled, these studies strongly suggest that in comparison with no ventilatory assistance, NPPV effectively supports ventilation and prolongs survival in patients with respiratory insufficiency caused by ALS. On the other hand, Cazzolli and Oppenheimer (235) found that after 5 yr of follow-up, only eight of 25 (32%) patients with ALS receiving NPPV were alive compared with 27 of 50 (54%) tracheostomy users. This finding raises the concern that NPPV may be less effective at prolonging survival than is tracheostomy ventilation among patients with neuromuscular diseases such as ALS that impair bulbar function.

Prophylactic use of NPPV. The use of NPPV to treat chronic respiratory failure caused by restrictive thoracic diseases has gained wide acceptance, but the optimal time for initiation has not been established. Some investigators have proposed that prophylactic initiation in progressive neuromuscular diseases, prior to the onset of symptoms or daytime hypoventilation, would retard the progression of respiratory dysfunction (25). Raphael and colleagues (243) tested this hypothesis in 76 patients with DMD who had not yet developed symptoms or daytime hypoventilation, randomizing them to receive nasal NPPV or standard therapy. Not only did treated patients have no slowing of disease progression but also, mortality was greater in the NPPV group, leading to premature termination of the trial. The investigators surmised that NPPV gave patients a false sense of security that caused them to excessively delay seeking medical attention when they developed respiratory infections, leading to secretion retention and death.

Shortcomings of the study, including failure to document patient compliance with the device or to use techniques to assist cough and an excess of patients with severe cardiac dysfunction in the NPPV group, raise doubts about the significance of the mortality findings. However, the study offered no evidence to suggest that prophylactic initiation of NPPV is beneficial. Presently, awaiting the onset of symptoms and daytime or nocturnal hypoventilation prior to initiation of NPPV is the most pragmatic approach since compliance with the therapy is often poor unless patients are motivated by the desire for symptom relief. Symptomatic patients who have

only nocturnal but no daytime hypoventilation as evidenced by frequent, sustained nocturnal oxygen desaturations, are also candidates for initiation. Masa and colleagues (244) showed improvements in dyspnea scores, morning headache, and confusion after 2 wk of nocturnal noninvasive ventilation in 21 such patients, whose proportion of sleep time with oxygen saturations < 90% averaged 40 to 50% while breathing room air before initiation and fell to 6% afterwards. Nineteen of these patients chose to continue NPPV therapy after completion of the trial.

Central hypoventilation and obstructive sleep apnea. The first case reports describing the use of nasal ventilation for chronic respiratory failure were in young children with central hypoventilation who had resolution of gas exchange abnormalities and symptoms after initiation of therapy (245, 246). Although no controlled studies have examined this application, enough anecdotal evidence has accrued so that consensus groups now consider therapy of central hypoventilation as appropriate for NPPV (193, 232). With regard to obstructive sleep apnea, nasal CPAP is considered the therapy of first choice. However, NPPV may be successful in improving daytime gas exchange and symptoms in patients with obstructive sleep apnea who continue to hypoventilate after use of nasal CPAP alone (247). Among 13 patients with severe obstructive sleep apnea whose hypercapnia (average Pa_{CO_2} 62 mm Hg) was unresponsive to CPAP, NPPV, using volume-limited ventilators, lowered Pa_{CO_2} to 46 mm Hg, and nine of the patients eventually stabilized receiving CPAP alone (247). In addition, bilevel ventilation has been used in some patients with obstructive sleep apnea to reduce discomfort and improve compliance by virtue of the reduction in positive pressure during expiration (248). However, Reeves-Hoche and colleagues (249) were unable to demonstrate improved compliance rates in patients with obstructive sleep apnea treated with bilevel ventilation compared with those receiving CPAP alone. Hence, use of NPPV for obstructive apnea should be reserved for those patients who have persisting hypoventilation despite adequate CPAP therapy to eliminate the obstructive component.

Obstructive lung diseases: COPD. In contrast to the consistently favorable results of studies on the use of NPPV in patients with chronic respiratory failure caused by restrictive thoracic or central hypoventilatory diseases, those on patients with severe obstructive lung diseases have yielded conflicting results. As discussed previously, patients with COPD tolerate negative pressure ventilation poorly. Investigators posited that with its convenience and portability advantages over negative pressure ventilation, NPPV would be better tolerated. In addition, patients with COPD have more frequent nocturnal oxygen desaturations than do normal persons, related to episodic hypoventilation, particularly during REM sleep (250–253). These desaturations are associated with arousals that shorten the duration and diminish the quality of sleep, an effect that is reversed by oxygen supplementation, at least in "blue and bloated" patients (252). Furthermore, patients with COPD have a 32% drop in inspiratory flow rate during REM sleep associated with a reduced tidal volume (254). By assisting ventilation, NPPV offers the potential of restoring inspiratory flow rate, eliminating episodes of hypoventilation, and improving nocturnal gas exchange, as well as the duration and quality of sleep. Initial support for these hypotheses came from promising results on the use of nasal NPPV in severe stable COPD derived from uncontrolled trials (255, 256) that observed improved daytime and nocturnal gas exchange and sleep efficiency in small groups of patients treated with nocturnal NPPV for 6 mo.

Subsequently, in a 3-mo crossover trial, Strumpf and colleagues (257) found improvement only in neuropsychologic function, but not in nocturnal or daytime gas exchange, sleep quality, pulmonary functions, exercise tolerance, or symptoms. This study also encountered a high dropout rate, with seven patients withdrawing because of mask intolerance, and only seven of 19 entered patients actually completing the trial. In contrast, in a study of nearly identical design, Meecham-Jones and colleagues (258) enrolled 18 patients with severe COPD, 14 of whom completed the study. Nocturnal and daytime gas exchange, total sleep time, and symptoms improved during NPPV use. These salutary effects of NPPV on sleep duration in patients with severe stable COPD were also observed in a more recent crossover trial on six patients with initial Pa_{CO_2} values of 58 mm Hg (259). In this brief study that monitored sleep on nights with and without NPPV, total sleep time and sleep efficiency were improved by NPPV, but sleep architecture and nocturnal gas exchange were unaffected.

Some insight into the explanation for the contradictory results of these studies may be gained by examining baseline characteristics of patients entering the similarly designed Strumpf and Meecham-Jones studies (Table 7). Despite less severe airway obstruction than patients in the Strumpf study (FEV_1 0.81 L versus 0.54 L), those in the Meecham-Jones study had greater hypercarbia (Pa_{CO_2}, 57 mm Hg versus 47 mm Hg), more frequent hypopneas, and more severe nocturnal oxygen desaturations. This suggests that different subsets of patients with COPD were entered into the respective studies and that those with greater CO_2 retention and more nocturnal oxygen desaturations may be more likely to benefit from NPPV. In addition, patients in the Meecham-Jones study used a patient-triggered ventilator mode and initiated NPPV during a brief inpatient stay, whereas those in the Strumpf study used a timed ventilator mode and were begun as outpatients. These observations raise the possibilities that the better outcomes in the Meecham-Jones study may have reflected enhanced patient-ventilator synchrony or inpatient acclimatization.

Unfortunately, two subsequent controlled trials have failed to substantiate the hypothesis that CO_2 retention predicts NPPV success in patients with severe COPD, despite attempts to enroll hypercapnic subjects. Gay and colleagues (260) screened 32 hypercapnic patients with severe COPD seen at the Mayo Clinic. After exclusion of patients with obstructive sleep apnea, another terminal illness, or spontaneous improvement in CO_2 retention during a run-in period, only 13 candidates remained to be randomized to receive NPPV or sham ventilation. Of the seven patients who received NPPV, only four

TABLE 7

COMPARISON OF 3-mo CROSSOVER TRIALS TESTING NPPV FOR SEVERE STABLE COPD

Baseline Data	Strumpf (Reference 257)	Meecham-Jones (Reference 258)
Patients, n	19	18
Number completed	7	14
FEV_1, L/s	0.54	0.82
Pa_{CO_2}, mm Hg	46	56
Hypopneas/h	< 5	10
Outcomes on NPPV		
Pa_{CO_2}, mm Hg	50	53†
Total sleep time, h (baseline-NPPV)*	3.2–3.8	3.2–5.7†
Quality of life	No change	Better†
Neuropsychological testing	Better†	Not tested

* Number in parentheses is baseline total sleep time
† Indicates $p < 0.05$ compared with baseline.

completed a 3-mo trial, whereas six of six "sham" patients completed the trial. Despite a mean initial Pa_{CO_2} of 55 mm Hg in the ventilated group, no significant improvements were noted in gas exchange, sleep quality, or walking endurance, and only one ventilated patient had a substantial reduction in Pa_{CO_2} (50 to 42 mm Hg). More recently, Lin (261) performed an 8-wk crossover trial consisting of consecutive, randomized 2-wk periods of no therapy, O_2 alone, NPPV alone, and NPPV combined with O_2. Among 12 patients with a mean initial Pa_{CO_2} of 50.5 mm Hg, NPPV conferred no added benefit over O_2 alone with regard to oxygenation, ventricular function, or sleep quality. In addition, NPPV reduced sleep efficiency and total sleep time. The investigators concluded that NPPV has nothing to offer over O_2 alone in patients with severe COPD. This and the Gay study used inspiratory pressures of 12 and 10 cm H_2O, respectively, that may have provided insufficient ventilatory assistance. In addition, the 2-wk trial periods used in the Lin study (261) may have been too brief to permit adequate adaptation to NPPV.

Despite their limitations, these studies highlight the difficulty in demonstrating benefit of noninvasive ventilation for severe COPD. Studies have lacked statistical power, and even in those with favorable results, benefit has been shown only for physiologic variables such as respiratory muscle strength and Pa_{CO_2}, or total sleep time and symptoms, but not for functional status, resource utilization, morbidity, or mortality. In addition, the two large follow-up studies on noninvasive ventilation (236, 238) found that patients with COPD had substantially lower continuation rates than did patients with neuromuscular or chest wall disorders (Figure 4). This suggests that patients with COPD are less tolerant or benefit less from NPPV than do most neuromuscular patients, a view that is widely held (193). Confirmatory findings were recently reported by Criner and colleagues (262), who initiated NPPV in 20 patients each with neuromuscular disease and COPD during a several-week stay in a specialized ventilator unit. Despite these optimal conditions, only 50% of patients with COPD as compared with 80% of those with neuromuscular disease were still using NPPV after 6 mo.

Further, no study as of yet has provided convincing evidence that survival in COPD is prolonged by NPPV. The continuation curve for patients with COPD in the English follow-up study (238) was virtually identical to that for survival in patients with COPD using oxygen supplementation in the Nocturnal Oxygen Therapy Trial (263), suggesting that any survival benefit of NPPV over that of O_2 therapy alone is minimal. Preliminary results from two large, multicenter trials on NPPV in severe, stable hypercapnic COPD being performed in Europe (264, 265) show no overall survival benefit in patients receiving NPPV compared with O_2 alone, although one of the studies suggests that patients older than 65 yr of age may have a slight improvement in survival (264). Also, a recent uncontrolled trial of 26 severely hypercapnic patients with COPD who had worsening hypercapnia with O_2 therapy alone observed a 5-yr survival rate of 68% in patients treated with NPPV, better than the survival rate in unventilated historically matched control subjects (266).

Overall, the results of long-term trials testing the efficacy of NPPV in severe, stable COPD have been disappointing, and this application remains controversial (267). However, it should be acknowledged that one randomized trial has yielded favorable findings, and several small uncontrolled series show promise among the patients with marked CO_2 retention (255, 256, 258, 266). The conflicting results highlight the need for more studies with greater statistical power testing more than just physiologic or sleep-related outcome variables. For instance, the long-term follow-up study by Leger and colleagues (236) found not only a sustained reduction in Pa_{CO_2} in patients with severe COPD but also a significant drop in hospital days, from 49 for the year before to 17 for the year after starting NPPV. A similar finding was recently reported in an uncontrolled trial of 15 severely hypercapnic patients with COPD whose hospital days dropped from 16 for the year before to 7 for the year after initiating NPPV (268). These latter studies indicate that the effect of NPPV on lowering health resource utilization in severe COPD deserves examination.

Another potential application of NPPV in patients with severe, stable COPD is to serve as an adjunct to exercise training in pulmonary rehabilitation programs. By unloading the inspiratory muscles, CPAP and PSV singly and in combination increase exercise capacity in patients with severe COPD (269, 270). Bianchi and colleagues (271) showed that, compared with CPAP or PSV, PAV brought about the greatest improvement in cycling endurance and reduction in dyspnea in 15 stable hypercapnic patients with COPD. This enhanced exercise capacity during ventilator use has not yet been shown to translate into a greater training effect or functional improvement during spontaneous breathing. It is also conceivable that if sufficiently portable PSV or PAV ventilators can be developed, patients with severe COPD will be able to use portable assisted ventilation to augment their performance of daily activities, much like portable O_2 is used today.

Obstructive lung diseases: cystic fibrosis and diffuse bronchiectasis. Small case series (272, 273) have reported improvement and stabilization of gas exchange abnormalities for periods as long as 15 mo in patients with end-stage cystic fibrosis awaiting lung transplantation. These patients had begun NPPV after they developed symptomatic hypercapnia (Pa_{CO_2} values > 54 mm Hg), but before an acute decompensation occurred. In a more recent study on six patients with cystic fibrosis, Gozal (274) showed that NPPV plus oxygen therapy markedly improved gas exchange in all sleep stages in comparison with oxygen therapy alone, although sleep duration and architecture were similar in the two conditions. Among patients with

TABLE 8

SELECTION GUIDELINES: LONG-TERM NONINVASIVE VENTILATION FOR RESTRICTIVE THORACIC OR CENTRAL HYPOVENTILATORY DISORDERS

Indications
1. Symptoms
Fatigue, morning headache, hypersomnolence, nightmares, enuresis, dyspnea, etc. or
2. Signs
cor pulmonale and
3. Gas exchange criteria
Daytime $Pa_{CO_2} \geq 45$ mm Hg or
Nocturnal oxygen desaturation ($Sa_{O_2} < 90\%$ for > 5 min sustained or $> 10\%$ of total monitoring time)
4. Other possible indications
Recovering from acute respiratory failure with persistent CO_2 retention
Repeated hospitalizations for acute respiratory failure
Failure to respond to CPAP alone if obstructive sleep apnea
Relative contraindications
1. Inability to protect airway:
Impaired cough
Impaired swallowing with chronic aspiration
2. Excessive airway secretions
3. Need for continuous or nearly continuous ventilatory assistance
4. Anatomic abnormalities that interfere with mask fitting
5. Poorly motivated patient or family
6. Inability to cooperate or comprehend
7. Inadequate financial or caregiver resources

diffuse bronchiectasis, Benhamou and colleagues (275) found that use of NPPV was associated with improved Karnovsky function scores and a reduction in days of hospitalization from 46 for the year before to 21 for the year after starting NPPV. However, in comparison with a historical control group, rates of deterioration in oxygenation were similar and no survival benefit was apparent. In fact, in the long-term English follow-up study (238), patients with end-stage bronchiectasis had poorer survivals than did the other patient subgroups, most dying within 2 yr. These studies suggest a role for NPPV in treating patients with cystic fibrosis and diffuse bronchiectasis who have developed severe CO_2 retention, and also in serving as a "bridge to transplantation," but the capacity to prolong life may be limited and controlled trials are needed.

Pediatric uses of NPPV for chronic respiratory failure. Since the first case reports on successful use of nasal NPPV in children with central hypoventilation (245, 246), relatively few reports of NPPV have appeared in the pediatric literature. Nonetheless, some of the experience in adults can be applied to children, because conditions like DMD or cystic fibrosis may impair respiratory function in older children. In their experience with 15 children having neuromuscular disease or cystic fibrosis treated with nasal NPPV and followed for periods ranging from 1 to 21 mo, Padman and colleagues (276) found that average Pa_{CO_2} values and hospital days fell, and only one child required an artificial airway. Preliminary reports from other investigators (277) have reported successful applications of NPPV in children with restrictive disorders as young as 2 yr of age. Interest in NPPV has been increasing among pediatric practitioners (180), but the lack of controlled studies limits conclusions that can be drawn regarding efficacy.

Selection of Patients with Chronic Respiratory Failure to Receive Noninvasive Ventilation

Restrictive thoracic and central hypoventilatory diseases. Guidelines for selecting patients with restrictive thoracic or hypoventilatory disorders to receive noninvasive ventilation are listed in Table 8. There is wide agreement that patients with daytime or sustained nocturnal hypoventilation should begin noninvasive ventilation, as long as they are capable of adequately protecting their upper airways (193, 232, 278). They should also have the typical symptoms attributable to chronic hypoventilation and poor sleep quality, such as morning headaches, daytime hypersomnolence, and energy loss (279). The duration of nocturnal desaturation that justifies the initiation of noninvasive ventilation has not been established, and the threshold of $< 88\%$ for > 5 consecutive minutes suggested by the recent consensus conference was based partly on Medicare guidelines for O_2 therapy (232). Patients with severe CO_2 retention, even with minimal symptoms, and those recovering from bouts of acute respiratory failure should also be considered for long-term noninvasive ventilation, particularly if there is persistent CO_2 retention or a history of repeated hospitalizations.

The consensus group suggested that noninvasive ventilation be initiated in symptomatic patients with severe pulmonary dysfunction (VC $< 50\%$ of predicted), even in the absence of CO_2 retention (232). Although such a decline in pulmonary function dictates closer patient monitoring for the appearance of other indications, evidence is lacking to support the initiation of noninvasive ventilation on the basis of pulmonary function alone, although declines in maximal inspiratory pressures are associated with the onset of CO_2 retention (280). Evidence is also deficient to support the prophylactic initiation of noninvasive ventilation in patients with restrictive thoracic diseases before the onset of symptoms or daytime hypoventilation (243). Even if prophylactic use had merit, few patients comply with noninvasive ventilation unless motivated by the desire for symptom relief, so this approach is impractical at best. On the other hand, close follow-up of patients with severe pulmonary dysfunction is critically important, so that NPPV is initiated promptly when guidelines are met, before the occurrence of a respiratory crisis.

Relative contraindications to the use of noninvasive ventilation in the chronic setting include impairment of upper airway function or severe cough limitation, particularly in the presence of copious secretions or chronic aspiration (Table 8). Aggressive treatment with cough-assisting techniques or devices as described earlier (91–94) may permit use of noninvasive ventilation in such patients who would not otherwise be candidates, but if the condition is too severe, tracheostomy is indicated in patients who desire maximal prolongation of life. The need for continuous or nearly continuous ventilatory assistance is also a relative contraindication to noninvasive ventilation. Some investigators have recommended consideration of tracheostomy ventilation when the need for ventilatory assistance exceeds 16 h daily (281). Tracheostomy should be considered for such patients, but many still prefer noninvasive ventilation (233). Lack of motivation or the inability to understand or cooperate with the therapy on the part of the patient or family, facial or other anatomic abnormalities that interfere

TABLE 9

RESTRICTIVE THORACIC DISEASES TREATED WITH NONINVASIVE VENTILATION

Diagnosis
Chest wall deformity
Kyphoscoliosis
S/P thoracoplasty for tuberculosis
Slowly progressive neuromuscular disorders
Postpolio syndrome
High spinal cord injury
Spinal muscular atrophy
Slowly progressive muscular dystrophies
Multiple sclerosis
Bilateral diaphragm paralysis
More rapidly progressive neuromuscular disorders*
Duchenne muscular dystrophy
Amyotrophic lateral sclerosis
Rapidly progressive neuromuscular disorders†
Guillain-Barré syndrome
Myasthenia gravis

* Tracheostomy ventilation should be considered in far-advanced cases.
† Not usually recommended unless upper airway protective mechanisms intact.

TABLE 10

SELECTION GUIDELINES: LONG-TERM NONINVASIVE VENTILATION FOR OBSTRUCTIVE LUNG DISEASES

1. Symptoms:
Fatigue, hypersomnolence, dyspnea, etc. and
2. Gas exchange abnormalities:
$Pa_{CO_2} \geq 55$ mm Hg or
Pa_{CO_2} 50 to 54 mm Hg and O_2 sat $< 88\%$ for $> 10\%$ of monitoring time despite O_2 supplementation and
3. Failure to respond to optimal medical therapy:
Maximal bronchodilator therapy and/or steroids
O_2 supplementation if indicated
4. Failure to respond to CPAP therapy if moderate to severe obstructive sleep apnea
5. Reassess after 2 mo of therapy; continue if compliance is adequate (> 4 h/24 h), and therapeutic response is favorable.

with the proper fitting of the device, and insufficient caregiver or financial resources are other relative contraindications. The clinician must render a judgment as to whether these are severe enough to preclude a trial of noninvasive ventilation.

The appropriateness of initiating noninvasive ventilation also depends on the nature of the restrictive thoracic disorder. As discussed previously, NPPV is used for a wide variety of patients with chest wall deformities and stable or slowly progressive neuromuscular disorders that require intermittent ventilatory assistance (Table 9). Patients with more rapidly progressive neuromuscular disorders such as DMD or ALS may be good candidates initially. However, if debility progresses to the point where ventilatory needs are nearly continuous or cough or bulbar function are severely impaired, invasive ventilation may be preferred by those who wish to optimize their chances for survival. Patients with rapidly progressive neuromuscular conditions such as Guillain-Barré syndrome or myasthenia gravis in crisis are usually poor candidates for noninvasive ventilation because swallowing impairment is usually present when ventilatory dysfunction is severe.

Obstructive lung diseases. An earlier consensus statement noted the discordant results of the available trials and concluded that more study is needed before NPPV in severe stable COPD can be recommended (193). A more recent consensus conference agreed that the data are scanty and conflicting, but opined that the available evidence suggests that certain subgroups of patients with COPD may benefit (Table 10) (232). Most trials that have observed benefit from either negative or positive pressure noninvasive ventilation in severe, stable COPD have enrolled patients with more CO_2 retention at baseline than trials with negative results. In addition, the uncontrolled cohort series of patients with cystic fibrosis and diffuse bronchiectasis used NPPV successfully in patients with severe CO_2 retention (272–276). Thus, the consensus opinion was that a trial of NPPV in patients with severe stable COPD is justified if CO_2 retention is severe (i.e., $Pa_{CO_2} > 55$ mm Hg).

Considering that the one controlled trial reporting beneficial effects of NPPV in severe, stable COPD enrolled patients with frequent hypopneas and oxygen desaturations during sleep (258), another indication suggested by the consensus group was sustained, severe nocturnal O_2 desaturation (i.e., $< 88\%$ for > 5 consecutive minutes). However, O_2 therapy alone has been shown to improve sleep quality, reduce drowsiness, and improve neuropsychologic function in such patients (250, 263). Therefore, the recommendation was made that sleep monitoring be performed during O_2 supplementation and that NPPV not be initiated unless symptoms failed to respond to a trial of long-term O_2 therapy. This includes patients who retain more CO_2 during O_2 therapy, a group that responded favorably to NPPV in an uncontrolled trial (266). The requirement for CO_2 retention was relaxed if these guidelines were met or if there was a history of repeated hospitalizations (i.e., Pa_{CO_2} between 50 and 54 mm Hg).

A number of caveats should be borne in mind when applying these guidelines. It should be emphasized that they are tentative, pending results of further controlled trials. Also, even for patients who meet the criteria, patient tolerance of NPPV may be poor (262). In order to maximize patient compliance, only symptomatic patients should be selected, such as those with fatigue or daytime hypersomnolence. As outlined in Table 10, noninvasive ventilation should not be initiated unless other therapies have been optimized, including oxygen supplementation or CPAP (if indicated). Whether noninvasive ventilation can be used as a replacement for or supplement to lung volume reduction surgery has not been determined.

In response to a rapid increase in billings for NPPV in severe, stable COPD, the Health Care Financing Agency (HCFA) that sets reimbursement policy for Medicare in the United States has recently formulated new guidelines based on the consensus recommendations (282). The HCFA guidelines differ from the consensus recommendations in a number of respects, however. Patients are deemed eligible if Pa_{CO_2} exceeds 51 mm Hg, but in contrast to the consensus guidelines, all patients must have sustained nocturnal O_2 desaturations while receiving their usual O_2 supplementation (282). In addition, obstructive sleep apnea must be excluded, although the method of exclusion is not specified, and repeated hospitalizations are not listed as a guideline. Further, all patients are reimbursed for an initial 2-mo trial with a ventilator lacking a backup rate (reimbursed at a lower rate than ventilators with a backup rate). If the need for a backup rate is demonstrated after the first 2 mo, the higher reimbursement can be provided. Because of the need to show sustained nocturnal O_2 desaturations and the lower initial reimbursement rate, the net effect of these guidelines has been to curb the use of NPPV for patients with severe, stable COPD.

MECHANISMS OF ACTION OF NONINVASIVE VENTILATION

Acute Respiratory Failure

The favorable effects of noninvasive ventilation in patients with acute respiratory failure are thought to be at least partly related to a reduction in inspiratory muscle work and avoidance of respiratory muscle fatigue (Figure 5) (112). Numerous studies have examined the effects of noninvasive ventilation on breathing pattern and indices of work of breathing in patients with either obstructive or restrictive diseases (112, 113, 283–285). In successfully treated patients, respiratory rate invariably falls as tidal volume is augmented (129, 130). Earlier studies on the effect of negative pressure ventilation on work of breathing obtained conflicting results. Braun and Rochester (286) found virtual elimination of diaphragmatic EMG activity in patients with COPD during tank ventilation, whereas Rodenstein and colleagues (287) found little reduction in work

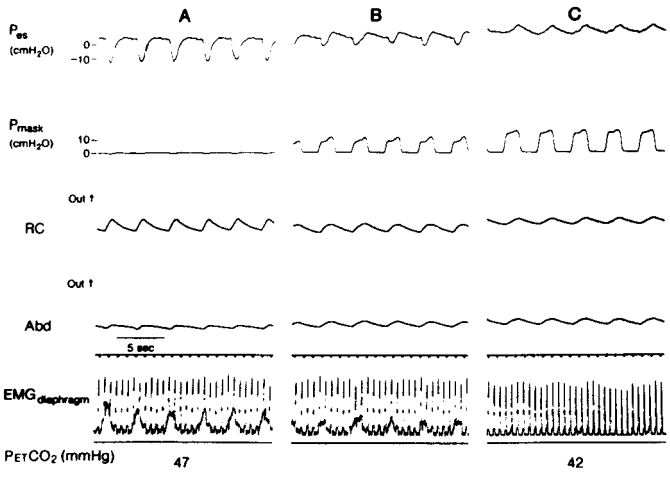

Figure 5. Tracings from a subject with COPD during spontaneous breathing (*A*) and during NPPV with mask pressure (Pmask) of 12 (B) and 15 (C) cm H_2O. NPPV reduced spontaneous inspiratory efforts as demonstrated by suppression of the phasic surface diaphragm EMG (EMGdi) and only positive inspiratory esophageal pressure (Pes) swings. The paradoxical abdominal (ABD) motion seen during spontaneous breathing (*A*) became synchronous with the rib cage (RC) during NPPV (*B* and *C*). From Reference 112, with permission.

of breathing unless the subject had been previously familiarized with negative pressure ventilation. Rather, the ventilator acted as a "metronome," serving to time the patient's breaths but not reducing inspiratory muscle effort. Belman and colleagues (285) compared negative pressure ventilation with NPPV, finding that the latter was more effective in reducing inspiratory muscle work.

Subsequently, most studies have focused on the efficacy of NPPV in resting respiratory muscles. Carrey and colleagues (112) found that PSV was very effective in reducing the diaphragmatic EMG signal in patients with either restrictive or obstructive ventilatory defects (Figure 5). Similar effects have been reported for obese patients, in whom bilevel ventilation was shown to reduce diaphragmatic pressure swings (288). Other studies have found that when applied singly, both inspiratory pressure (284) and CPAP (289) reduce ventilatory muscle work in patients with COPD, but the greatest reduction in esophageal and transdiaphragmatic pressure swings occurs when the two are combined as inspiratory pressure support plus PEEP (290, 291). In this context, the extrinsic PEEP is thought to counterbalance the inspiratory threshold work related to intrinsic PEEP, and the pressure support augments tidal volume for a given inspiratory effort.

Studies on acute applications of NPPV have also observed prompt improvements in gas exchange (114–125, 128–132). Augmentation of ventilation that usually occurs within the first hour of therapy is undoubtedly responsible for some of this improvement. Also, some of the improvement in oxygenation is related to the patient's ability to tolerate a higher $F_{I_{O_2}}$ without further hypoventilating. In addition, improvements in ventilation/perfusion ratios or even shunt undoubtedly occur in patients with acute pulmonary edema or ARDS, in whom the application of expiratory pressure should have an effect similar to that of PEEP in invasively ventilated patients (99).

Most often, NPPV has little effect on blood pressure (128–132) presumably because inflation pressures are relatively low compared with those used with invasive ventilation. On the other hand, CPAP or intermittent positive pressure ventilation may have salutary or adverse hemodynamic effects in patients with cardiac dysfunction (292–294), depending on the patient's fluid volume and left ventricular systolic function. In patients with a high fluid volume and impaired systolic function, increased intrathoracic pressure associated with CPAP or positive pressure ventilation has a salutary effect by diminishing venous return and reducing left ventricular afterload. If mean systemic venous pressure is low and systolic function is normal, on the other hand, increased intrathoracic pressure can impair cardiac performance. Bradley and colleagues (292) found that CPAP increased cardiac output in patients with a pulmonary artery occlusion pressure exceeding 12 mm Hg, whereas cardiac output fell if occlusion pressures were lower.

Unloading of the respiratory muscles during noninvasive ventilation requires that the patient coordinate breathing efforts with ventilator action, permitting a reduction in spontaneous inspiratory effort in response to the exogenously administered pressure. This adaptation is partly volitional when patients are awake, and the findings of Rodenstein and colleagues (295) indicate that familiarization with the noninvasive technique can facilitate the response. However, the precise mechanisms by which these adaptations take place have not been delineated. Presumably, respiratory drive is diminished, as evidenced by the prompt reduction in respiratory rate and respiratory muscle activity that almost invariably occurs when NPPV is applied successfully. In addition, air leaking is rendered inevitable by the open breathing circuit design of noninvasive ventilation, and upper airway structures must be positioned to facilitate air entry into the lungs. Mechanisms by which this positioning occurs are not well understood.

Chronic Respiratory Failure

During long-term noninvasive ventilation, the question of how upper airway structures permit the entry of air into the lower airways becomes even more complicated, because noninvasive ventilation is used mainly during sleep. Because NPPV offers no direct conduit to the lower airways, gas is free to leak around the mask, through the nose, or via the mouth, depending on the type of interface used. Air leaking is universal during nocturnal noninvasive ventilation, but sufficient air usually enters the lungs to assist ventilation (296). Unfortunately, the adaptations that permit air entry into the lungs during NPPV are as poorly understood during sleep as they are during wakefulness.

Resistance to airflow in the nasal passages is undoubtedly an important factor in the efficacy of nasal ventilation, although its contribution has not been fully examined. In one study, large amounts of air leaking through the mouth during nasal CPAP increased nasal resistance (297). This effect was abated by provision of heated, humidified air, consistent with the idea that nasal mucosal cooling was responsible for the effect. Increases in nasal resistance caused by this mechanism, upper airway infection, or allergy are likely to reduce delivered tidal volumes during NPPV, but no studies have examined this question. Studies on patients using nasal CPAP nocturnally suggest that passive positioning of the soft palate is important in maintaining patency of the upper airway (298). The importance of the soft palate and other upper airway structures in maintaining an adequate pathway for air entry into the lungs during NPPV is underlined by the observation that patients treated with nasal CPAP experience increased air leaking through the mouth after uvulopharyngoplasty (299).

Glottic aperture is also important in regulating the flow of gas into the lower airways during NPPV. In normal volunteers receiving volume-controlled nasal ventilation, Jounieaux and colleagues (300, 301) found that, compared with the awake state, glottic aperture narrows and delivered tidal volume falls during lighter stages of sleep (Stages 1 or 2). In deeper stages of sleep (Stages 3 or 4), the glottic aperture widens, permitting more ventilation, but if minute volume is increased excessively, the glottic aperture narrows once again, partly related to a reduction in Pa_{CO_2}. These findings indicate that both sleep stage and the amount of ventilatory assistance influence glottic aperture, which is a potentially important determinant of the efficacy of noninvasive ventilation. These findings apply mainly to controlled modes of nasal ventilation (302); a more recent study from these investigators showed that glottic aperture was not important when NPPV was administered via a pressure-limited bilevel ventilator in the spontaneous mode (303).

The mechanisms by which the respiratory center inhibits spontaneous respiratory muscle activity in response to ventilatory assistance when the patient is asleep are also unclear. Airway receptors that sense airflow, stretch receptors in the lung, or muscle proprioceptors could provide negative feedback to the respiratory center. Alternatively, chemoreceptors in the bloodstream or central nervous system could sense a small decline in Pa_{CO_2} or increase in pH that could blunt respiratory drive. Regardless of the mechanism, though, respiratory muscle activity is suppressed by NPPV during sleep, particularly in patients with weakened respiratory muscles (304).

Another mechanism that remains undefined is how nocturnal noninvasive ventilation stabilizes or improves daytime gas exchange during spontaneous breathing in patients with chronic respiratory failure. In these patients, intermittent ventilation for as little as 4 to 6 h nightly brings about sustained reduc-

tions in daytime Pa_{CO_2}, associated with a gradual resolution of symptoms such as hypersomnolence and morning headache. Three theories have been proposed to explain the sustained improvement. One postulates that noninvasive ventilation rests chronically fatigued respiratory muscles, thereby improving daytime respiratory muscle function (212, 305). Supporting this theory are studies demonstrating that respiratory muscles do indeed rest during noninvasive ventilation (112, 285, 290, 291) and that indices of respiratory muscle strength and endurance may improve in patients with chronic respiratory failure after varying periods of noninvasive ventilatory assistance (214–216, 229). On the other hand, chronic respiratory muscle fatigue has never been adequately defined or convincingly demonstrated in these patients (306, 307). Further, other studies have failed to demonstrate improvement in respiratory muscle function even after initiation of noninvasive ventilation (218–221). In addition, some studies have demonstrated that patients with neuromuscular disease have stable Pa_{CO_2} for years despite a progressive decline in pulmonary function (199).

A second theory postulates that noninvasive ventilation improves respiratory system compliance by reversing microatelectasis of the lung, thereby diminishing daytime work of breathing (308, 309). This theory derives from studies showing improvements in FVC without changes in indices of respiratory muscle strength after periods of positive pressure ventilation. Once again, however, data are conflicting, with a number of studies showing no changes in vital capacity after periods of noninvasive ventilation (218–221). In addition, Estenne and colleagues (310) used CT scanning of the chest to show that microatelectasis is not an important contributor to chest wall restriction in patients with respiratory muscle weakness.

A third theory proposes that noninvasive ventilation lowers the respiratory center "set point" for CO_2 by ameliorating chronic hypoventilation (195, 305, 306, 311). The respiratory center in patients with respiratory insufficiency is thought to adjust its output so that the work of the respiratory muscles will not exceed the level that would precipitate muscle fatigue, an adaptation sometimes referred to as "central" fatigue (305). During deeper stages of sleep, particularly REM, upper respiratory muscle tone and the activity of nondiaphragmatic inspiratory muscles diminish (312). In patients with ventilatory impairment, this adaptation may be exaggerated, leading to progressive nocturnal hypoventilation. Repeated episodes of nocturnal hypoventilation are thought to lead to a gradual accumulation of bicarbonate, desensitization of the respiratory center to CO_2 and worsening daytime hypoventilation (312). Nocturnal ventilatory assistance reverses nocturnal hypoventilation and allows a gradual downward resetting of the respiratory center set point for CO_2, thereby reducing daytime hypercarbia. In addition, the prevention of nocturnal hypoventilation may reduce arousals that lead to sleep fragmentation (313). In this way, NPPV may improve quantity and quality of sleep, translating into less fatigue and improved daytime function.

Evidence for this theory derives from studies showing that when ventilatory assistance is discontinued for a night in patients with chronic respiratory failure who have been using nightly noninvasive ventilation, the degree of nocturnal hypoventilation is less than before initiation, suggesting a resetting of respiratory center sensitivity for CO_2 (197, 305). In addition, nocturnal ventilation, oxygen saturation, sleep quality, and daytime symptoms deteriorate without reductions in respiratory muscle strength or vital capacity when nocturnal NPPV is temporarily discontinued in patients with restrictive thoracic disease whose chronic respiratory failure had previously been reversed by it (230, 231). The nocturnal hypoventilation and symptoms promptly improve after resumption of NPPV. More recently, Annane and colleagues (314) prospectively followed 16 patients with chronic respiratory failure caused by restrictive thoracic disorders for 3 yr after starting NPPV. Compared with baseline values, Pa_{CO_2} was improved, the maximal inspiratory pressure was unchanged, and the slope of the ventilatory response curve was increased for the duration of the follow-up period. These studies suggest that amelioration of nocturnal hypoventilation with resetting of respiratory center CO_2 sensitivity and improved sleep quality may be important mechanisms contributing to the efficacy of long-term NPPV. The stability of pulmonary function in the withdrawal and long-term follow-up trials (230, 231, 314) suggests that respiratory muscle resting or reversal of atelectasis are less important mechanisms than resetting of the CO_2 set point. However, the three theories are not mutually exclusive, and all could contribute more or less depending on the patient.

Interestingly, daytime assisted ventilation appears to be as effective at reversing hypoventilation as nocturnal. Schonhofer and colleagues (315) provided at least 8 h/24 h of NPPV to 30 patients with chronic respiratory failure caused by restrictive thoracic disorders, half during the daytime when they were kept awake using a signal generator, and the other half at night. After a month, the decline in daytime Pa_{CO_2} was equivalent in both groups. Although these investigators monitored neither daytime sleep nor symptomatic responses, their findings indicate that resetting of the respiratory center sensitivity for CO_2 does not require *nocturnal* ventilatory assistance. Although nocturnal use of NPPV is clearly more convenient, these findings indicate that patients unable to tolerate nocturnal NPPV may still benefit from daytime assistance.

Clearly, much remains to be learned regarding specific mechanisms of action of noninvasive ventilation. Understanding of these mechanisms is complicated by the application of noninvasive ventilation in both acute and chronic settings using many different techniques for patients with varying etiologies of respiratory failure. The ability to unload respiratory muscles appears to be key, particularly in the acute setting. Mechanisms controlling upper airway responses and respiratory center adaptations are less well understood and also appear to be critical to success.

TABLE 11

GOALS OF NONINVASIVE VENTILATION

Short-term (including acute)
1. Relieve symptoms
2. Reduce work of breathing
3. Improve or stabilize gas exchange
4. Optimize patient comfort
5. Good patient-ventilator synchrony
6. Minimize risk
7. Avoid intubation
Long-term
1. Improve sleep duration and quality
2. Maximize quality of life
3. Enhance functional status
4. Prolong survival

PRACTICAL APPLICATION OF NPPV

Initiation

Once an appropriate candidate for noninvasive ventilation has been selected, the process of initiation raises a number of practical issues. A proper site for initiation must be identified, a ventilator and interface must be chosen, and initial settings must be selected (316). Although little scientific evidence is available to guide these decisions, they should be made carefully, because

success or failure may hinge on them. Focusing on the major goals of noninvasive ventilation may help in making selections (Table 11). Noninvasive ventilation shares with invasive mechanical ventilation the goal of improving gas exchange, either nocturnal, daytime, or both. But even more than with invasive ventilation, noninvasive ventilation seeks to alleviate patient symptoms and optimize comfort. Because of the open-circuit design of NPPV, success depends largely on patient cooperation and acceptance. Once the patient accepts the therapy, the other goals become achievable. The following will present recommendations for initiation, citing evidence when available, pointing out controversy where it exists, and attempting to present a balanced consideration of the opposing views.

Location. In the acute setting, noninvasive ventilation can be initiated wherever the patient presents with acute respiratory distress; in the emergency department (129, 161, 192), critical care unit (125, 130), intermediate or respiratory care unit (129), or hospital ward (314, 317). After initiation, however, transfer to a location that offers continuous monitoring is recommended until the patient stabilizes. The patient's acuity of illness and the risk of deterioration if an accidental disruption occurs should dictate the intensity of monitoring. During transfers, ventilatory assistance and monitoring should be continued, because acutely ill patients can rapidly deteriorate (129). Recent preliminary evidence suggests that less acutely ill patients with COPD can be managed effectively on a medical ward, but if pH is < 7.30, admission to a more intensively monitored setting is advised (134).

For stable patients with chronic respiratory failure, initiation may take place during an inpatient admission, in a sleep laboratory during the daytime or during an overnight stay (304, 318), in a physician's outpatient office (with therapists from the home respiratory vendor present), or in the patient's home. Although there are strong proponents for one location or another, no study has demonstrated the superiority of any one. Routine hospitalization is unnecessary unless warranted by the patient's medical condition. Use of the sleep laboratory offers the advantage of precise titration of initial pressure or volume settings during sleep monitoring (304, 318), but it adds to costs and may delay implementation because of scheduling problems. Also, considering that successful adaptation may require several months (230), information obtained from a single night in the sleep laboratory may not be relevant later on. Until outcome studies demonstrate the superiority of one location over another, the choice of location will be based on practitioner preference. Perhaps more important than the specific location is the availability of skilled attentive practitioners to help during the initiation and adaptation processes.

Selection of a Ventilator and Ventilator Mode

Evidence to guide ventilator selection is lacking, so the decision is based largely on practitioner experience. In acute care settings, critical care ventilators or portable positive pressure devices are used in volume- or pressure-limited modes. Critical care ventilators offer more sophisticated alarm and monitoring capabilities and can generate higher inspiratory pressures than portable bilevel systems, but they are more expensive and may have difficulty coping with the inevitable air leaks. Newer bilevel devices have been designed specifically for use with NPPV and have features aimed at enhancing leak compensation and patient comfort such as adjustable triggering and cycling mechanisms (319) and "rise times" (the time to reach the preset inspiratory pressure).

A laboratory study that compared a number of bilevel ventilators with a critical care ventilator found that triggering, cycling and leak compensatory mechanisms were superior in several of the bilevel ventilators (320). However, other laboratory studies have found that some bilevel ventilators have less inspiratory flow acceleration than do critical care ventilators, contributing to an increase in inspiratory work (321). Also, because they utilize a single tube for both inspiration and expiration, bilevel ventilators contribute to CO_2 rebreathing unless used with a nonrebreathing expiratory valve that increases expiratory resistance and expiratory work of breathing (65, 322). Comparisons of bilevel and critical care ventilators in intubated patients have demonstrated that gas exchange is equivalent, but work of breathing is increased during bilevel ventilation if minimal expiratory pressure levels (2 to 3 cm H_2O) are used (323). However, if expiratory pressures of 5 cm H_2O are used, the two types of ventilators perform equally well in supporting gas exchange and reducing work of breathing (324), presumably because of counterbalancing of auto-PEEP. For delivery of noninvasive ventilation, clinical outcome studies using bilevel ventilators report success rates that compare favorably with those for critical care ventilators (129, 130), but no controlled trials have directly compared the two. Thus, the selection of either system can be justified, and the choice is often based on availability and financial considerations. Further, recent developments have blurred the distinctions between the ventilators, with bilevel ventilators adding monitoring and alarm capabilities.

A number of studies have directly compared volume- and pressure-limited modes. One early study found roughly equivalent efficacy of pressure- and volume-limited modes in acutely improving gas exchange (325). Two subsequent studies directly comparing pressure- and volume-limited modes for treating acute respiratory failure (137, 323) observed nonsignificant trends for greater efficacy with pressure support ventilation. However, both also found enhanced patient comfort or "compliance" with pressure support. Thus, although either mode can be used with the expectation of similar rates of success, pressure-limited modes appear to be more readily accepted by patients. The triggering mechanism may also be important in reducing the work of breathing. Nava and colleagues (326) found that compared with pressure triggering during either volume- or pressure-limited NPPV, flow triggering decreased inspiratory work of breathing by roughly 15% as determined by the esophageal pressure time product, although patient comfort ratings were similar for the two triggers.

In the chronic setting, several studies have compared performance of portable volume- and pressure-limited ventilators. Restrick and colleagues (327) found no difference in overnight oxygenation when patients used pressure support or volume-limited ventilators, each for one night. Schonhofer and colleagues (328) administered nasal volume-limited ventilation for 1 mo followed by pressure-limited ventilation, both in the controlled mode, to 30 consecutive patients with mainly restrictive forms of chronic respiratory failure. Only two patients failed to improve with volume-limited ventilation, whereas 10 had increased Pa_{CO_2} or symptomatic deterioration when switched to pressure-limited ventilation. Smith and Shneerson (329), on the other hand, observed improved daytime blood gases in 10 patients switched from volume- to pressure-limited ventilation. These were not randomized, prospective trials, and specific characteristics of the ventilators or settings may have influenced results. Nonetheless, it is fair to conclude that these studies demonstrate no clear advantage of one ventilator mode over the other.

Thus, the choice between the two comes down to clinician preference and a consideration of the particular advantages and disadvantages. In general, volume-limited ventilators have greater pressure-generating and alarm capabilities than do

most pressure-limited ventilators, and they usually have a built-in backup battery. They may be preferred for patients with little or no spontaneous breathing capability, although pressure-limited ventilators can also be used successfully for these patients. Volume-limited ventilators may also be preferred for patients with severe neuromuscular weakness who can be taught to "stack" breaths to achieve large tidal volumes, enhancing airflow during coughing and aiding in the expulsion of secretions (91). Pressure-limited ventilators, on the other hand, are usually more portable and less expensive, have better leak-compensating capabilities, and lack alarms that can needlessly awaken patients at night during transient air leaking. For these reasons, pressure-limited ventilators are usually preferred for patients requiring only nocturnal or partial daytime ventilation.

Newer ventilators designed specifically for noninvasive ventilation are able to deliver both volume- and pressure-limited modes, with the capability of adjusting triggering and cycling sensitivity, "rise time," and inspiratory duration to optimize patient comfort. PAV offers promise as a mode for noninvasive ventilation. As discussed earlier, this new mode has the capability of closely matching patient breathing pattern and enhancing comfort. A recent physiologic evaluation of PAV administered noninvasively to patients with COPD and acute respiratory failure showed improvements in tidal and minute volumes and in gas exchange as well as reductions in indices of work of breathing (330). In addition, a preliminary report suggests that the PAV mode increases patient acceptance of NPPV when compared to a pressure support mode using a "critical care" ventilator (331). Ventilators offering the PAV mode are currently available in Europe and Canada and have not yet been approved by the Food and Drug Administration in the United States.

Interface Selection

Characteristics of the various interfaces available were discussed earlier. A recent study showed better tolerance for nasal masks among patients with chronic respiratory failure, but oronasal masks and nasal "pillows" were more efficient in lowering Pa_{CO_2} (43). However, patient traits or preferences may still favor the selection of one particular device over another. In the acute setting, nasal or oronasal masks are most commonly used. Nasal masks are usually better tolerated by patients with claustrophobia, whereas oronasal masks are preferred in edentulous patients or those with large oral leaks during use of nasal masks. In the chronic setting, nasal masks are most often used, although oronasal masks that are specifically designed for use with noninvasive ventilators are becoming more popular. Other types of nasal masks such as nasal pillows are useful when patients develop ulcers of the nasal bridge. In addition, some centers use mouthpiece ventilation, especially in patients who need nearly continuous ventilatory assistance (46).

Regardless of the mask selected, proper fit is of paramount importance in optimizing comfort. Fitting gauges should be used to facilitate proper sizing and strap tension should be minimized. Masks with thin cellophane flaps are available with some masks to permit leak-free sealing over the face with reduced strap tension. Also, some nasal masks are supplied with forehead spacers that should be used to relieve pressure on the bridge of the nose. Newer, more compact masks and masks with gel seals are well tolerated by patients and are gaining popularity, but no clinical studies have evaluated their efficacy in providing NPPV. Practitioners must be prepared to try different mask sizes and types in an effort to enhance patient comfort. In the acute setting, attaching a bag to the noninvasive ventilator that contains a variety of mask types and sizes is advisable to facilitate rapid selection of an acceptable mask.

Initial Ventilator Settings

The range of initial inspiratory pressures used with PSV by different investigators is quite large. Some start with low inspiratory pressures (8 to 10 cm H_2O) and gradually titrate upward as tolerated by the patient (12). Others start with higher initial inspiratory pressures (20 cm H_2O) and adjust downward if patients are intolerant (130, 332). The former approach prioritizes patient comfort in an effort to maximize patient compliance with therapy, whereas the latter approach prioritizes ventilatory assistance in order to stabilize gas exchange. Reported success rates for the two approaches are similar, and no studies have directly compared them. For volume-limited ventilation, an initial V_T of 10 to 15 ml/kg has been recommended, in excess of the standard recommendations for invasive ventilation because of the need to compensate for air leaks (225). Parreira and colleagues (333) found that a V_T of 13 ml/kg optimized assisted minute volume in a group of patients with restrictive thoracic disorders.

Expiratory pressure (or PEEP) is used routinely with bilevel ventilators, and is optional with volume-limited ventilators. "Bilevel"ventilators require a bias flow during expiration to flush CO_2 from the single ventilator tube and avoid rebreathing (65). Minimal expiratory pressure with these ventilators is in the 2 to 4 cm H_2O range. Higher expiratory pressure (typically 4 to 6 cm H_2O) is used to counterbalance intrinsic PEEP during treatment of COPD exacerbations. Expiratory pressure is also added to improve oxygenation in patients with diffuse pneumonia or acute lung injury, or to prevent apneas and hypopneas in patients with sleep-disordered breathing. In the latter circumstance, titration in a sleep laboratory may permit expeditious determination of the minimal expiratory pressures necessary to overcome sleep-associated breathing abnormalities. Elliott and Simonds (334) found that 5 cm H_2O expiratory pressure lowered mean nocturnal transcutaneous P_{CO_2} more than the 2 cm H_2O minimal expiratory pressure in patients with chronic respiratory failure caused by restrictive thoracic diseases using bilevel ventilation. However, the higher expiratory pressure

TABLE 12

PROTOCOL FOR INITIATION OF NONINVASIVE POSITIVE PRESSURE VENTILATION

1. Appropriately monitored location; oximetry, respiratory impedance, vital signs as clinically indicated
2. Patient in bed or chair sitting at $\geq$ 30-degree angle
3. Select and fit interface
4. Select ventilator
5. Apply headgear; avoid excessive strap tension (one or two fingers under strap); encourage patient to hold mask
6. Connect interface to ventilator tubing and turn on ventilator
7. Start with low pressures/volumes in spontaneously triggered mode with backup rate; pressure-limited: 8 to 12 cm H_2O inspiratory; 3 to 5 cm H_2O expiratory volume-limited: 10 ml/kg
8. Gradually increase inspiratory pressure (10 to 20 cm H_2O) or tidal volume (10 to 15 ml/kg) as tolerated to achieve alleviation of dyspnea, decreased respiratory rate, increased tidal volume (if being monitored), and good patient-ventilator synchrony
9. Provide O_2 supplementation as needed to keep O_2 sat $>$ 90%
10. Check for air leaks, readjust straps as needed
11. Add humidifier as indicated
12. Consider mild sedation (i.e., intravenously administered lorazepam 0.5 ng) in agitated patients
13. Encouragement, reassurance, and frequent checks and adjustments as needed
14. Monitor occasional blood gases (within 1 to 2 h and then as needed)

shortened total sleep time and offered no apparent benefit to patients with COPD. Thus, unless there is an indication to use higher levels as discussed above, expiratory pressure should be kept just above the minimal level (in the 3 to 6 cm H_2O range).

The assist/control (or spontaneous/timed) mode is commonly used to administer noninvasive ventilation, but the need for routine use of a backup rate has not been established. In the acute setting, the backup rate is used to prevent apneas and to assure cycling of the ventilator in the face of air leaks that may interfere with ventilator triggering. In the chronic setting, a backup rate set sufficiently high to control breathing nocturnally (usually slightly below the awake spontaneous breathing rate) is recommended for patients with neuromuscular disease in order to maximize respiratory muscle rest (230, 328). In patients with severe stable COPD, on the other hand, the need for a backup rate is not clear, considering that the one controlled trial that found significant benefit attributable to NPPV in these patients using a spontaneous ventilator mode without a backup rate (258). In an earlier study (327), these investigators found that compared with a spontaneous mode, use of a backup rate had no effect on nocturnal gas exchange in patients with chronic respiratory failure. On the other hand, Parreira and colleagues (333) found that minute volume was optimized when patients with restrictive thoracic disorders used a relatively high backup rate of 23/min. Considering that current HCFA reimbursements are approximately double for ventilators with a backup rate compared with those without, this issue is not trivial, and further study is needed to determine whether backup rates contribute to the efficacy of NPPV.

Adjuncts to Noninvasive Ventilation

With bilevel ventilators, supplemental oxygen can be provided directly through tubing connected to a nipple in the mask or to a T-connector in the ventilator tubing, with liter flow adjusted to keep O_2 saturation above 90 to 92%. With critical care ventilators, standard oxygen blenders can be used to provide the desired $F_{I_{O_2}}$. The ability to provide high oxygen concentrations accurately makes use of a critical care ventilator preferable in patients with severe oxygenation defects. In patients with restrictive thoracic disorders, amelioration of chronic hypoventilation usually eliminates the need for O_2 supplementation, unless there is underlying parenchymal lung disease. Humidification is usually unnecessary for short-term (i.e., < 1 d) applications, unless there is excessive air leaking, because normal air conditioning functions of the upper airway are left intact. With excessive air leaking, a heated humidifier may maintain a lower nasal resistance (296). In the chronic setting, humidification is usually provided, particularly during the winter months in colder climates. Nasogastric tubes are not routinely recommended as adjuncts to noninvasive ventilation, even when oronasal masks are used.

Role of the Clinician

The successful initiation of noninvasive ventilation is highly dependent on patient cooperation. For this reason, an experienced clinician conveying an air of confidence and assuredness to patients is crucial to success. The clinician should serve the role of facilitator, motivating the patient, explaining the purpose of each piece of equipment, and preparing the patient for each step in the initiation process. Patients should be reassured, encouraged to communicate any discomfort or fears, and coached in ways to coordinate their breathing with the ventilator. When using nasal masks, patients are instructed to breathe nasally and to keep their mouths closed.

Specific steps in the initiation process are shown in Table 12. After the mask and ventilator are selected, the mask is applied to the patient's face. Allowing the patient to hold the mask in place or even use a mouthpiece initially imparts a sense of control and may alleviate some anxiety (67). The ventilator is connected to the interface and turned on, starting with lower pressures and adjusting upward (or alternatively, higher pressures may be use initially, depending on clinician preference, as discussed above). Oxygen is supplemented as needed, and the patient is closely observed for discomfort, air leaking, or difficulty synchronizing with the ventilator. The clinician promptly responds to difficulties, making appropriate adjustments or alterations. Close adherence to this process during the initial hour or two of NPPV use will maximize the likelihood of success.

Monitoring

Monitoring of patients receiving noninvasive ventilation aims at determining whether the initial goals are being achieved (Table 11). As stressed above, other goals are unachievable unless the patient tolerates noninvasive ventilation, so monitoring of patient comfort and tolerance are key.

Subjective responses. Noninvasive ventilation aims to alleviate respiratory distress in the acute setting and fatigue, hypersomnolence, and other symptoms of impaired sleep in the chronic setting. In addition, the modality should be administered with minimal discomfort to the patient. These aspects can be easily assessed using bedside observation and patient queries, although practitioners should be wary of stoic patients. Patients who minimize or deny discomfort may have great difficulty successfully adapting to noninvasive ventilation, so clinicians should ask patients repeatedly about discomfort related to the mask or airflow, and observe for nonverbal signs of distress or discomfort.

Physiologic responses. One of the most consistent signs of a favorable response to noninvasive ventilation is a drop in respiratory rate within the first hour or two (191, 192). In concert with this, patients breathe in synchrony with the ventilator and sternocleidomastoid muscle activity diminishes. Abdominal paradox, if initially apparent, subsides and heart rate usually falls. The absence of these signs of improvement portends a poor response, and measures should be promptly taken to correct the situation. Air leaking and patient-ventilator asynchrony should be monitored and corrected by coaching or adjustments of ventilator settings. Some investigators also monitor tidal volumes, aiming for delivered volumes in excess of 7 ml/kg (332). Relying on ventilator monitoring to follow tidal volumes may be misleading, however, particularly during use of bilevel ventilators. These integrate the inspired flow signal and may be very inaccurate in the face of air leaks. Also, tidal volumes delivered by portable volume-limited ventilation may differ substantially from preset volumes (335).

Gas Exchange. In the acute setting, gas exchange is monitored using continuous oximetry and occasional blood gases. The aim is to maintain adequate oxygenation while awaiting an improvement in ventilation that may be gradual (130). In chronic stable patients, the improvement in daytime gas exchange occurs slowly, over a period of weeks, depending on the duration of daily ventilator use. Some patients adapt slowly and require several months before they sleep through the night using the ventilator. Arterial blood gas measurement should be delayed until the patient is consistently using the ventilator for a period of time likely to improve gas exchange; usually at least 4 to 6 h/24 h.

Some clinicians advocate the use of noninvasive measures to track gas exchange responses (91). Unfortunately, noninvasive CO_2 monitors have not been demonstrated to be suffi-

ciently accurate to entirely replace blood gas determinations in either the acute or the chronic setting (336). Nonetheless, noninvasive CO_2 monitoring may be useful for trending purposes in patients with normal lung parenchyma such as those with neuromuscular disease. Because of variable air leaks and breathing patterns and dilution caused by bias flow with some ventilators, recordings of end-tidal CO_2 must be interpreted with great caution if obtained from a mask during NPPV, particularly if the patient has parenchymal lung disease.

Sleep. The role of sleep monitoring in the evaluation and subsequent monitoring of patients using NPPV for chronic respiratory failure has not been established. Some investigators (318) favor initiation of NPPV during or after formal sleep testing, whereas others initiate NPPV without any sleep monitoring. If both approaches prove to be equal in achieving the goals of noninvasive ventilation, it would be difficult to argue that routine sleep studies are necessary. For pragmatic reasons (tight sleep laboratory schedules and patient reluctance to spend a night away from home), many clinicians initiate noninvasive ventilation without a formal sleep study, and reserve follow-up sleep studies for patients having problems adapting. Follow-up monitoring may consist of home nocturnal oximetry, portable multi-channel recorders, or full polysomnography. The utility of each of these techniques needs to be examined. Lacking guiding evidence, one pragmatic approach is to screen patients using home oximetry and to perform more sophisticated studies when the oximetry results are deemed inadequate. It must be borne in mind, though, that oximetry recordings may be insensitive in detecting sleep-associated breathing abnormalities and more sophisticated monitoring may be indicated in the face of persisting symptoms.

Adaptation

The process of adaptation differs considerably between the acute and chronic settings. In the acute setting, the aim is to assist ventilation promptly, so inspiratory pressures are raised quickly as tolerated. The patient also uses the ventilator for more time initially, with increasing periods of time off the ventilator as the underlying condition improves. Some investigators encourage use most of the time initially as dictated by the patient's respiratory distress during ventilator-free intervals (129). Others have described "sequential" use (126) wherein periods of use alternate with lengthy ventilator-free periods, and total daily use averages only 6 h. When no respiratory distress recurs during ventilator-free intervals, ventilator assistance is discontinued. The total duration of ventilator assistance depends on the speed of resolution of the respiratory failure. Patients with acute pulmonary edema require an average of 6 to 7 h of ventilator use (152), whereas patients with COPD average 2 d or more (129). Some patients may continue nocturnal ventilation after discharge from the hospital, although there are no guidelines for selection of such patients.

In the chronic setting, patients start more gradually and increase periods of use as tolerated. Many begin with only an hour or two of use during the daytime and at night and gradually extend these periods to the whole night over several weeks or even months. Compared with the acute setting, urgency in the chronic setting is less, and because the intent is to use the ventilator during sleep, great care must be exercised in ascertaining that comfort is optimized. During this period, frequent visits from a home respiratory therapist are helpful to assure optimization of comfort and to deal promptly with any problems that arise. Criner and colleagues (262) found that 36% of patients required further adjustments in mask or ventilator settings, even after discharge from an inpatient ventilator unit.

Once the patient is sleeping for at least several hours at night, physician office visits with measurement of daytime arterial blood gases are useful, and nocturnal oximetry may be monitored. Ventilator pressures or volumes are then increased as tolerated to achieve the desired improvements in gas exchange. No consensus on an ideal level for daytime Pa_{CO_2} has been reached, but most investigators target levels in the mid-40s mm Hg. On the other hand, in the investigators' experience, a daytime Pa_{CO_2} as high as 60 mm Hg or higher may be tolerated without hypersomnolence or evidence of cor pulmonale, as long as oxygenation is adequate. These higher levels may be preferable in patients with very severe ventilatory impairment as long as oxygenation remains adequate, because less work is required during spontaneous breathing. To avoid excessive increases in Pa_{CO_2}, however, patients with progressive neuromuscular disease usually require gradual increases in

TABLE 13

FREQUENCY OF ADVERSE SIDE EFFECTS AND COMPLICATIONS OF NPPV WITH POSSIBLE REMEDIES

	Occurrence (%)*	Possible Remedy
Mask-related		
Discomfort	30–50	Check fit, adjust strap, new mask type
Facial skin erythema	20–34	Loosen straps, apply artificial skin
Claustrophobia	5–10	Smaller mask, sedation
Nasal bridge ulceration	5–10	Loosen straps, artificial skin, change mask type
Acneiform rash	5–10	Topical steroids or antibiotics
Air Pressure or Flow-related		
Nasal congestion	20–50	Nasal steroiids, decongestant/antihistamines
Sinus/ear pain	10–30	Reduce pressure if intolerable
Nasal/oral dryness	10–20	Nasal saline/emollients, add humidifier, decrease leak
Eye irritation	10–20	Check mask fit, readjust straps
Gastric insufflation	5–10	Reassure, simethacone, reduce pressure if intolerable
Air Leaks	80–100	Encourage mouth closure, try chin straps, oronasal mask if using nasal mask, reduce pressures slightly
Major Complications		
Aspiration pneumonia	< 5	Careful patient selection
Hypotension	< 5	Reduce inflation pressure
Pneumothorax	< 5	Stop ventilation if possible, reduce airway pressure if not Thoracostomy tube if indicated

* Occurrences estimated from reported occurrences in studies from Tables 3 and 6 and from authors' experiences.

inspiratory pressure (to the low 20s cm H_2O) and longer periods of assisted ventilation per 24 h (until continuously).

ADVERSE EFFECTS AND COMPLICATIONS OF NONINVASIVE VENTILATION

Both in the acute and chronic settings, noninvasive ventilation is safe and well tolerated when applied optimally in appropriately selected patients. Although this statement applies to both NPPV as well as alternative noninvasive ventilators, the following will focus on NPPV. Complications of body ventilators have been discussed in detail elsewhere (16). The most frequently encountered adverse effects and complications are minor and are related to the mask and ventilator airflow or pressure (Table 13). Nasal pain, either mucosal or on the bridge of the nose, and nasal bridge erythema or ulceration from mask pressure account for a large portion of reported complications (225, 337). These can be ameliorated by minimizing strap tension, using forehead spacers, routinely applying artificial skin to the bridge of the nose in the acute setting, or switching to alternative interfaces such as nasal pillows.

Common adverse effects related to air flow or pressure (Table 13) include conjunctival irritation caused by air leakage under the mask into the eyes and sinus or ear pain related to excessive pressure. Refitting the mask or lowering inspiratory pressure may ameliorate these. Nasal or oral dryness caused by high airflow is usually indicative of air leaking through the mouth. Measures to minimize leak may be useful, but nasal saline or emollients and heated humidifiers are often necessary to relieve these complaints. As noted previously, high nasal airflow related to air leaking through the mouth increases nasal resistance (297), so measures to control the leak should be undertaken. Nasal congestion and discharge are also frequent complaints, and may be treated with topical decongestants or steroids, and oral antihistamine/decongestant combinations. Gastric insufflation occurs commonly, may respond to simethicone, and is usually well tolerated.

Some air leaking through the mouth (with nasal masks), through the nose (with mouthpieces), or around the mask (with all interfaces) is virtually universal with NPPV. In the acute setting, control of leaks is important, because air leaking through the mouth is associated with the reappearance of substantial phasic diaphragm EMG activity (112), and patients who fail NPPV have larger mouth leaks than do those who succeed (191). On the other hand, leaks large enough to render NPPV ineffective have been reported in only a small minority of patients treated for chronic respiratory failure (225, 296). Ventilation is sustained because pressure-limited ventilators compensate for leaks by increasing inspiratory flow during leaking, and tidal volumes on volume-limited ventilators can be increased to compensate. Clinicians are cautioned to avoid excessive increases in tidal volume, however, because these may cause narrowing of the glottic aperture (300), and large leaks may contribute to arousals and poor sleep quality (296, 313). Measures to reduce air leaking include patient instructions to keep the mouth closed, application of chin straps, bite blocks, or switching to oronasal masks or mouthpieces. Air leaking continues to be a formidable problem during NPPV. Further studies are needed to better define the problem, to assess the efficacy of current methods for coping with leak, and to identify new therapeutic strategies.

Failure of NPPV has been reported in 7 to 42% of patients (103–125, 128–132, 224–229). The highest success rates are seen for patients with COPD in the acute setting, and for neuromuscular patients in the chronic setting. The most common reasons for failure are failure to improve ventilation, intolerance related to mask discomfort, a sensation of excessive air pressure, or claustrophobia (337). Uncomfortable patients become agitated and have difficulty coordinating their breathing with the ventilator, thus receiving no effective ventilatory assistance. Failure to assist ventilation may also be caused by inadequate inflation pressures, nasal obstruction, secretion retention, or excessive air leaking. In order to minimize failure rates, clinicians should be prepared to try different masks and to make frequent readjustments in strap tension and ventilator pressure. Coaching, encouragement, efforts to control air leaks, and judicious use of sedatives may improve success rates.

Patient-ventilator asynchrony may also contribute to NPPV failure, particularly in the acute setting. Calderini and colleagues (338) demonstrated marked asynchrony when NPPV was used in the PSV mode, particularly during air leaking. Meyer and colleagues (296) observed a similar phenomenon in which the ventilator failed to sense inspiratory effort or the onset of expiration. The ventilator cycles at the set backup rate and sustains inspiration for the maximal duration as set by the manufacturer (as long as 3 s for some bilevel devices). The patient must exert greater effort during expiration, contributing to respiratory distress (60). Minimizing air leaks and using ventilators that allow setting of inspiratory trigger sensitivity and a shorter maximal inspiratory duration (0.5 to 1.5 s, depending on the patient's inspiratory time) may ameliorate this problem (339).

Daytime gas exchange may fail to improve in occasional patients using long-term noninvasive ventilation, most often related to insufficient hours of nocturnal use because of patient noncompliance. Failure to improve may also be related to inadequate inspiratory pressure, tidal volume or ventilator rate, or excessive air leaking through the mouth. Daytime gas exchange may also deteriorate after prior stabilization. Progression of the patient's underlying neuromuscular or respiratory disorder may also be responsible (200). The deterioration often responds to increases in inspiratory pressure, tidal volume, ventilator rate, or duration of assisted ventilation/24 h. If not, nocturnal monitoring should be performed to assess patient synchrony with the ventilator and the severity of air leaking. If gas exchange fails to improve despite these measures or the patient fails to tolerate NPPV, trials with alternative noninvasive ventilators may be successful. If the patient has persisting symptomatic hypoventilation despite prolonged trials with noninvasive ventilators or loses the ability to protect the upper airway, tracheostomy ventilation may be necessary if the patient desires maximal prolongation of life.

When Pa_{CO_2} fails to improve, the possibility that rebreathing is contributing should also be considered, particularly when patients are using a bilevel device that has a single ventilator tube for both inspiration and expiration. Ferguson and Gilmartin (65) have demonstrated that rebreathing may interfere with the ability of these ventilators to lower CO_2 when used with certain expiratory valves at low expiratory pressures. This problem should be minimized as long as expiratory pressures of at least 4 cm H_2O are used to provide adequate bias flow. Also, more evaluation of this phenomenon is needed to determine its clinical significance, since available studies have been performed mainly in laboratory settings (65, 321, 322).

As previously discussed, hemodynamic effects of positive pressure ventilation, whether administered invasively or noninvasively, may be adverse or beneficial depending on fluid status and cardiac function (293, 294). In general, NPPV is well tolerated hemodynamically, presumably because of the low inflation pressures used compared with invasive ventilation. However, caution is advised when applying any form of ventilation to patients with a tenuous hemodynamic status or

underlying cardiac disease. A trial of bilevel ventilation for patients with acute pulmonary edema observed an increased rate of myocardial infarction associated with a greater early drop in blood pressure compared with CPAP alone (152). Thus, in these patients, clinicians are encouraged to begin with CPAP alone or bilevel ventilation using relatively low inflation pressures (11 to 12 cm H_2O inspiratory, 4 to 5 cm H_2O expiratory pressures) while monitoring the clinical response. Also, NPPV should be avoided in patients with uncontrolled ischemia or arrhythmias until these problems are stabilized.

Patients with other forms of acute respiratory failure appear to tolerate NPPV quite well. Diaz and colleagues (340) reported a fall in cardiac output without any change in mixed venous P_{O_2} in patients with acute exacerbations of COPD treated with NPPV. This suggests that the change in cardiac output was related to a fall in oxygen consumption attributable to a reduction in work of breathing as evidenced by a drop in respiratory rate from 26 to 19/min. Thorens and colleagues (341) studied hemodynamic responses to NPPV in 11 patients with acute or chronic respiratory failure and cor pulmonale. Right ventricular function improved associated with a drop in plasma brain natriuretic peptide level, but no significant changes in levels of other hormones in the renin-angiotensin system were observed.

Major complications of noninvasive ventilation occur infrequently in appropriately selected patients and can be minimized by excluding inappropriate patients. Aspiration pneumonia has been reported in as much as 5% of patients (125). Rates of aspiration are minimized by excluding those with compromised upper airway function or problems clearing secretions and permitting at-risk patients nothing by mouth until they are stabilized. A nasogastric tube can be inserted if the patient has excessive gastric distention, an ileus, nausea or vomiting, or is deemed to be at high risk for gastric aspiration. However, such patients are not ideal candidates for NPPV, and nasogastric or orogastric tubes should not be routinely used because they interfere with mask fitting, promote air leaking and add to discomfort. NPPV should not be applied to patients with high esophageal and/or tracheal injuries. Probably because of the low inflation pressures used with NPPV compared with invasive ventilation, pneumothoraces occur very infrequently. Nonetheless, inspiratory pressures should be kept at the minimum effective level in patients with bullous lung disease.

SUMMARY AND CONCLUSIONS

Use of NPPV has rapidly proliferated during the past decade. Previously, body ventilators such as negative pressure devices were the main noninvasive means of assisting ventilation. After the introduction of the nasal mask to treat obstructive sleep apnea during the mid-1980s and the subsequent development of nasal ventilation, NPPV became the ventilator mode of first choice to treat patients with chronic respiratory failure. More recently, NPPV has been attaining acceptance for certain indications in the acute setting, as well.

On the basis of controlled trials demonstrating marked reductions in intubation rates as well as improvements in morbidity, mortality, and complication rates, NPPV is now considered the ventilatory mode of first choice in selected patients with COPD exacerbations. The indications for NPPV are not as clear in patients with non-COPD causes of acute respiratory failure. For acute pulmonary edema, CPAP alone drastically reduces the need for intubation, although studies have not demonstrated reductions in morbidity or mortality rates. NPPV avoids intubation and reduces complication rates in patients with hypoxemic respiratory failure, but more controlled trials are needed to establish precise indications. In the meantime, NPPV administration to patients with non-COPD causes of acute respiratory failure appears to be safe as long as patients are selected carefully with particular attention to the exclusion of inappropriate candidates.

A possible role is also emerging for NPPV in the facilitation of weaning patients from invasive mechanical ventilation. In this context, noninvasive ventilation can be used to permit earlier removal of invasive airways than would otherwise be the case, to prevent reintubation in patients developing postextubation respiratory failure, and to serve a prophylactic role in postoperative patients who are at high risk for pulmonary complications.

For chronic respiratory failure, a wide consensus now favors the use of NPPV as the ventilatory mode of first choice for patients with neuromuscular diseases and chest wall deformities, despite a lack of randomized controlled trials. Central hypoventilation and failure of obstructive sleep apnea to respond to CPAP are also considered acceptable indications, although evidence to support these latter applications is sparse. For patients with severe stable COPD, some evidence supports the use of NPPV in severely hypercapnic patients, particularly if there is associated nocturnal hypoventilation. However, the data are conflicting and do not permit the formulation of firm selection guidelines.

NPPV has emerged as the noninvasive ventilation mode of first choice over alternatives such as negative pressure ventilation or abdominal displacement ventilators. However, these latter techniques are still used in some areas of the world and may be effective for patients who fail NPPV because of mask intolerance. Noninvasive ventilation has undergone a remarkable evolution over the past decade and is assuming an important role in the management of both acute and chronic respiratory failure. Appropriate use of noninvasive ventilation can be expected to enhance patient comfort, improve patient outcomes, and increase the efficiency of health care resource utilization. Over the next decade, continued advances in technology should make noninvasive ventilation even more acceptable to patients. Future studies should better define indications and patient selection criteria, further evaluate efficacy and effects on resource utilization, and establish optimal techniques of administration.

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