

International Consensus Conferences in Intensive Care Medicine: Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure

ORGANIZED JOINTLY BY THE AMERICAN THORACIC SOCIETY, THE EUROPEAN RESPIRATORY SOCIETY, THE EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE, AND THE SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE, AND APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2000

Noninvasive positive pressure ventilation (NPPV) was applied first to patients with chronic pulmonary disease but is now being used to support those with acute respiratory failure (ARF). An International Consensus Conference in Intensive Care Medicine considering the role of NPPV in ARF was held in Paris, France, from April 13–14, 2000; sponsored by the Critical Care Assembly of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the European Society of Intensive Care Medicine (ESICM), and the Société de Réanimation de Langue Française (SRLF).

The methods of the Consensus were established by the National Institutes of Health (1) and adapted subsequently for use in critical care medicine (2). Briefly, the process comprised four phases. First, five key questions were formulated by the scientific advisors designed to address issues integral to the evaluation of noninvasive ventilatory support in its current and future roles. Second, a comprehensive literature search was performed and key articles precirculated to a jury of 10 clinician scientists who were not experts in the field under discussion. Third, authorities in NPPV selected by the Organizing Committee and scientific advisors delivered focused presentations during a two-day symposium attended by the jury and about 150 delegates. Each presentation was followed by debate and discussion. Finally, the jury summarized the available evidence in response to the questions over the two days immediately after the conference.

For the purposes of this report, NPPV was defined as any form of ventilatory support applied without the use of an endotracheal tube, and was considered to include continuous

positive airway pressure (CPAP), with or without inspiratory pressure support; volume- and pressure-cycled systems, proportional assist ventilation (PAV), and adjuncts such as the use of helium–oxygen (heliox) gas mixtures. The term acute respiratory failure (ARF) was considered to include patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), those with acute exacerbations of obstructive airflow limitation (i.e., asthma and COPD); acutely decompensated patients with the obesity hypoventilation syndrome (OHS) and cardiogenic pulmonary edema (CPE); patients developing ARF in the perioperative period; and those with either difficulty weaning from invasive mechanical ventilatory support, or in whom endotracheal intubation (ETI) was considered inappropriate. The information presented to the jury was designed to address the following five questions.

QUESTION 1: WHAT ARE THE RATIONALE, POTENTIAL BENEFITS, AND GOALS FOR NPPV?

Patients require ventilatory assistance to reduce the Pa_{CO_2} (Figure 1) and/or to improve oxygenation (Figure 2). If they can receive appropriate noninvasive ventilatory assistance, patients are spared the discomfort and risks associated with endotracheal intubation (ETI). Although studies suggest that NPPV is associated with a reduced incidence of nosocomial pneumonia, methodological problems mandate reinvestigation of this issue. Potential benefits must be balanced against the discomfort of a nasal or facial mask and risks specific to NPPV (e.g., failure to provide sufficient oxygenation or CO_2 elimination, eye or nasal trauma, gastric distension/aspiration).

The goals of NPPV differ depending upon the clinical context. During acute decompensations of asthma or COPD, the goal is to reduce CO_2 by unloading the respiratory muscles and augmenting alveolar ventilation, thereby stabilizing arterial pH until the underlying problem can be reversed. When employed during episodes of hypoxemic ARF the goal is to ensure an adequate Pa_{O_2} until the underlying problem can be reversed. When applied continuously to patients with chronic ventilatory failure the goal of NIPPV is to provide sufficient oxygenation and/or CO_2 elimination to sustain life by reversing atelectasis or resting the respiratory muscles. When applied intermittently to patients with OHS, the goal is to limit sleep- and position-induced adverse changes in oxygenation and CO_2 elimination and their pathophysiological sequelae by stenting the upper airway, increasing lung volume, and augmenting alveolar ventilation. In cardiogenic pulmonary edema, the goal of NPPV is to improve oxygenation, reduce work of breathing, and increase cardiac output.

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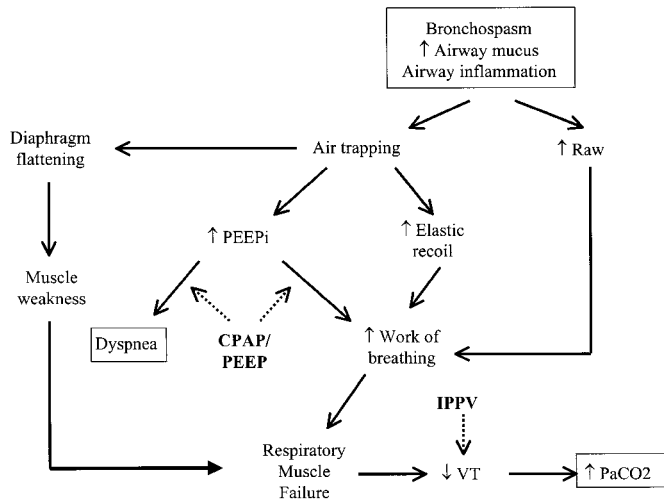


Figure 1. When PaCO_2 is increased, and minute ventilation is normal or increased, the respiratory muscles are failing to generate sufficient alveolar ventilation to eliminate the CO_2 being produced. Means of correcting this pathophysiology include increasing alveolar ventilation by increasing tidal volume and/or respiratory rate, and reducing CO_2 production (\dot{V}_{CO_2}) by decreasing the work of breathing. Respiratory muscle failure can occur when the work of breathing is normal (e.g., numerous acute or chronic neuromuscular problems), or increased (e.g., patients with COPD, asthma, or the obesity hypoventilation syndrome), and presumably because of inadequate delivery of oxygen to the respiratory muscles (e.g., approximately one-third of patients presenting with cardiogenic pulmonary edema). When PaCO_2 is increased and minute ventilation is low the level of consciousness is generally impaired. Such patients usually require intubation for airway protection in addition to ventilatory assistance, unless the hypercapnia can be reversed within minutes.

Determining whether NPPV Is a Valuable Approach in Clinical Practice

The clinical and physiologic rationales for NPPV suggest it may have advantageous (e.g., avoidance of ETI), and/or disadvantageous (e.g., failure to provide adequate gas exchange) effects. Similarly, NPPV may decrease (e.g., reduced requirement for ICU) or increase (e.g., costs of staff training/education and patient contact time) resource utilization. These potentially competing effects will determine whether NPPV is a valuable procedure and mandate careful assessment of the epidemiology of potential target populations, the effects on patient outcomes and costs, and the rigor with which studies were conducted.

Epidemiology and Potential Target Populations for NPPV

Most clinical data are derived from interventional trials, which often did not keep comprehensive logs of excluded patients. Reports of nontrial data have detailed the number of candidates for NPPV (numerator) without recording the total number of cases (denominator). However, a single-center study in the United Kingdom suggested up to 20% of hospitalized patients with chronic obstructive pulmonary disease (COPD) may be candidates for NPPV (3). Second, a survey of NPPV use in 42 medical intensive care units (ICUs) in France, Switzerland, and Spain demonstrated NPPV was used prior to mechanical ventilation in 16% of cases (range, 0–67%) (4). Last, a survey of hospitals in the United Kingdom found that 52% do not have the capability to provide NPPV and 68% of those who do use NPPV to treat fewer than 20 patients per year (5). There are no data from surgical ICUs and almost no information on non-COPD patients.

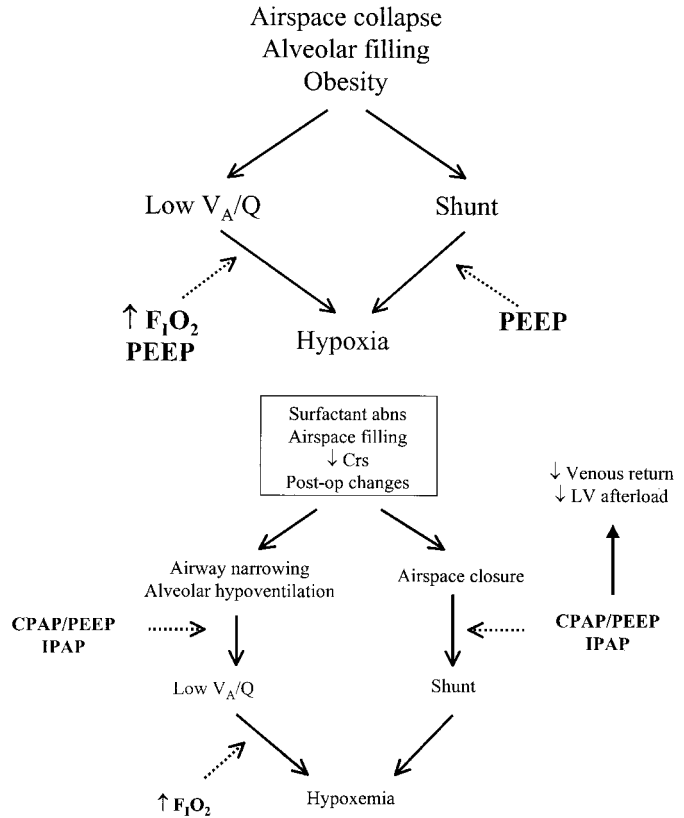


Figure 2. Hypoxemia develops as a result of alveolar hypoventilation (which is accompanied by increases in PaCO_2 and is addressed in Figure 1) and from perfusion going to areas where the ratio of alveolar ventilation (\dot{V}_A) to perfusion (\dot{Q}) is < 1.0 (i.e., low \dot{V}_A/\dot{Q} or, in the extreme, shunt, where perfusion is going to areas of no ventilation). Hypoxemia is treated by augmenting the FiO_2 (the lower the \dot{V}_A/\dot{Q} , the less the effect), and by recruiting airspaces. Airspace derecruitment occurs when the transpulmonary pressure falls below the airspace collapsing or closing pressure (as occurs in numerous conditions that alter surfactant or that decrease the lung or the chest wall compliance), and when the transpulmonary pressure applied during inhalation fails to exceed airspace opening pressure. Accordingly, airspace opening can be facilitated by increasing the transpulmonary pressure applied at end exhalation (CPAP) and at end inhalation (i.e., IPAP). An additional beneficial effect of CPAP and IPAP may be seen in patients with cardiogenic pulmonary edema, as they all reduce venous return and functionally reduce left ventricular afterload. abns = abnormalities; Crs = respiratory system compliance.

Patient-centered Outcomes and Costs

Patient-centered outcome trials have principally addressed rates of ETI, pneumonia, length of ICU or hospital stay, and mortality; together with patient comfort, compliance, and/or tolerance. Criteria for ETI have varied and included subjective decision making as well as that made by physicians not directly involved in the trial. Criteria for the diagnosis of ventilator-associated pneumonia or hospital discharge have been suboptimal or unspecified; and tolerance and comfort not objectively defined. To determine economic value, costs should be assessed to determine if NPPV is cost-effective (after effectiveness is determined) or less expensive (after equivalence has been demonstrated) (6). One cost-effectiveness study from the United Kingdom has demonstrated NPPV for COPD patients to have decreased costs and mortality compared with standard ward care, although the control arm had a high mortality (7). Studies of NPPV costs have highlighted the need to consider numerous costs, including those associated with personnel and

patient training and education, personnel time, and capital equipment as well as other direct and indirect health care expenditures. Lost wages, pain and suffering, and postdischarge healthcare costs over an extended time horizon are also relevant (8).

Study Design Considerations in the Evaluation of Questions 2–5

Important caveats regarding the study designs used in evaluating novel clinical interventions (Table 1) are relevant to NPPV. First, matching patients in nonrandomized trials is problematic, especially in the non-ICU setting, where severity of illness scoring systems are not validated. Second, small, heterogeneous samples means randomization processes may fail to distribute confounding variables equally. Third, the intervention may have undetected adverse effects in different study subgroups, decreasing mortality overall despite increasing deaths in a particular subgroup. Fourth, because all studies using NPPV are by necessity unblinded, end points may be influenced by confounding interventions such as increased care and surveillance. This effect can be minimized by standardizing care processes (9). Fifth, NPPV trial end points may in-

volve subjective elements. Standardizing assessment (used in some studies) and employing blinded observers may help. Finally, many studies have been single-center trials, conducted by investigators with significant expertise in the use of NPPV, and may overestimate effectiveness with widespread use.

Conclusions

- The pathophysiology of the conditions leading to hypercarbic or hypoxemic ARF is amenable to interventions available within the context of NPPV.
- Depending on the specific condition leading to respiratory failure, there is a physiologic rationale for the application of both inspiratory assistance and/or positive end-expiratory pressure.
- If adequate alveolar ventilation and oxygenation can be safely provided, NPPV has the potential of reducing the morbidity, and possibly the mortality, associated with hypercarbic or hypoxemic respiratory failure.
- Although there have been many carefully conducted randomized trials assessing NPPV, methodologic limitations affect the interpretation of current evidence.

TABLE 1
RANDOMIZED CONTROLLED TRIALS OF NONINVASIVE POSITIVE PRESSURE VENTILATION

Study (Reference)	Population	Site	Intervention		Sample Size		Study Design		Results (Effect of NPPV)			
			NPPV	Control	NPPV	Control	Co-intervention Standardized	Intubation Criteria Standardized	ETI or Failure Criteria	Mortality	Physiology Improved	Complications
Bersten and coworkers, 1991 (20)	ACPE	ED-ICU	CPAP	UMC	19	20	No	Yes	↓	↔	Yes	NR
Bott and coworkers, 1993 (40)	COPD	Ward	ACV	UMC	30	30	No	No	↓	↓*	Yes	NR
Wysocki and coworkers, 1995 (35)	ARF (no COPD)	ICU	PSV + PEEP	UMC	21	20	Yes	Yes	↔	↔	NR	↔
Brochard and coworkers, 1995 (43)	COPD	ICU	PSV	UMC	43	42	Yes	Yes	↓	↓	Yes	↓
Kramer and coworkers, 1995 (36)	ARF	ICU	IPAP + EPAP	UMC	16	15	No	Yes	↓	↔	Yes	↔
Barbe and coworkers, 1996 (39)	COPD	Ward	IPAP + EPAP	UMC	20	20	Yes	No	↔	↔	Yes	NR
Mehta and coworkers, 1997 (21)	ACPE	ED-ICU	IPAP + EPAP	CPAP	14	13	Yes	No	↔	↔	Yes	↑†
Nava and coworkers, 1998 (48)	COPD (weaning)	ICU	PSV + PEEP	PSV + PEEP (invasive)	25	25	No	Yes	NR	↓	Yes	↓
Celikel and coworkers, 1998 (64)	COPD	ICU	PSV + PEEP	UMC	15	15	Yes	No	↓‡	↔	Yes	NR
Antonelli and coworkers, 1998 (18)	AHRF	ICU	PSV + CPAP	ACV + PEEP, SIMV + PSV + PEEP	32	32	Yes	Yes	↓§	↔	Yes	↓
Wood and coworkers, 1998 (32)	ARF, AHRF	ED	IPAP + EPAP	UMC	16	11	No	Yes	↔	↔	No	↔
Confalonieri and coworkers, 1999 (24)	CAP + ARF, AHRF	Intermediate care	PSV + CPAP	UMC	28	28	No	Yes	↓	↔	Yes	↔
Girault and coworkers, 1999 (49)	ARF (weaning)	ICU	PSV + PEEP; ACV + PEEP	PSV + PEEP (invasive)	17	16	No	Yes	↔	↔	Yes	↔
Jiang and coworkers, 1999 (51)	Post extubation	ICU	IPAP + EPAP	UMC	47	46	No	No	↔	↔	NR	NR
Antonelli and coworkers, 2000 (19)	ARF (solid organ transplantation)	ICU	PSV + PEEP	UMC	20	20	Yes	Yes	↓	↓	Yes	↓
Martin and coworkers, 2000 (44)	ARF, AHRF	ICU	IPAP + EPAP	UMC	32	29	No	No	↓	↔	NR	↔
Plant and coworkers, 2000 (7)	COPD	Ward	Pressure cycled	UMC	118	118	Yes	Yes	↓	↓	NR	NR

Definition of abbreviations: ACPE = acute cardiogenic pulmonary edema; ACV = assist control (volume-cycled) ventilation; AHRF = acute hypoxemic respiratory failure; ARF = acute hypercapnic respiratory failure; ED = emergency department; EPAP = expiratory positive pressure; ETI = endotracheal intubation; intermediate care = intermediate respiratory care unit; IPAP = inspiratory positive airway pressure; NR = not reported; postextubation = studies using NPPV to prevent reintubation after extubation; PSV = pressure support ventilation; SIMV = synchronous intermittent mandatory ventilation; UMC = usual or standard medical care; weaning = studies that used NPPV to facilitate weaning from mechanical ventilation.

* After exclusion of four patients who did not tolerate NPPV (no difference in mortality with intention-to-treat analysis).

† All patients in the control group were intubated.

‡ Includes patients in the control group who required NPPV after satisfying failure criteria.

§ Increased incidence of myocardial infarction.

|| ICU mortality (no difference noted in hospital mortality).

Recommendations

1. To better understand the pathophysiology, studies should address
 - The relative importance of inspiratory assistance versus end-expiratory pressure in treating acute exacerbations of asthma, COPD, and cardiogenic edema
 - Means of rapidly identifying patients who will improve in response to NPPV (possibly changes in tidal volume)
 - Whether the physiologic differences between asthma and COPD (e.g., elastic recoil) alter the response to NPPV
2. Further information should be gained concerning the epidemiology of potential target populations, especially in terms of incidence and case definition.

QUESTION 2: WHAT EQUIPMENT AND WHICH MODES OF VENTILATION SHOULD BE USED?

Optimal implementation of NPPV involves selecting the appropriate patient interface (the mask), connected to a ventilator suitable for the operational environment and capable of delivering air-oxygen mixtures at variable flow rates and pressures. Monitoring patient response involves both appropriate equipment and skilled staff. Inexpert management of equipment or ventilation mode may be responsible for failure of the technique.

Interface

The patient interface most commonly employed is a full-face or nasal mask secured firmly, but not tightly, with a headstrap. The full-face mask delivers higher ventilation pressures with less leak, requires less patient cooperation, and permits mouth breathing. However, it is less comfortable, impedes communication, and limits oral intake. The nasal mask needs patent nasal passages and requires mouth closure to minimize air leaks. It is more commonly used for chronic ventilatory failure and, with these provisos, tends to be better tolerated. Gas leaks around the mask or from the mouth limit the efficacy of the device, make monitoring of tidal volume difficult, and represent an important cause of failure (10). Leaks may also indicate low compliance or ventilation close to total lung capacity. Both devices can lead to pressure necrosis of the skin over the nasal bridge (10). Avoiding this complication requires careful attention, the use of cushioning materials, and "rest" periods in which nasal pillows or a conventional oxygen mask is used. Large NPPV masks increase dead space and nonrebreathing (i.e., dual tube) delivery circuits should be employed. Inadequate humidification may cause patient distress, especially if pipeline or cylinder gas is used. Other complications include gastric distension and claustrophobia. Ventilatory support should be introduced gradually, starting with CPAP and adding inspiratory pressure support as required. The process should be controlled by an experienced attendant working with the patient and observing his or her response and comfort, using manual mask application at first to minimize the sense of claustrophobia.

Ventilatory Modes

NPPV can be applied with pressure generators or volume preset ventilators. CPAP is delivered either by a flow generator with high-pressure gas source, or using a portable compressor. CPAP alone can be applied in various forms of hypoxemic ARF provided the patient can breath spontaneously. In pressure-limited modes, tidal volume (V_T) may vary. When there is no spontaneous inspiratory effort or it is adequate to trigger the ventilator, the respiratory rate and the inspiratory-to-expi-

ratory ratio can be imposed by the attendant (pressure-controlled ventilation, PCV). During pressure-support ventilation (PSV), the ventilator is triggered by the patient and cycles to expiration either when it senses a fall in inspiratory flow rate below a threshold value, or at a preset time. These modes can be applied by conventional ventilators, or via bilevel positive airway pressure generators that provide high-flow CPAP and cycle between a high inspiratory pressure and a lower expiratory pressure. These devices reliably detect inspiratory effort even in the presence of circuit leaks. Modern ICU ventilators can also provide biphasic positive airway pressure ventilation, alternating at fixed intervals between two pressures and permitting unrestricted breathing at both levels. NPPV can be given using volume-limited modes. During volume-cycled NPPV, the ventilator delivers a set V_T for each breath and inflation pressures may vary. The assist/control mode (ACV) ensures that tidal breaths are triggered or imposed depending on the presence and magnitude of inspiratory efforts. Spontaneous breathing can be assisted using volume support ventilation, a mode in which the ventilator adjusts inspiratory pressures to deliver a preset V_T in response to inspiratory effort. In PAV the ventilator generates volume and pressure in proportion to the patient's effort, facilitating a ventilatory pattern that matches metabolic demand on a breath-by-breath basis (11). PAV may optimize patient-ventilator interaction by shifting responsibility of guiding the ventilatory pattern from the caregiver to the patient. To date, there are no conclusive data specifically to recommend the use of PAV in NPPV.

Application

All modes have theoretical advantages and limitations. Volume cycled support can be safely used in patients with changing respiratory impedance. By contrast, because peak mask pressure is not limited when volume-targeted modes are used, these are more susceptible to leaks, gastric distension, pressure sores, and skin necrosis. Provided that lung compliance remains constant, PSV can ensure reliable ventilation while minimizing side effects and improving patient comfort. However, leaks may be responsible for prolonged inspiratory flow despite expiratory efforts and patient-ventilator asynchrony (12). Time-cycled, pressure-targeted modes can overcome this problem. During assisted ventilation, sensitive triggering systems with short response times decrease work of breathing and enhance patient-ventilator synchrony. To date, flow-triggered systems appear superior to pressure-triggered systems (13, 14).

All modes of NPPV have been used to achieve significant physiological or clinical benefit. In ARF secondary to acute exacerbations of COPD, ACV, PSV, and PAV have all led to improvements in minute ventilation, respiratory rate, and arterial blood gases while unloading the respiratory muscles and relieving respiratory distress (15, 16). Volume- and pressure-controlled modalities appear to reduce inspiratory workload better than PSV (17). Addition of positive end-expiratory pressure (PEEP) counteracts the effect of intrinsic PEEP (PEEPi), thereby reducing diaphragmatic effort and oxygen consumption. Clinical studies in hypoxemic ARF of different etiologies indicate that NPPV can improve arterial blood gases, respiratory rate, dyspnea, and use of accessory muscles (18, 19). In acute CPE, mask CPAP decreases respiratory rate, corrects respiratory acidosis, and improves hemodynamics (20). Other ventilatory modes, including PSV, are equally efficient in reducing respiratory workload and improving physiological variables, but may be associated with adverse hemodynamic effects (21).

Few studies have examined differences between the various NPPV modes in terms of physiological response. In acute

hypercapnic exacerbations of COPD, two studies failed to find any differences in clinical outcome or arterial blood gas tensions between patients ventilated in ACV and PSV modes (22, 23). Both modalities improved breathing pattern and provided respiratory muscle rest. Assist-control ventilation produced a lower respiratory workload, but with greater respiratory discomfort, more frequent loss of control of breathing, and diminished ability to compensate for mask leaks than PSV (17). In the absence of evidence favoring a specific ventilatory mode, choice should be based on local expertise and familiarity; and tailored to the etiology, stage, and severity of the pathophysiologic process responsible for ARF. Controlled modes may be preferred for patients with severe respiratory distress, unstable ventilatory drive or respiratory mechanics, apneas, or hypoventilation. In other conditions, assisted modalities can be safely implemented.

Type of Ventilator and Alarms

NPPV can be satisfactorily performed using portable or (many) standard ICU ventilators, a choice that should be dictated by personal experience, the patient's condition and therapeutic requirements, and—importantly—the location of care. Given that the risk of subsequent endotracheal intubation may be as high as 40% in hypoxemic ARF (24), such patients should be managed in an area where ICU staff and equipment are immediately accessible. Selection and setting of alarms are determined by the choice of a volume- or pressure-regulated mode. As the existence of mask leaks is associated with a higher incidence of failure, close monitoring for leaks is mandatory to optimize ventilatory settings and practical implementation of NPPV.

Monitoring

Monitoring levels should be determined by the patient's condition and the site of care. Clinical assessment (patient comfort, use of accessory muscles, presence or absence of stress responses) as well as cyanosis, tachycardia, and tachypnea and conventional vital signs (blood pressure, level of consciousness) should be monitored. Arterial blood gas analysis may be required to document base deficit and P_{aCO_2} ; pulse oximetry should be used for continuous monitoring of oxygenation. Patients with acute hypoxemia, persistent acidosis, or nonrespiratory organ system involvement, or whose condition is deteriorating, require a higher level of monitoring, which may include central venous access and arterial cannulation.

Conclusions

- There is no evidence to support the use of particular patient interface devices. Clinical experience suggests that full-face masks improve efficacy by reducing leaks and are more appropriate for use in the setting of severe hypoxemic ARF.
- To be effectively initiated in all clinical areas, a wide array of interfaces must be available for immediate use.
- Choice of mode should be based on local expertise and familiarity, tailored to the etiology and severity of the pathophysiological process responsible for ARF.
- Ventilator settings should be adjusted to provide the lowest inspiratory pressures or volumes needed to produce improved patient comfort (a decrease in respiratory rate and respiratory muscle unloading) and gas exchange.
- The type of ventilator and level of monitoring should be determined by the severity of illness and location of care.

Recommendations

Health technology research in this area should focus on improvements to the patient–ventilator interface, further evalua-

tion of different ventilatory modes, and the development of systems which automatically adapt ventilatory assist to changes in the patient's condition

QUESTION 3: WHO SHOULD ADMINISTER NPPV AND IN WHAT LOCATION?

Although the majority of studies have been conducted in intensive or respiratory care units, NPPV (unlike invasive mechanical ventilation) provides an opportunity for delivering ventilatory support elsewhere. NPPV need not be delivered continuously to be effective, can be reasonably initiated in the earliest stages of ARF, and administered by means of small, portable equipment. Potentially, NPPV can be administered in the emergency department, intermediate care unit, or general respiratory ward by physicians, nurses, or respiratory care practitioners. Potential benefits of use outside the ICU include early intervention to prevent further respiratory deterioration (7), access to respiratory support for patients who would not otherwise be admitted to the ICU (25–29), and the provision of support in a less intimidating setting. The location in which NPPV is best performed depends on numerous unit-specific factors, including staff experience and availability of resources (e.g., number of beds, personnel, and technical equipment); and on the etiology of ARF and the severity of illness, which determine the likelihood of NPPV success (30). Selection of patients who may benefit from NPPV is based on initial evaluation and/or the response to a short-term trial. The latter requires a skilled team and adequate monitoring to avoid delay in instituting invasive ventilatory support should NPV fail (31, 32). For the first few hours, one-to-one monitoring by a skilled and experienced nurse, respiratory therapist, or physician is mandatory. Monitored parameters should include Sa_{O_2} , arterial blood gases (P_{aCO_2} , pH), vital signs, patient comfort, mask leaks, and the patient's capacity to handle expectorated secretions. Failure to respond to NPPV may be indicated by persistently abnormal blood gases (28, 30), breathing pattern, and frequency, the development of hemodynamic instability or encephalopathy, and failure to tolerate the device. The optimal location for patients receiving NPPV depends on the capacity for adequate monitoring, staff skill and experience in explaining the procedure, their knowledge of the equipment used, and awareness of potential complications. The success rate of NPPV is remarkably similar when comparing clinical trials performed in a research setting with those carried out by usual care providers (33). Similarly, uncontrolled, observational studies in a community teaching hospital (34), and a prospective survey of 42 ICUs in Europe, indicate that 60–65% of patients with various forms of ARF can be successfully treated with NPPV (4).

Initiation of NPPV in the Emergency Department

Retrospective analyses, uncontrolled studies, and some randomized, controlled trials (RCTs) indicate that NPPV can be successfully initiated in the emergency department (ED) (35–37). Similarly, trials showing benefit of NPPV in CPE have included patients in whom CPAP was started in the ED (21). A single negative, randomized controlled trial of NPPV in the ED showed a trend toward increased mortality, although the study had numerous design limitations (32).

Administration of NPPV in the General Ward

In an RCT conducted in an intermediate care unit, NPPV led to a reduction in the need for intubation and duration of stay when compared with standard treatment of patients with COPD and community-acquired pneumonia (24). Observa-

tional and case-controlled studies indicate that NPPV administered in a general respiratory ward can reduce the need for ETI (38). Several RCTs of patients with acute exacerbations of COPD have been carried out in the general ward setting with mixed results (39, 40).

In a multicenter trial of patients with exacerbations of COPD (pH 7.25–7.35, Pa_{CO₂} > 45 mm Hg, respiratory frequency > 23), NPPV was initiated and maintained by the ward staff according to a strict protocol and after extensive training. Using prospectively defined criteria, NPPV reduced the need for ETI and hospital mortality. In a subgroup analysis, patients with a pH < 7.30 after 4 h of therapy had a prognosis worse than that seen in comparable studies conducted in the intensive care unit (7).

Influence of NPPV on Workload

An early, uncontrolled report indicated that NPPV created an excessive workload for ICU nurses (41). Subsequent controlled investigations including evaluations of respiratory therapist time have shown this not to be the case (24, 36). When invasive ventilation and NPPV were compared, no differences were found in the time doctors, nurses, or therapists spent at the bedside during the initial 6 h of ventilatory support. In the subsequent 42 h, less nursing time was required to monitor patients receiving NPPV (42). Studies of NPPV administered in the respiratory ward noted that nursing time was not significantly different when comparing patients managed using NPPV with control subjects (40).

Conclusions

- No RCTs have compared NPPV initiated and maintained in the ICU with that performed in other venues.
- NPPV can be effectively delivered outside the context of a clinical trial.
- Available studies indicate that NPPV can be initiated outside the ICU.
- Most investigators have managed patients in an ICU or equivalent environment.
- The best venue depends on local factors such as the training and experience of the staff, available resources (beds, staff, equipment), and monitoring capacity.
- Delivery of NPPV does not appear to increase nursing or respiratory therapist workload.

Recommendations

- NPPV can be initiated in the ED when staff have been adequately trained.
- Until more data are available, most patients receiving NPPV should be managed in an ICU or within a system of care capable of providing high-level monitoring, with immediate access to staff skilled in invasive airway management.
- In selected patients with exacerbations of hypercapnic COPD (pH \geq 7.30), NPPV may be initiated and maintained in the ward when staff training and experience are adequate.
- When NPPV is initiated outside the ICU, failure to improve gas exchange, pH, respiratory rate, or dyspnea, or deterioration in hemodynamic or mental status, should prompt referral to the ICU service.

QUESTION 4: WHAT ARE THE INDICATIONS FOR NPPV IN PATIENTS WITH ARF?

Indications for NPPV depend on the goals of therapy for patients with ARF at the time of intervention. The absence of

large-scale, controlled studies and diverse results obtained in different populations mean NPPV cannot be unequivocally indicated in all patients with ARF. Reasonable therapeutic goals of NPPV include avoidance of ETI; unloading respiratory muscles, which should decrease respiratory rate and the sensation of dyspnea, and increase patient comfort; improving alveolar gas exchange and thus oxygenation and acidosis; decreasing heart rate and improved hemodynamic status; decreasing ICU length of stay and its associated complications, such as nosocomial infection; decreasing hospital stay; and reducing mortality. On the basis of these criteria most patients with ARF should be given the opportunity to receive NPPV and any associated benefit. However, despite a number of uncontrolled but encouraging early studies, subsequent controlled investigations have provided a more balanced picture as to appropriate indications and expectations for the technique. There is general agreement concerning the contraindications for NPPV (Table 2).

NPPV in Patients with ARF Due to Hypoventilation

In a randomized study, patients with acute exacerbations of COPD leading to hypoxemia and hypercapnia received either conventional treatment (CT) or CT plus volume-limited NPPV (40). Compared with CT, patients receiving NPPV displayed significant improvements in pH and Pa_{CO₂} within the first hour of treatment. None of the patients randomized to NPPV required ETI; and their 30-d mortality was significantly lower. Two other studies randomized patients with acute exacerbations of COPD to full-face mask PSV or standard therapy (36, 43). Both reported significant improvements in vital signs and a reduced rate of ETI, fewer other complications, and decreased length of hospital stay and in-hospital mortality for those treated with NPPV. The majority of complications and deaths in the control group were attributable to ETI and subsequent mechanical ventilation, but their mortality was higher (29%) than reported in other studies (43). One study compared PEEP plus PSV with standard therapy for patients stratified according to COPD or non-COPD-related disease (44). The rate of ETI was significantly lower with NPPV compared with standard therapy, although ICU mortality was similar for both treatment groups when considering patients with hypoxemic ARF. Moderate and severe status asthmaticus can result in respiratory failure. However, there are few (uncontrolled) studies comparing CPAP and PSV, and delivery of heliox mixture, that show beneficial effects in reducing ETI and improving alveolar gas exchange (45, 46).

NPPV in Patients with ARF Due to Hypoxemia

Three randomized trials have tested the hypothesis that NPPV prevents ETI in patients with hypoxemic ARF, compared with those that received medical treatment related to the etiology

TABLE 2
CONTRAINDICATIONS TO NPPV

Cardiac or respiratory arrest
Nonrespiratory organ failure
Severe encephalopathy (e.g., GCS < 10)
Severe upper gastrointestinal bleeding
Hemodynamic instability or unstable cardiac arrhythmia
Facial surgery, trauma, or deformity
Upper airway obstruction
Inability to cooperate/protect the airway
Inability to clear respiratory secretions
High risk for aspiration

Definition of abbreviation: GCS = Glasgow Coma Scale.

of ARF with O₂ supplementation. The first found no reduction in the rates of ETI or mortality in patients treated with NPPV, although its use in a subset of patients with PaO₂ > 45 mm Hg was associated with significantly decreased ETI, ICU LOS, and mortality. However, in the subset of patients with pneumonia randomized to receive NPPV, all required ETI (35). Another study reported that NPPV was associated with a significant reduction in the rate of ETI and ICU LOS. However, NPPV did not change the duration of hospitalization or inpatient mortality in patients with ARF secondary to community-acquired pneumonia (24). In patients with hypoxemic ARF following solid organ transplantation NPPV resulted in lower ETI rates, fewer fatal complications, and reduced ICU LOS and mortality. However, hospital mortality did not differ between NPPV and standard therapy groups (19). NPPV has also been compared with invasive ventilatory support in patients with hypoxemic ARF. NPPV was as effective in improving gas exchange, but was associated with fewer serious complications and shorter ICU LOS. The investigators recommended that NPPV may *substitute* for invasive ventilatory support in such patients.

NPPV in Patients with CPE

Two randomized controlled studies showed that CPAP (10–15 cm H₂O) administered via face mask rapidly improved vital signs and oxygenation, and reduced the need for ETI in patients with acute pulmonary edema (20, 47). More recently, CPAP with PSV was shown to increase the rate of myocardial infarction in CPE, although patients in this group had higher rates of chest pain as compared with patients treated with CPAP alone (21).

Conclusions

- Significant controversy exists concerning the exact indications for NPPV in patients with hypoxemic ARF.
- The addition of NPPV to standard medical treatment of patients with ARF may prevent ETI, and reduce the rate of complications and mortality in patients with hypercapnic ARF.
- Several randomized, controlled studies support the use of NPPV as an appropriate treatment in selected patient populations with ARF. A single study has demonstrated NPPV to be an adequate alternative to conventional ventilatory support in such patients. More studies are required to confirm this finding.
- Larger, controlled studies are required to determine the potential benefit of adding NPPV to standard medical treatment in the avoidance of ETI in hypoxemic ARF.

Recommendations

- Patients hospitalized for exacerbations of COPD with rapid clinical deterioration should be considered for NPPV to prevent further deterioration in gas exchange, respiratory workload, and the need for ETI.
- The application of CPAP by face mask, in addition to standard medical treatment, may improve gas exchange and hemodynamic status and prevent ETI in patients with chronic pulmonary emphysema (CPE).
- RCTs are needed that directly compare ICU and non-ICU management of patients with hypercapnic respiratory failure.

QUESTION 5: WHAT ARE THE OTHER INDICATIONS FOR NPPV IN THE ACUTE CARE SETTING?

Data suggest that new indications for NPPV may include assistance in weaning and the avoidance of reintubation, the

support of patients with acute exacerbations of open heart surgery (OHS), in the perioperative period, and in patients deemed not to be intubated.

Use during Weaning and to Avoid Reintubation

Nosocomial pneumonia is common (25%) in patients mechanically ventilated for more than 3 d and has adverse effects on outcome and cost. By contrast, some patients require reintubation after weaning, which is a risk factor for nosocomial pneumonia and may represent an independent adverse prognostic factor. Two randomized trials performed in Europe have investigated these issues in patients with acute exacerbations of chronic hypercapnic respiratory failure (48, 49). After intubation and conventional mechanical ventilation for a period of 2–6 d, and after failure of a conventional T-piece trial, patients were randomized to receive standard weaning using PSV via an ET, or to be extubated to NPPV. Both studies showed a significant decrease in the period of mechanical ventilation when using the noninvasive approach, but only one revealed a significant increase in 3-mo survival, probably through a decrease in the rate of nosocomial pneumonias. Both studies were restricted to a selected population of patients with COPD, and other types of intubated patients were not investigated. Failure of extubation and reintubation are not infrequent clinical problems in the ICU setting. The factors related to higher rates of pneumonia and mortality in this population remain unidentified, but instability between extubation and reintubation may be responsible. If this period is prolonged the probability of complications and death increases. Bearing in mind the importance of these issues, the early institution of NPPV in this population is theoretically attractive. Indeed, NPPV could be potentially applied after extubation to most ICU patients. Retrospective, controlled studies seem to confirm the utility of NPPV in the setting of failed extubation (50), although a randomized, controlled study did not find overall benefit (51). NPPV may be effective in patients suffering unplanned extubation, which occurs in 3 to 13% of intubated patients (52).

Obesity Hypoventilation Syndrome

Observational trials suggest that NPPV is effective in OHS (53–55). If the patient presents with severe obstructive apneas, nasal CPAP and oxygen or bilevel positive pressure ventilation is indicated. If hypoventilation with central apneas or a hypopneic profile is present, NPPV with a volume-present respirator is safer as first line support.

Patients Deemed “Not to Be Intubated”

The use of NPPV may be justified in selected patients who are “not to be intubated” with a reversible cause of ARF. NPPV may provide patient comfort and facilitate physician–patient interaction in the assessment of the reversibility of ARF. Studies evaluating the clinical efficacy of NPPV in patients who are “not to be intubated” are retrospective or uncontrolled prospective investigations (27, 28). These studies suggest that NPPV can reduce dyspnea and preserve patient autonomy, given careful and selective application.

Surgical Patients

Randomized, controlled studies of various forms of NPPV applied after cardiopulmonary bypass surgery have shown improved gas exchange and lung mechanics, and decreased extravascular lung water content, but did not modify the prevalence of atelectasis (56–59). The impact of these effects on relevant clinical outcomes was less clear. Similarly, after thoracic surgery for lung resection (60) or scoliosis (61), bilevel

NPPV demonstrated short-term physiologic benefits on gas exchange without significant hemodynamic effects. NPPV was well tolerated, but no clinical end points were investigated. After upper abdominal surgery, NPPV (mask CPAP) increased lung volume more rapidly and decreased atelectasis 72 h postoperatively compared with conventional therapy (62). In morbidly obese patients after gastroplasty, bilevel NPPV significantly improved arterial oxygenation on the first postoperative day, a physiological benefit associated with a more rapid recovery of pulmonary function (63). In solid organ transplant recipients with acute hypoxemic respiratory failure, NPPV reduced the rate of ETI, the incidence of fatal complications, ICU LOS of survivors, and ICU mortality compared with the provision of supplemental oxygenation alone. Hospital mortality did not differ between the two groups (19).

Conclusions

- Shortening weaning time and avoiding reintubation represent promising indications for NPPV.
- NPPV is beneficial in the management of ARF in patients with OHS.
- NPPV may improve comfort and achieve other end-of-life goals.
- NPPV in postoperative patients has the potential to improve many *physiologic* parameters without apparent serious side effects. Whether NPPV can also modify relevant *clinical* outcomes in these patients is less clear and requires further investigation.

Recommendations

Randomized controlled studies with the end points of clinical outcome and cost-effectiveness evaluation in shortening weaning, avoiding reintubation, for exacerbations of OHS, and in specific postoperative patient groups, should be performed.

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APPENDIX

The following experts delivered the presentations: A. Agusti (Spain), N. Ambrosino (Italy), M. Antonelli (Italy), C. Brun-Buisson (France), J. C. Chevrolet (Switzerland), G. Criner (U.S.), M. Elliott (U.K.), P. Gay (U.S.), C. Girault (France), P. Jolliet (Switzerland), V. Jounieaux (France), F. Lofaso (France), J. Mancebo (Spain), G. U. Meduri (U.S.), S. Mehta (Canada), J. F. Muir (France), S. Nava (Italy), J. C. Richard (France), D. Robert (France), A. Rossi (Italy), B. Schönhofer (Germany), M. Vitacca (Italy), J. A. Wedzicha (U.K.), and M. Wysocki (France).