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INSIDE

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Emergency Colectomy For Fulminant *C. Difficile* Colitis

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this retrospective study of* C. difficile *colitis due to a hypervirulent strain, 53% of 165 patients died. Emergency colectomy was associated with a decreased mortality, especially among very elderly patients, those who were immunosuppressed, those with extreme leukocytosis, those with moderate hyperlactatemia, and those requiring vasopressors.*

Source: Lamontagne, et al. *Ann Surg.* 2007;245(2):267-272.

Using laboratory results from a recent 30-month period for case finding, Lamontagne and colleagues reviewed the medical records of all patients with fulminant *Clostridium difficile*-associated disease (CDAD) who received care in the ICUs of 2 tertiary-care hospitals in Quebec. During the period of this study Quebec was experiencing an outbreak of a particularly virulent strain of *C difficile* (hypervirulent toxintype III NAP1/027), which produces levels of toxins A and B that are 16 to 23 times higher than historical strains. Fulminating CDAD was defined as one or more of a positive *C difficile* cytotoxin assay, endoscopic evidence of pseudomembranous colitis, or histopathologic evidence of pseudomembranous colitis from biopsy, colectomy specimen, or autopsy. All patients who were admitted to the ICU because of the CDAD or developed it while in the ICU were included.

The authors identified 165 cases of CDAD (in 161 patients) during the study period. Twenty-four percent were healthcare-associated. The patients' ages ranged from 39 to 93 years (median, 75 years). Thirty percent of them were immunosuppressed (leukemia, lymphoma, organ transplantation, neutropenia, and/or > 1 month treatment with corticosteroids). In addition to diarrhea, manifestations of CDAD included abnormal plain abdominal films in 64% of 149 patients, signs of colitis in 78% of 85 abdominal CT scans, and pseudomembranes in 87% of 38 patients who underwent endoscopy. Median peak leukocyte

count was 30.9 x 109 cells/L (interquartile range, 20.8-44.1 x 109 cells/L). Serum lactate levels ranged between 0.7 and 23.0 mmol/L (median, 3.1 mmol/L; IQR 2.1-5.6 mmol/L).

Thirty-eight patients (23%) underwent colectomy, which was subtotal or total in 35. Listed indications for colectomy were persistent vasopressor-requiring shock (15 patients), megacolon (11 patients), lack of response to medical treatment (10 patients), and perforation (2 patients). Compared to the patients who did not undergo colectomy, those who did had fewer comorbidities (assessed by Charlson score), higher leukocyte counts (20 x 109 cells/L in 95% vs 73%), and more frequent shock requiring vasopressors (71% vs 52%).

Mortality ascribed to CDAD within 30 days of ICU admission was 87/165 (53%). Thirty-eight (43%) of those deaths occurred within 48 hours of ICU admission. Among the entire cohort, by multivariate analysis, death was more likely to occur in patients aged 75 years or older, who were immunosuppressed, those requiring vasopressors, those in whom peak leukocyte count exceeded 50 x 109 cells/L, and those with lactate levels of 5 mmol/L or higher (all, $P < 0.05$). Mortality among the patients who underwent colectomy was 34%, compared with 58% in patients treated medically ($P = 0.02$). Subgroup analysis suggested that patients most likely to benefit from emergency colectomy were those older than 65, those with leukocyte counts > 20 x 109 cells/L, and those with moderate elevations of serum lactate (2.2-4.9 mmol/L).

COMMENTARY

C difficile, which was identified as the causative agent in pseudomembranous colitis in 1978, has emerged as a pathogen of increasing importance in critical care. The incidence of CDAD appears to be on the rise everywhere, and more and more areas are reporting the emergence of hypervirulent strains associated with increased morbidity and mortality. When patients develop very high leukocyte counts in the ICU—especially exceeding 25 or 30 x 109 cells/L—CDAD should be considered, even if they have not been on multiple or broad-spectrum antibiotics.

This retrospective study highlights the frequency and potential lethality of CDAD, and it suggests that emergency colectomy can be life-saving. However, because of its design it cannot establish the latter with certainty, nor tell us for sure how to select patients for this procedure. For example, surgeons may have selected patients more likely to survive for colectomy and been reluctant to operate on those with immunosuppression or more comorbidities, influencing the observed mortality differences in those groups. The authors acknowledge these and other limitations. In spite of these, however, this study calls needed attention to the seriousness of CDAD today, particularly in the presence of hypervirulent toxin production, and to emergency colectomy as a potentially life-saving procedure. ■

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Special Feature

Three Current Controversies in Mechanical Ventilation

By David J. Pierson, MD, Editor

THE LITERATURE ON THE TECHNICAL AND CLINICAL aspects of mechanical ventilation for patients with acute respiratory failure continues to expand, with nearly 50,000 citations appearing in *PubMed* for the topic "mechanical ventilation," and more

than a thousand articles in English reporting the results of clinical trials under this heading published during the last 5 years. In spite of this avalanche of publications—or maybe because of it—many aspects of ventilator management remain unsettled and controversial.

To address several clinically important areas in which clinicians commonly disagree, last fall the American Respiratory Care Foundation convened a group of recognized experts on ventilator management and critical care, charging them with identifying the issues involved in each area and performing evidence-based reviews of current knowledge, in an attempt to bring clarity and up-to-date practice to the bedside in the ICU. Articles reviewing the issues addressed, along with transcripts of the vigorous discussions that accompanied them, appear in the April and May issues of *Respiratory Care*.[1,2] Most of the topics discussed at the conference dealt with mechanical ventilation, and in this essay I summarize the controversies addressed during 3 of these discussions that pertain to most ventilated patients.

Should All Patients with Acute Respiratory Failure Get A Trial of Noninvasive Ventilation Before Intubation?

During the last decade noninvasive positive-pressure ventilation (NPPV) has become the standard of care for acute respiratory failure complicating COPD. Numerous well-designed randomized controlled trials have shown that the use of NPPV, as compared to usual management, reduces the need for intubation, decreases complications, shortens ICU and hospital stays, costs less, and saves lives. It is often the case in medicine that a therapy shown to be effective in one clinical setting tends to "metastasize," and to be applied to patients with other diagnoses and in other clinical settings than those in which its benefits have been demonstrated. This has definitely been the case with NPPV. Although NPPV is still not used when it should be by many clinicians, paradoxically it has become the default initial approach for anyone in respiratory distress in the hands of others.

Consider the following patients with acute respiratory failure:

- An elderly patient with advanced COPD presents with 3 days of increasing dyspnea, a $PaCO_2$ of 85 mm Hg, and a pH of 7.24.
- A patient with cardiomyopathy and recurrent episodes of congestive heart failure presents with acute shortness of breath and typical findings of pulmonary edema on chest X-ray.
- A young asthmatic is seen in the emergency department with severe wheezing, obvious signs of hyperinflation, a heart rate of 140 beats/min, and a pulse oximetry saturation of 88% while breathing nasal oxygen at 2 L/min.
- Three months following liver transplantation, a patient presents with fever, dyspnea, bilateral infiltrates on chest X-ray, and a PaO_2 of 80 mm Hg on 100% oxygen by mask.
- A middle-aged motorcyclist collides with a truck and presents with multiple rib fractures, bilateral lung contusions, and a PaO_2 of 80 mm Hg on 100% oxygen by face mask.
- A patient with amyotrophic lateral sclerosis and a history of recurrent aspiration presents with respiratory distress, signs of lobar pneumonia, and acute-on-chronic respiratory acidosis.
- A patient develops increasing respiratory distress and hypoxemia 12 hours following extubation after coronary artery bypass grafting.

These hypothetical patients represent the spectrum, with respect to the advisability of NPPV as an initial approach to ventilatory support, from "clearly indicated" to "clearly contraindicated" as supported by the evidence. In their article, Hess and Fessler[3] review this evidence, which is now extensive for several of the clinical circumstances illustrated above.

The evidence best supports the use of NPPV in patients who fit the first two descriptions above: exacerbation of COPD and acute cardiogenic pulmonary edema (although in the latter setting continuous positive airway pressure may be as effective as NPPV). In acute severe asthma, fewer patients have been studied and the evidence is less clear-cut, since in the great majority of instances either the attack will improve without the need for ventilatory assistance or the patient will require intubation because of altered mental status or other contraindications to NPPV.

Several series have reported avoidance of intubation and improved outcomes in patients with acute respiratory failure complicating solid-organ transplantation or other forms of immunocompromise when NPPV is used. Such series have generally excluded patients with the factors shown in Table 1 as relative or absolute contraindications to NPPV. The same is true for acute hypoxemic (as opposed to hypercapnic) respiratory failure in other types of patients. Patients with depressed mental status or impaired bulbar function are more likely than others to aspirate when NPPV is used, and the latter is generally regarded as inadvisable in these settings.

Table 1: Should Noninvasive Ventilation Be the Initial Approach for most Patients with Acute Respiratory Failure?

NPPV is a Reasonable Choice*	NPPV is Ill-Advised or Contraindicated
Exacerbation of COPD	Extubation failure
Cardiogenic pulmonary edema (CPAP alone may be as effective)	Hemodynamic instability Cardiac or respiratory arrest
ARF following lung resection†	Very severe hypoxemia or acidosis
ARF after solid-organ transplants and in other immunocompromised patients	Multiple severe acute comorbidities Facial trauma or deformity
As transitional support during weaning	Coma
In do-not-intubate patients	Uncooperative patients

*In absence of contraindications

†Limited data

ARF, acute respiratory failure; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease

NPPV has been shown in several studies to shorten the period of invasive mechanical ventilation and to decrease the need for reintubation when used as an adjunct to weaning in selected patients. In these studies the patients have been extubated directly to NPPV as part of a deliberate step-down protocol. However, failed extubation, the situation in which a patient who has been extubated in the usual sequence subsequently develops recurrent respiratory failure, is a distinctly different setting. In extubation failure, NPPV has been shown not only to be ineffective in forestalling reintubation but also associated with worse outcomes. When a patient has been extubated following mechanical ventilation for acute respiratory failure and subsequently develops respiratory distress, hypoxemia, and/or acute respiratory acidosis, that patient should be reintubated without a trial of NPPV.

In general, the more severely ill the patient is, and the more additional active medical issues (co-morbidities) are present, the less likely NPPV is to be successful. This has recently been confirmed by Confalonieri and associates,[4] who derived a predictive equation for success vs failure of NPPV in acute respiratory failure complicating COPD, using a database of more than 1000 patients, and validated it in a second, prospective patient series. These authors used their predictive equation to produce color-coded charts for both initial assessment and patient status after 2 hours of NPPV, to indicate the relative likelihood of failure based on the patient's arterial pH, APACHE II score, Glasgow Coma Scale score, and other clinical data.[4] These charts are also reproduced in the article by Hess and Fessler.[3]

The bottom line is that NPPV is life-saving in several clinical settings and should be more widely applied as the standard of care in those settings, but that it is also not a panacea and can be ineffective or frankly harmful if applied inappropriately or in the wrong patients. The pro-con article by Hess and Fessler nicely summarizes the current evidence supporting this important modality and its practical implications for the ICU.

Should Tidal Volume Initially Be 6 mL/kg for All Patients with Respiratory Failure?

The landmark Acute Respiratory Distress Syndrome (ARDS) Network tidal volume study[5] showed that limiting delivered tidal volume to 6 mL/kg predicted body weight, as compared to 12 mL/kg, substantially reduced mortality and improved other outcomes in patients with acute lung injury (ALI) or ARDS. Similar benefits have been found in other studies using various forms of low-tidal-volume, lung-protective ventilation. In addition, compelling findings in animal studies and highly suggestive data in patients indicate that excessive lung stretch involving large tidal volumes can cause ALI/ARDS.[6] In light of the benefits of low-tidal-volume ventilation with respect to ALI/ARDS, there has been considerable discussion about whether low tidal volumes should be used in managing all patients who require mechanical ventilation—not just those who have or are at risk for developing ALI/ARDS. This issue was debated by Steinberg and Kacmarek[7] at the controversies conference.

During the conference, consensus (if not unanimity) was reached on most of the debated topics. However, whether all ventilated patients should receive 6 mL/kg was one for which this was not the case, with the proponents of both positions holding them vigorously and the assembled experts being more evenly split than was the case with most other questions.[8]

Table 2: Should All Ventilated Patients Receive an Initial Tidal Volume of 6 mL/kg (Predicted Body Weight)?

Arguments in Favor	Arguments Against
Low-tidal-volume ventilation improves mortality in ALI/ARDS	Plateau pressure may be a better goal than tidal volume in preventing VILI
Ventilation with large tidal volumes causes lung injury in animals and is associated with the development of ALI/ARDS in patients	Hypercapnia and respiratory acidosis may be more common with low tidal volumes
Low tidal volumes minimize hyperinflation in COPD and asthma	Atelectasis may be increased
Low tidal volumes may be beneficial in CHF and cardiogenic pulmonary edema	More sedation may be necessary for patients to tolerate ventilatory support
Low-tidal-volume ventilation is safe	Low tidal volumes are associated with poorer arterial oxygenation
	VILI from larger tidal volumes is very unlikely in patients without ALI/ARDS

ALI, acute lung injury, ARDS, acute respiratory distress syndrome; CHF, congestive heart failure, VILI, ventilator-induced lung injury

Table 2 summarizes the main points for and against the routine use of low tidal volumes. The "con" position revolves around two main issues: that low-tidal-volume ventilation may be harmful, and that the target tidal volume of 6 mL/kg predicted body weight is not the appropriate target, especially in ALI/ARDS.

In the ARDS Network and other studies, arterial oxygenation has not been as good, particularly in the first few days of ventilatory support, in the patients receiving low tidal volumes as in those on higher volumes. Low-tidal-volume ventilation may cause hypercapnia, or worse hypercapnia, as compared to the use of larger volumes, and more sedation (or even paralysis) may be required in order for patients to tolerate it, although published studies so far do not confirm this. And atelectasis may be more common when low tidal volumes are used, although the clinical importance of this observation is uncertain. In general, participants in the conference did not regard the potential adverse effects of low-tidal-volume ventilation—either in patients with ALI/ARDS or in ventilated patients in general—as of sufficient importance to outweigh its potential benefits.

The biggest controversy has to do with how best to gauge the risk of VILI and the excess mortality associated with high-tidal-volume, high-pressure ventilation. The "plateau pressure" faction contends that limiting trans-pulmonary pressure is the essential element, and that end-inspiratory plateau pressures less than 30 or 35 cm H_2O are clinically safe regardless of the tidal volume delivered. The "tidal volume" faction points to data from the ARDS Network study[9] showing that mortality in that trial was correlated with both tidal volume and plateau pressure, observed mortality decreasing progressively even at pressures below 30 cm H_2O. The arguments here were mainly in the context of how best to manage ALI/ARDS, and data from patients without ALI or ARDS or substantial risk for developing these conditions are largely nonexistent.

The bottom line is that although no one doubts that lung-protective ventilation saves lives in ALI/ARDS, the experts disagree on whether limiting tidal volume or end-inspiratory plateau pressure (or both) is the crucial management element. Clearly, ventilating ALI/ARDS patients with tidal volumes substantially over 6 mL/kg and plateau pressures exceeding 30-35 cm H_2O when these could readily be reduced by ventilator adjustment is contrary to present evidence. Using a tidal volume of 6 mL/kg (predicted body weight) in all ventilated patients to prevent VILI seems unnecessary in many instances and may cause practical problems with patient tolerance, although this practice is gaining in acceptance and becoming more widespread.

Should All Ventilated Patients Be Monitored with Capnography?

Capnometry (digital display of data) and capnography (graphical display of data) can be either time-based or volume-based. The technology for expired CO_2 monitoring has improved substantially over the last 15-20 years, and current apparatus accurately and rapidly provides end-tidal partial pressure ($PetCO_2$) and volume as well as calculation of dead-space ventilation. Manufacturers of end-tidal CO_2 monitoring devices point out that arterial blood gases (ABGs) are invasive and expensive, and that continuous direct monitoring of gas exchange via ABGs is not a practical option in today's ICU. Capnography is touted by its proponents for titrating ventilator settings, detecting airway mishaps, monitoring the course of a patient's critical illness, guiding weaning, and diagnosing such events as acute pulmonary embolism and the onset of ARDS.[10]

Capnography is the gold standard for confirmation of endotracheal intubation, several studies having demonstrated its clinical superiority over auscultation, the self-inflating bulb, and trachea light. For more than 20 years it has also been a standard of care for continuous patient monitoring in the operating room. However, whether capnography accurately indicates what is going on in a mechanically ventilated patient in the ICU remains hotly contended. The issues involved, and the available evidence, are discussed at length by Cheifetz and Myers.[11]

Table 3 lists the arguments for and against the use of capnography for the routine monitoring of ventilated patients. The claimed advantages and values of continuous capnographic monitoring in the ICU are mainly extrapolated from data generated in the operating room, and few studies have examined the clinical accuracy of capnography in critically ill patients. What data are available from this setting tend to emphasize its differences from the controlled anesthesia environment.

Table 3: Should All Ventilated Patients Be Monitored with Capnography?

Arguments in Favor	Arguments Against
Capnography is the standard of care for confirming tracheal intubation	$PetCO_2$ does not equal $PaCO_2$
Capnography assures the integrity of the ventilator circuit	Changes in $PetCO_2$ may represent changes in tidal volume, breathing pattern, dead space, perfusion, body position, or other functions
Capnography is a standard of care for monitoring in the operating room	$P(a\text{-}et)CO_2$ varies unpredictably, especially in very sick patients
It is non-invasive	
It is readily available	The more abnormal the patient's lung function, the less predictable is the relationship between end-tidal and arterial CO_2 tensions
Capnography allows ventilator adjustment (rate, tidal volume, PEEP) without having to draw ABGs	It can provide a false sense of security
It permits detection of potentially life-threatening adverse events without the clinician having to suspect them	It does not replace ABG analysis
It is safe	

ABG, arterial blood gases, $PetCO_2$, end-tidal PCO_2, $P(a\text{-}et)CO_2$, arterial-to-end tidal PCO_2, difference, PEEP, positive end-expiratory pressure

One study of mechanically ventilated patients with severe head trauma[12] found that the gradient between arterial and end-tidal PCO_2 values ($P(a\text{-}et)CO_2$) before and after endotracheal suctioning varied between -5.5 mm Hg and +19.7 mm Hg, and that the two values had least agreement in patients with atelectasis, pneumonia, or a chest tube. On the basis of their measurements these authors concluded that $PetCO_2$ was less valid as a surrogate for $PaCO_2$ in patients who were spontaneously breathing, were on assist-control ventilation, had PEEP > 5 cm H_2O, or had worse oxygenation according to PaO_2/FIO_2 ratio, or any combination of these factors.[12] In another study of simultaneous $PetCO_2$ and $PaCO_2$ values in patients with severe trauma, only 40% of the changes showed a linear relationship, and changes in $PetCO_2$ falsely predicted the changes in $PaCO_2$ in 27% of instances.[13]

The bottom line here is that capnography is no substitute for either an arterial PCO_2 or a skilled clinician at the bedside, particularly in an unstable patient with underlying pulmonary dysfunction and multiple comorbidities. The more physiologically normal the patient, the more accurately capnography reflects lung function and gas exchange, but, it could be argued, the less that patient needs the monitor. When polled at the conclusion of the discussion, only a small minority of the conference participants agreed with the starting premise that all ventilated patients should be monitored with capnography from intubation to extubation.[8] ■

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For Ventilated Patients, Is Sleep Better with PAV Than with Pressure Support?

By Dean R. Hess, PhD, RRT

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Dr. Hess reports no financial relationship to this field of study.

Synopsis: *Patient-ventilator dys-synchrony causes sleep disruption. Proportional assist ventilation may be more efficacious than pressure support ventilation in matching ventilatory requirements with ventilator assistance, resulting in less patient-ventilator dys-synchrony and better quality of sleep.*

Source: Bosma K, et al. *Crit Care Med.* 2007; 35:1048-1054.

THE OBJECTIVE OF THIS STUDY WAS TO EVALUATE the role of patient-ventilator dys-synchrony in the

etiology of sleep disruption, and to determine whether optimizing patient-ventilator interactions by using proportional assist ventilation (PAV) improves sleep. It was a randomized crossover clinical trial that enrolled 13 patients during weaning from mechanical ventilation. Patients were randomized to receive pressure-support ventilation (PSV) or PAV on the first night and then crossed over to the alternative mode for the second night. Polysomnography and measurements of light, noise, esophageal pressure, airway pressure, and flow were performed from 10 PM to 8 AM. Ventilator settings (pressure level during PSV, and resistive and elastic proportionality factors during PAV) were set to obtain a 50% reduction of the inspiratory work (pressure time product per minute) performed during a spontaneous breathing trial.

Arousals per hour of sleep time during PSV and PAV were 16 (range 2-74) and 9 (range 1-41), respectively ($p = 0.02$). Overall sleep quality was significantly improved on PAV ($p < 0.05$) due to the combined effect of fewer arousals/hour, fewer awakenings/hour (3.5 [range, 0-24] vs 5.5 [1-24]), and greater rapid eye movement (9% [range, 0-31] vs 4% [0-23]), and slow wave sleep (3% [range, 0-16] vs 1% [0-10]). Tidal volume and minute ventilation were lower on PAV, allowing for a greater increase in $PaCO_2$ during the night. Patient-ventilator dys-synchronies/hour were lower with PAV than with PSV (24 ± 15 vs 53 ± 59; $p = 0.02$) and correlated with the number of arousals/hour ($R^2 = 0.65$, $p = 0.0001$).

COMMENTARY

It has been increasingly appreciated in recent years that abnormalities of sleep are common in critically ill patients. Measures to improve the quantity and quality of sleep in critically ill patients include attention to mode of mechanical ventilation, decreasing noise, and sedative agents.[1] I first appreciated this from papers published by Meza et al[2] and Parthasarathy and Tobin.[3] The results of both of these papers showed that PSV induces central apneas during sleep. In a study of 11 critically ill patients during 1 night of sleep, Parthasarathy and Tobin[3] observed greater sleep fragmentation during PSV than during assist-control ventilation. Central apneas were more common during PSV than assist-control ventilation. In this study, the most important determinant of apneas was the difference between PCO_2 during resting breathing and the apnea threshold. When the resting PCO_2 was close to the apnea threshold, central apneas were more likely to develop. In other words, hypocapnea occurs during wakefulness with PSV, and lack of that wakefulness drive with sleep results in apnea in the absence of a back-up rate. Toublanc et al[4] recently reported a study of 20 patients randomized to assist-control ventilation or PSV with 6 cm H_2O. Assist-control ventilation was significantly associated with a better sleep quality than those recorded during PSV, again suggesting that a back-up rate may improve sleep quality during mechanical ventilation.

PAV is a spontaneous breathing mode in which the ventilator applies pressure in proportion to the inspiratory effort. This differs from PSV, in which the ventilator applies the same pressure regardless of inspiratory effort. During PAV, patient-ventilator synchrony may be optimized since both the amplitude and time course of ventilator assistance are linked to the amplitude and time course of inspiratory effort.

In this study, PSV was set at the level of pressure required to obtain a 50% decrease in pressure-time product (PTP) per minute relative to the values obtained during spontaneous breathing. Values of resistance and elastance obtained during spontaneous breathing were adjusted to obtain a PTP/min equal to 50% of the value obtained during spontaneous breathing. On PSV, 9.2 ± 2.8 cm H_2O of ventilator-applied pressure was required to achieve a 54 ± 3% reduction in the inspiratory muscle load relative to spontaneous breathing. On PAV, the 53 ± 5% reduction of the PTP/min was obtained by setting the flow assistance to 5.8 ± 2.9 cm H_2O/L/sec and the volume assistance to 8.9 ± 2.6 cm H_2O/L. PEEP and FIO_2 were set equivalently in both modes at 5.5 ± 0.2 cm H_2O and 0.37 ± 0.05, respectively.

The ratio of the pressure applied to airway (airway opening PTP) to the pressure generated by the respiratory muscles (esophageal PTP) correlated significantly with the number of arousals per hour (R2 = 0.71) and the number of patient-ventilator dys-synchronies was regardless of the ventilatory mode (R2 = 0.52). In other words, the greater the proportion of ventilator support relative to patient effort, the more likely was patient dys-synchrony and sleep disordered breathing. It follows that there was as strong association between sleep disordered breathing and dys-synchrony. Morning minute ventilation was higher and $PaCO_2$ was lower with PSV than PAV.

In this study, dys-synchrony and sleep disordered breathing were less with PAV than with PSV. Auto-triggering, ineffective triggering, and delayed cycling were more prevalent during PSV than PAV. It is unclear why auto-triggering should be more prevalent during PSV if the trigger sensitivity is set correctly, and the authors provide no explanation for this finding. Ineffective triggering may be the result of increased support during PSV which lowers respiratory drive, although no index

of respiratory drive was reported. Delayed cycling during PSV is most likely due to the fixed 25% flow cycle with this mode on the ventilator used in this study.

An important finding is that setting support based on wakefulness criteria might result in excessive support during sleep. Although this was less likely during PAV, it can occur regardless of mode. Moreover, patient-ventilator dys-synchronies may be reduced during PSV by tailoring the trigger sensitivity, rise time, and cycling-off criteria to suit the respiratory mechanics and breathing pattern of the individual patient and then adjusting these variables as necessary to compensate for changes during sleep and wakefulness.[5] Lowering the level of inspiratory assistance may decrease the amount of dys-synchrony and improve sleep quality. Some clinicians increase the level of support at night, which may ironically lead to dys-synchrony and sleep-disordered breathing. Although not evaluated in this study, setting a backup rate (assist-control ventilation) may also decrease the occurrence of patient-ventilator dys-synchrony and sleep disordered breathing.

In conclusion, sleep disordered breathing during mechanical ventilation is related to patient-ventilator dys-synchrony. With spontaneous breathing modes, a higher level of ventilator assistance increases the likelihood of dys-synchrony and arousals during sleep. Approaches to this problem include the use of PAV rather than PSV, appropriately setting rise time and cycle-off criteria during PSV, decreasing the amount of inspiratory support, and using a mode with a back-up rate such as assist-control. ■

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CME Questions

18. Emergency colectomy in patients with *C. difficile* colitis was associated with decreased mortality in ICU patients in which of the following settings?
a. immunosuppression
b. extreme leukocytosis (> 50 x 109 cells/L)
c. very elderly patients (age 75 yr or older)
d. all of the above
e. none of the above

19. The etiologic agent most associated with pseudomembranous colitis is:
a. escherichia coli strain 0157
b. shigella species
c. salmonella species
d. clostridium *difficile*
e. Norwalk-like virus

20. In which one of the following conditions is noninvasive positive-pressure ventilation most clearly indicated on the basis of available evidence?
a. acute severe asthma
b. exacerbation of chronic obstructive pulmonary disease
c. acute respiratory failure following lung resection
d. acute respiratory failure following extubation
e. none of the above

Answers: 18 (d); 19 (d); 20 (b)

CME / CE Objectives

After reading each issue of *Critical Care Alert*, readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

In Future Issues:

Steroids to Prevent Postextubation Stridor?

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

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light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■