

CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

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Medicine Residents Lack Vital Knowledge on Mechanical Ventilation

ABSTRACT & COMMENTARY

Source: Cox CE, et al. Effectiveness of medical resident education in mechanical ventilation. *Am J Respir Crit Care Med.* 2003;167:32-38.

IN THE UNITED STATES, PHYSICIANS TRAINED IN INTERNAL MEDICINE provide a substantial portion of the care of critically ill patients. Physicians trained in internal medicine direct 63% of ICUs, and national surveys report that 59% of general internists use mechanical ventilation in their practice. To evaluate how successful internal medicine residency programs have been in providing education about the management of patients who require mechanical ventilation, Cox and colleagues administered a validated 19-item test to a nationwide sample of 347 senior internal medicine residents in 26 residency programs. The programs were chosen to reflect a diverse sample in terms of geographic region, program size, urban, suburban, or rural setting, and university vs community hospital affiliation.

Of the 347 senior residents asked to participate, 75% responded. The mean test score was 74% ± 14% correct (range, 37-100%). Of respondents, 10% answered less than half of all questions correctly and one-third answered fewer than 70% correctly. Important items representing evidence-based standard of critical care answered incorrectly included: use of appropriate tidal volume (6 mL/kg) in ARDS (48% incorrect), identifying a patient ready for a weaning trial (38% incorrect), and recognizing indications for noninvasive ventilation in a patient with chronic obstructive pulmonary disease (27% incorrect). Most respondents accurately identified pneumothorax (86% correct) and increased auto-PEEP (93% correct). Better scores were associated with several factors: "closed" vs "open" ICUs ($P = 0.005$); having more than 15 senior residents in the residency program ($P = 0.003$); having more than 5 pulmonary and critical care attending physicians on staff ($P = 0.005$); and graduation from a US vs an international medical school ($P < 0.0001$). Only 46% of the respondents reported being satisfied with their

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mechanical ventilation training. Conversely, most (92%) program directors thought their residents had adequate knowledge about mechanical ventilation by graduation.

■ **COMMENT BY LESLIE A. HOFFMAN, PhD, RN**

The major finding of this study was that internal medicine residents are not receiving adequate knowledge to provide effective care for mechanically ventilated patients. Important deficiencies were found in several areas where research findings have convincingly shown the ability to lower mortality and reduce health care costs (eg, use of a lung-protective ventilatory strategy for patients with ARDS and prompt recognition of patients ready for a weaning trial). Among the 48% of respondents who answered the ARDS question incorrectly, 85% indicated that they would use a tidal volume nearly double the recommended 6 mL/kg of ideal body weight. Although 93% identified clinical findings suggestive of severe hypotension related to auto-PEEP, 35%

were unable to choose a ventilator setting that would decrease it.

The research team was rigorous in designing the test, a case-based, multiple-choice examination written in the style of the American Board of Internal Medicine certification test. To establish validity, the test was administered in a proctored setting at 5 randomly selected university-affiliated training sites. A total of 132 participants returned tests, including 103 internal medicine residents, 19 pulmonary and critical care fellows, and 10 attending physicians. The percentage of correct answers ranged from 67% to 17% for first-year residents to 95% to 6% for attending physicians. Test scores increased significantly with each year of training ($P < 0.0001$). There were also significant differences in scores between each year of training ($P < 0.001$) but not between fellows and attending physicians ($P = 0.35$).

These study findings provide convincing evidence that knowledge regarding basic mechanical ventilator management needs to be improved. Given current constraints on time and resources, it is unlikely that this goal can be accomplished unless training becomes more structured and creative. Cox et al suggest several approaches for accomplishing this goal, including the use of evidence-based learning objectives, monitoring educational outcomes using competency-based assessment, and providing a brief, early “hands on” course in mechanical ventilation management.

In addition, medical training programs should consider incorporating training using high-fidelity human simulators (HFHS), given their ability to simulate a wide variety of typical and emergent scenarios likely to be encountered in the critical care setting. The University of Pittsburgh School of Nursing has incorporated HFHS training in the nurse anesthesia program for 4 years with excellent results and recently expanded HFHS training to include all undergraduate nursing students. In the HFHS lab, students are presented with a learning situation controlled by an operator who resides behind a 1-way mirror. They learn to act quickly to reverse emergent cardiopulmonary events and see consequences of their effective (or ineffective) actions. Through “debriefing” sessions, faculty members review the videotaped scenarios with the student and critique decision making and its consequences. Educators are under pressure to do more with less. Given this expectation and findings of this study, it is imperative to improve clinician education using the most advanced educational tools. ■

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Automatic Tube Compensation: A Better Weaning Test?

ABSTRACT & COMMENTARY

Synopsis: *In this small study, differences in the respiratory rate to tidal volume ratio (RTVR) after 1 hour of spontaneous breathing with ATC were a good predictor of whether patients would remain extubated or require reintubation. But was it really better than other tests?*

Source: Cohen JD, et al. Automatic tube compensation-assisted respiratory rate to tidal volume ratio improves the prediction of weaning outcome. *Chest*. 2002;122:980-984.

THE USE OF AUTOMATIC TUBE COMPENSATION (ATC) is becoming more common during mechanical ventilation to reduce the work of breathing during spontaneous ventilation. This feature is available on the Evita ventilator manufactured by Dräger (Lubeck, Germany). ATC consists of added pressure support at a level automatically calculated to balance the predicted additional work imposed by the endotracheal tube. The theory is that ATC (at 100%) creates a breathing work condition identical to that present following extubation. The amount of support can be set as a percentage of this optimal value (eg, 50%).

Cohen and associates determined classic weaning parameters with and without ATC (100%) in 35 patients who successfully completed a 1-hour spontaneous breathing trial (SBT) followed by extubation. Twenty-five of the patients remained extubated without signs of respiratory failure, and 10 required reintubation within 48 hours. Demographic information, severity of illness at presentation, cause of respiratory failure, peak airway pressure (Paw), auto-PEEP level, respiratory rate, tidal volume, minute ventilation, occlusion pressure (P₀₁), heart rate, systolic pressure, and RTVR with and without ATC were determined before and after the SBT (when appropriate).

The only differences between the 2 groups with respect to the assessments made prior to the SBT were in the RTVR with and without ATC. Following the 1-hour SBT, these remained significantly different, as did the peak airway pressure, respiratory rate, and tidal volume. When a multivariate analysis was used on all the data, only the RTVR with and without ATC, both before

and after the SBT, and the Paw were significant predictors of success or failure. In each case, the receiver operating characteristic (ROC) value (indicating the degree to which the assessment was different from random in predicting extubation success) was 0.70 or more. The best fit of the ROC curves was obtained when the RTVR on ATC was divided by the Paw following the SBT, which had a ROC value of 0.84, a good balance between sensitivity and specificity. Cohen et al suggest using this index in predicting weaning success.

■ COMMENT BY CHARLES G. DURBIN, Jr., MD

Adding ATC is suggested as a way to reduce the work of breathing for the patient that is imposed by the endotracheal tube. While some patients seem to be more comfortable on this mode, the actual value of ATC in mechanical ventilation and specifically in weaning has not been determined. Cohen et al suggest a novel way of using this technique to improve prediction of weaning outcome. They had to work hard to do this. While the advanced statistical analysis applied to this data suggests the superiority of a complex series of evaluations, more traditional indices also performed reasonably well. The differences in respiratory rate (22.6 in patients successfully extubated and 28.2 in those requiring reintubation) was also highly predictive of success or failure. In fact, Cohen et al did not test it, but the change in respiratory rate during the SBT appears highly predictive. Likewise, the change in peak airway pressure and the change in tidal volume also appear to be highly predictive. I think it is important to carefully review some of the data in this report before accepting the conclusions suggested.

The RTVT by itself was highly predictive. Adding ATC to this measurement contributed little improvement in prediction (the area under the ROC). It was only when the RTVT on ATC was divided by the Paw following the SBT that a significant improvement in ROC appeared. The same improvement would have occurred using the RTVT without ATC in this ratio, although they did not perform (or at least report) this analysis. A more honest title for this paper would have been: "Dividing the respiratory rate to tidal volume ratio by the peak airway pressure predicts extubation success." This paper's title appears to be a way of advertising the unique ventilator mode of a particular ventilator and really has nothing to do with the major findings of the study. By applying a series of complicated statistics to derived parameters, Cohen et al were able to manipulate their data to support their bias.

It is important to understand the patient population studied. Although none of the patients would have

failed traditional weaning criteria, almost 30% of these patients required reintubation. This is an incredibly high percentage. When this group is evaluated, many of them (40%) had nonrespiratory reasons for reintubation, including new sepsis and poor secretion clearance. The comparison groups thus are not reflective of the usual ICU extubation issues, and the results of the analyses are suspect.

The take-home message from my analysis of this paper is that testing patients for weaning success while on ATC is not necessary. The usual parameters (ie, respiratory rate and RTVT) following a SBT should still be considered the tarnished “gold standards.” Energy devoted to improvement in these predictors is probably wasted as new approaches to support of patients with respiratory failure, namely, noninvasive ventilation, are likely to replace many of the current reintubations. ■

Patients, Nurses, and Physicians Have Differing Views of Quality in the ICU

ABSTRACT & COMMENTARY

Synopsis: *Physicians rated the quality of ICU care higher than nurses, and these health care providers' opinions did not correlate with those of patients. Patients' perceived satisfaction with their care was rated higher by physicians than by either nurses or patients.*

Source: Shannon SE, et al. *J Nurs Scholarsh.* 2002;34(2):173-179.

THROUGH A SECONDARY ANALYSIS FROM A MULTISITE study of critical care unit outcomes and organizational features, Shannon and colleagues compared patient, nurse, and physician assessments of quality of care and patient satisfaction in selected ICUs. Data regarding patient satisfaction and quality of care were collected from 489 patients, 518 nurses, and 515 physicians in 25 ICUs from 14 hospitals in the Pacific Northwest. The majority of the ICUs were small, mixed, medical-surgical units (average 12 beds/unit), in a mix of tertiary-care and community hospitals (9 ICUs nonteaching and 16 teaching [9 members of the Council of Teaching Hospitals and 7 nonmembers]), with an average of 316 total beds. Patients' perceptions of quality and satisfaction with care during a critical care stay were measured by 3 subscales from the Medicus Viewpoint Instrument, administered within 48 hours of

ICU transfer. Nurses' and physicians' views of unit quality and patient satisfaction were obtained from portions of the Charns Organizational Diagnosis Survey. The unit of analysis was the critical care unit ($n = 25$). Data were normalized to a common scale (0-100) for analysis.

Physicians' opinions about unit quality were higher (83.55) than patients' views (81.69). Nurses' ratings of unit quality were the lowest (73.86). Nurses and patients had similar views of patient satisfaction (81.43 and 81.28, respectively). Physicians' opinions about perceived patient satisfaction were higher (86.24). Correlation analyses revealed that opinions of quality and patient satisfaction varied considerably within and between units. Care providers' opinions did not correlate with patients' views of quality of care ($r = -0.146$, nurses; $r = 0.103$, physicians). Physicians' and nurses' views of unit quality of care and patient satisfaction were moderately correlated. These ratings were strongly related to MD-RN collaboration and nurse job satisfaction.

■ COMMENT BY KAREN JOHNSON, PhD, RN

How many signs/posters are currently displayed in your ICUs that address patient satisfaction? If yours is like mine, probably quite a few! Patients' viewpoints and satisfaction with care have become particularly important in the current economic climate of acute and critical care. Patient satisfaction is both a process of care and an outcome measure.

As an outcome measure, institutions use various methods to evaluate how well patients are satisfied with care received. This study demonstrates that we cannot use health care professionals' perceptions of patient satisfaction and perceived quality of care as proxies for patients' views. These results indicated that health care providers may evaluate patient satisfaction through rose-colored glasses. Organizational harmony may affect health care providers' perceptions of patient satisfaction. If life in the unit is good (in particular good RN-MD collaboration), perceived patient satisfaction and quality of care are good; if life in the unit is bad, perceived patient satisfaction and quality of care are bad.

These findings may become increasingly important as institutions consider future organizational changes that affect staff attitudes and perceptions. These organizational changes and their linkages to patient outcomes and patient satisfaction are in desperate need of process and outcome evaluation strategies. We must remind ourselves that patient satisfaction and perceived quality of care as outcome measures are a reflection of our

process of care that incorporates patient satisfaction and quality of care on a daily basis. ■

Special Feature

Reversible Myocardial Dysfunction in Acute Noncardiac Illness

By Francisco Baigorry, MD, PhD

REVERSIBLE MYOCARDIAL DYSFUNCTION MAY BE much more common in critical illness than has been generally appreciated.¹ Moreover, a significant proportion of patients admitted to medical ICUs due to noncardiac illnesses have underlying cardiac abnormalities, which can be detected with surveillance echocardiography at time of admission.² In this essay I will consider some aspects of this phenomenon to warn about its early recognition and appropriate therapy during hemodynamic resuscitation.

A broad array of conditions associated with tissue inflammation and metabolic stress may be associated with reversible myocardial dysfunction. Such conditions include massive neurologic injury (stroke and cranial trauma), severe acute respiratory failure, anaphylaxis, trauma, postorgan transplant, severe pancreatitis, postcardiac arrest, and a variety of other severe illnesses.¹ Reversible myocardial dysfunction also is a key component of the cardiovascular dysfunction of sepsis and septic shock. It may occur in up to 40% of cases of sepsis.³

The pathogenic mechanisms that may underlie this phenomenon are not fully understood. Potential pathogenic mechanisms include the following:^{1,4}

1. direct ischemic injury to the heart (eg, myocardial infarction, chronic myocardial ischemia, postcardiac arrest);
2. free radical injury (eg, myocarditis, reperfusion injury);
3. cytokine-mediated myocardial injury (eg, septic shock, myocarditis) associated with nitric oxide and peroxynitrite generation; and
4. noncytokine-related mediator injury (eg, anaphylaxis-associated leukotriene production) among others.

This dysfunction is frequently associated with an increase in enzyme markers⁵ and electrocardiographic changes.⁶ It can worsen the prognosis. Interestingly, it has been shown that the cardiac ejection fraction of

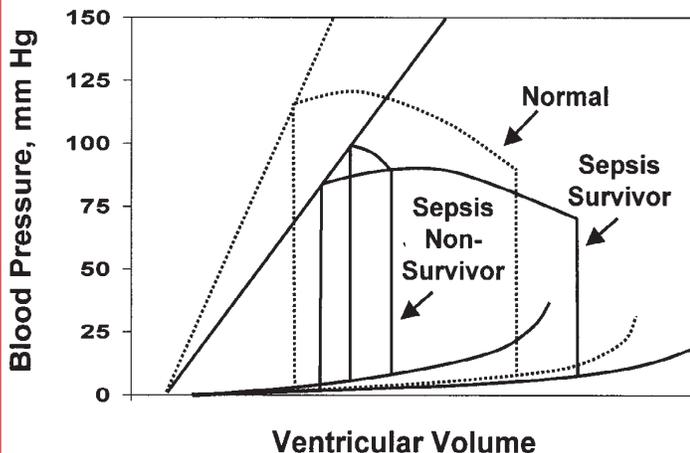
nonsurvivors was higher than of survivors of septic shock. In addition, end-diastolic volume was increased in the survivors but was not increased in the nonsurvivors of septic shock. How can we reconcile these apparently contradictory observations? It was put, with commendable clarity, by Walley in a classic essay on this subject some years ago.⁷ During sepsis, a decrease in systolic contractility results in a shift to the right of the end-systolic pressure/volume relationship and, if not compensated for, would result in a decrease in stroke volume and cardiac output. Compensatory mechanisms must act to account for the more common hyperdynamic circulation of early sepsis.

Three such compensatory mechanisms exist. First, when patients are seen early and are adequately volume resuscitated, an increase in end-diastolic pressure is one mechanism that may help maintain stroke volume and cardiac output. Second, the decrease in afterload of sepsis is also a compensatory response to some extent in that it improves stroke volume and can prevent a decrease in ejection fraction.⁸ Third, dilation of the diastolic ventricle due to decreased diastolic stiffness is the expected response to the decrease in systolic contractility. When this occurs, stroke volume and cardiac output can be maintained even in the face of relatively low filling pressures. This third compensatory response is associated with improved survival rates.⁹

Thus, myocardial depression could exist in the absence of depression of cardiac output. On the other hand, if the ventricle cannot increase volume, or volume decreases during diastole, then the ability to generate a stroke volume is impaired at both ends (*see Figure 1*). Lack of this normal response to decreased systolic contractility accounts for progressively decreasing cardiac output and hypotension and is associated with nonsurvival.^{9,10}

Increased cardiac index and oxygen delivery with a pulmonary arterial occlusion pressure of < 18 mm Hg have been suggested as therapeutic goals for resuscitation and subsequent management.¹¹ A meta-analysis of hemodynamic optimization in high-risk patients suggests that, when implemented early and aggressively, goal-directed therapy reduces mortality and the prevalence of organ failures.¹¹ Rivers and colleagues¹² specifically studied whether a goal-directed therapy before admission to the intensive care unit could reduce mortality and multi-organ dysfunction in patients with sepsis and septic shock. They also found that early goal-directed therapy provides significant benefits in terms of outcome in this kind of patients. Interestingly, the monitoring of patients randomly

Figure 1



Theoretical ventricular pressure/volume loops for normal subjects and for survivors and nonsurvivors of sepsis. In both survivors and nonsurvivors, contractility is decreased by a decreased slope of the end-systolic pressure-volume relationship. Diastolic ventricles of survivors dilate as the normal compensatory response to decreased systolic contractility. Pathologic alterations of the myocardium prevent diastolic dilation in nonsurvivors.

Adapted from: Walley KR. Ventricular Dysfunction During Sepsis. Berlin, Germany: Springer; 1995.

assigned to early goal-directed therapy included a central venous catheter capable of measuring central venous oxygen saturation. Moreover, during the initial 6 hours, these patients more frequently received inotropic support. This makes me think about the possibility that measuring central venous saturation allowed the identification of inappropriate cardiac output in a significant proportion of studied patients and that this could be an important aspect to improve the outcome.

Many methods to noninvasively measure cardiac output are currently available for use in the ICU. These include applications of the Fick principle, Doppler technology, thoracic-electrical bioimpedance, and pulse contour analysis devices (see Table 1).¹³

Each of the methods in the Table has advantages and disadvantages. The indirect Fick methods are convenient and relatively easy to apply to mechanically ventilated patients but may not be accurate enough for initial diagnostic information in a patient with significant lung disease or multi-organ failure. The esophageal Doppler monitor, although more invasive than others, may be a better alternative for the critically ill patient. The bioimpedance methods tend to lose accuracy in the setting of intrathoracic fluid shifts, which may limit its use in the intensive care setting. The pulse con-

Table

Features of Available Minimally Invasive Techniques for Monitoring Cardiac Output¹³

Method	Accuracy	Estimate of Cardiac Preload?	Special Considerations
Indirect Fick	fair	no	Patient must be intubated; Accuracy limited by pulmonary disease
Esophageal Doppler	good	yes ^a	Patient movement is a problem; requires specialized training
Thoracic electrical bioimpedance	good	no	Decreased accuracy with abnormal cardiac rhythm or severe peripheral edema
Transpulmonary pulse contour	very good	yes ^b	Requires proximal access
Lithium dilution	very good	no	Does not require catheter in central circulation

a corrected flow time

b intrathoracic blood volume

Adapted from: Chaney JC, Derdak S. Minimally invasive hemodynamic monitoring for the intensivist: Current and emerging technology. Crit Care Med. 2002;30:2338-2345.

tour devices offer a beat-to-beat measurement of cardiac output and have shown good correlation with pulmonary artery thermodilution during times of stable hemodynamics. These devices should be recalibrated frequently in patients with unstable hemodynamics. Pulse contour devices also allow estimation of intrathoracic blood volume to assess cardiac preload. Provided that the clinician understands the strengths and limitations of each device to effectively use the information derived from them, it would be expected these methods help us in timing decision making in hemodynamic resuscitation.

Simplified treatment algorithms are now being proposed using some of these techniques, for instance, using the analysis of arterial pressure pulse variation in patients with mechanical ventilation¹⁴ and aortic flow measured with transesophageal pulsed Doppler.¹⁵ However, there is the risk that all these techniques may delay or prolong resuscitation of our patients. In the meantime, the early use of transesophageal echocardiography (when available) and pulmonary artery balloon-tip thermodilution catheter must be considered the gold standard for the evaluation of circulatory function in the ICU patient (see Figure 2).¹⁶

To summarize, reversible myocardial dysfunction

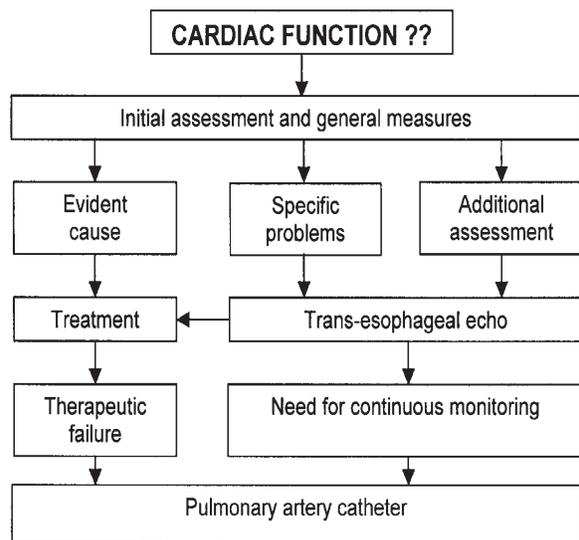
may occur in cases of critical pathology. The true frequency of this phenomenon in the critically ill appears to be significantly higher than is generally appreciated. It seems to worsen the patient's prognosis when it occurs, but an early and aggressive goal-directed therapy reduces mortality and the prevalence of organ failures. Many methods to noninvasively measure cardiac output are currently available for use in the ICU. It remains unknown whether these new monitoring techniques may help us in timing decision making in hemodynamic resuscitation and have an effect on patient outcome. ■

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Figure 2

Algorithm for use of the pulmonary artery catheter and TEE in the ICU patient



Adapted from: Boldt J. Clinical review: Hemodynamic monitoring in the intensive care unit. *Crit Care.* 2002;6:52-59.

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CME / CE Questions

28. Program characteristics associated with higher test scores regarding knowledge of mechanical ventilation were associated with all of the following except:

- a. a closed ICU policy.
- b. having 16 or more senior residents in the program.
- c. having 5 or more pulmonary and critical care attending physicians on staff.
- d. graduate of a medical school located in the United States.
- e. plans for future fellowship in pulmonary or critical care medicine.

29. The majority of senior internal medicine residents correctly answered questions about which of the following?

- a. Detecting the presence of a pneumothorax
- b. Selecting a low tidal volume for managing ARDS
- c. When to use noninvasive ventilation in COPD
- d. Identifying a patient ready for a weaning trial
- e. All of the above

30. The use of automatic tube compensation during a trial of spontaneous breathing:

- a. adds significantly to predicting weaning failure.
- b. facilitates extubation in surgical but not medical patients.
- c. should be considered the "state of the art" in weaning evaluation.
- d. has not been shown to help determine weaning success.
- e. is available on most newer ventilators.

31. Weaning success is best predicted by:

- a. determining the respiratory rate to tidal volume ratio following a 3-hour trial of spontaneous breathing.
- b. extubating the patient and instituting noninvasive ventilation if failure occurs.
- c. the patient's respiratory rate with 50% automatic tube compensation.
- d. evaluating the fall in airway pressure when 100% ATC is instituted.
- e. None of the above

32. Which of the following statements accurately reflects the results of the study by Shannon et al on the perceptions of ICU care quality by patients, nurses, and physicians?

- a. Patients rate the quality of care higher than do physicians.
- b. Nurses rate the quality of care as being the highest.
- c. Physicians' opinions on patient satisfaction were lower than nurses' opinions.

- d. The opinions of care providers did not correlate with those of patients.
- e. None of the above

33. Which of the following correctly ranks the ratings by the different groups of the quality of care in the ICU?

- a. Physicians highest, nurses lowest
- b. Patients highest, nurses lowest
- c. Nurses highest, patients lowest
- d. Nurses highest, physicians lowest
- e. Patients highest, physicians lowest

34. As far as reversible myocardial dysfunction is concerned, which of the following assertions are true?

- a. It is exceptional in patients with noncardiac critical illness.
- b. It is always associated with low cardiac output.
- c. It occurs in only 5% of cases of sepsis.
- d. It is rarely associated with an increase in enzyme markers and electrocardiographic changes.
- e. Early recognition and therapy during hemodynamic resuscitation seem to improve outcome.

35. Potential pathogenic mechanisms of reversible myocardial dysfunction include:

- a. direct ischemic injury to the heart.
- b. cytokine-mediated myocardial injury.
- c. free radical injury.
- d. All of the above
- e. a and b but not c

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Critical Care Alert*. Send your questions to: Robin Mason, *Critical Care Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Critical Care Alert* via the internet by sending e-mail to robin.mason@ahcpub.com. ■

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:

Intensivist care improves ICU outcome

EPO Safe Despite Paris Report, Experts Say

Misinformation About Oxygen Therapeutics Still Widespread

RECENT REPORTS FROM PARIS THAT SCORES OF PATIENTS DEVELOPED APLASTIC ANEMIA AFTER RECEIVING EPREX, the oxygen therapeutic drug known generically as erythropoietin (EPO), have some stateside researchers puzzled. A huge number of patients have been treated with EPO throughout the western world, says Aryeh Shander, MD, medical director of the New Jersey Institute for the Advancement of Bloodless Medicine, but the number who contracted aplastic anemia is extremely small.

“Similar numbers of patients receive Eprex in Germany and in France, yet the number of patients who develop aplastic anemia is much higher in France than in Germany,” Shander says.

David J. Pierson, MD, professor of medicine at the University of Washington and medical director of respiratory care at Harborview Medical Center in Seattle, observes that despite educational efforts, a lot of misinformation and unwarranted fear about blood products and their infection risks remains within the medical community.

The question of whether the aplasia is due to subcutaneous injection of patients with chronic renal failure, the population that has experienced aplastic anemia, needs more investigation, Shander says. “For these patients, IV administration may be the safer way to go.”

EPO, one of three classes of oxygen therapeutics presented at a conference organized last year by the American Association of Blood Banks, is the all-time best-selling genetically engineered drug. It’s also one of the largest-selling drugs of any kind in the world: Worldwide, more than \$13 billion worth of EPO products were sold in 2001.

Most of the 141 cases of red cell aplasia reported in EPO users have involved Eprex, marketed by Johnson & Johnson in Europe, Canada and Australia. Shander points out that aplastic anemia has occurred in patients treated with other brands of EPO, including Procrit, Johnson & Johnson’s brand name for the EPO it sells stateside.

Restrictive Laws May Be Premature

Shander adds that in some cases when EPO administration has been stopped until patients recover from aplastic anemia, the condition doesn’t recur when the drug is reintroduced. He notes the possibility of EPO-restrictive legislation passed because of public response to incomplete news reports.

“If the public panics, the legislature reacts, not always in ways that are rational,” Shander says. “It may actually prevent the majority of patients from receiving a fairly safe drug.”

Shander and his colleagues define oxygen therapeutics as drugs that deliver oxygen, not as blood substitutes.

“We need more data about the efficacy of these agents in acute anemia such as trauma,” Shander says. “The advantage is that they can be given before the ambulance reaches the hospital because they don’t require type and crossing the way blood does. The problem is that we don’t know if giving them early on will result in increased survival or increased morbidity.”

Shander says a great deal of such trauma-efficacy testing is currently under way, but says he can’t reveal the “where, who or how” of these tests.

He adds that current data from trials for perfluorocarbon (PFC), the oxygen therapeutic that could be manufac-

tured at the lowest cost, is shaky.

“The design for the PFC study may have been too complex,” Shander says. “Whatever happened, right now the hemoglobin-based oxygen carriers are our therapeutic mainstay.”

It’s important for critical care practitioners to understand that each of the oxygen therapeutic products currently available or nearing completion of FDA phase III trials has its own chemistry, biologic activity, half-life and specific characteristics, says Harvey G. Klein, MD. Klein, who heads the department of transfusion medicine at the Warren G. Magnuson Clinical Center of the National Institutes of Health in Bethesda, Md, is also past president of the American Association of Blood Banks. However, he adds that each has potential in as yet inadequately explored applications.

These agents, Klein says, carry oxygen in a manner fundamentally differently from red blood cells. “They are very small molecules that actually go right through the vessels into the tissues,” Klein says. “Critical care physicians should be asking if this could have new applications for which blood is not very helpful. It’s conceivable there will be some benefit to MI and stroke patients, and in severe sickle cell crisis.”

Klein observes that the Food and Drug Administration, which appears to be concerned about wider use of oxygen therapeutics once they are licensed, expects manufacturers to provide data for other uses before a specific-use application will be approved.

Availability of Oxygen Therapeutics Will Drive Education

A. Gerson Greenburg, MD, Ph.D., surgeon in chief at Miriam Hospital in Providence, RI, and professor of surgery at Brown University, agrees that doctors still need to better understand the indications for transfusion of red cells. “Having the option of oxygen therapeutics will drive educational efforts to apply guidelines,” Greenburg notes.

Though costs of these therapeutic agents are likely to be higher than blood, Greenburg notes that the true costs of both blood and blood products tends to be elusive because blood, the essential element, is donated. He adds that the phase III cardiac surgery trial for the Canadian-made hemoglobin-based oxygen carrier Hemosol showed a decrease in the use of banked blood and blood products, an unexpected but welcome factor that could increase the overall blood supply by the percentage of blood it saves.

“If currently 20% of the blood supply goes to cardiac surgery and the savings is a decrease of 50%, the impact on the overall blood supply would be 10%, which is sig-

nificant,” Greenburg says.

A study Greenburg and colleagues performed found that the actual use of banked red cells was roughly 10% of the amount used in standard practice, a reduction which effectively increased the available blood supply by 18%.

Despite such impressive figures, Shander doesn’t foresee a time when transfusing blood will be completely unnecessary. “We may become more restrictive about whose blood we select, and having more alternatives means we can reduce the size of the blood pool and therefore the risk of blood-borne diseases,” he says. “And these new agents make it possible to easily measure the cost-benefit of blood. But I can categorically say there will always be some need to transfuse blood. When the benefit exceeds the risk and when fresh blood is available and easy to give, you’d probably rather give it.” (For more information contact Aryeh Shander, MD, at [888] 766-2566; Harvey G. Klein, MD, at [301] 496-9702; and A. Gerson Greenburg, MD, at [401] 793-2500.) ■

Study: Respiratory Isolation Measures Underused

DESPITE MEASURES TAKEN FOLLOWING THE RESURGENCE of TB cases in the late 1980s and early 1990s, many health care workers still poorly understand respiratory isolation procedures, says Kevin P. Fennelly, MD, MPH, researcher at the Center for Emerging Pathogens of the New Jersey Medical School in Newark.

Because that resurgence was successfully quashed, today’s health care workers, including intensive care personnel, are less likely to have such expertise because they have less clinical experience with the disease, adds Fennelly. The decrease in TB incidence to historically low levels also creates problems for public health officials working to sustain existing disease control programs and systems because low incidence doesn’t indicate the extent of the efforts required for TB control.

He notes that part of the impetus for the Centers for Disease Control and Prevention (CDC) in-progress revision of its 1994 “Guidelines for Preventing the Transmission of Mycobacterium Tuberculosis in Health Care Facilities”¹ is that a good deal of research has been done since the original document.

“More importantly, there’s been a realization that the document was written at a time when there appeared to be some uncertainties in the risk of transmission,” he says. Fennelly’s facility is one of three National Tuberculosis Model Centers funded by the CDC that

offers training curricula, course materials and technical assistance.

Three Things to Watch

Basically, Fennelly says, controlling *M tuberculosis* transmission in the ICU boils down to three categories: administrative, engineering and personal respiratory protection.

Administrative controls entail having a system in place so that health care workers are well educated about TB and have a high index of suspicion, Fennelly says. The most important of these is having a set of policies and procedures for assuring rapid identification and treatment of potential TB-carrying patients.

Patients suspected of having TB should be placed in respiratory isolation in an airborne infection isolation room without delay, Fennelly says, and sputum specimens and other respiratory secretions sent for smears immediately. He notes that there has been a huge problem because results of such diagnostics can come back months after the patient has died from HIV and TB, leaving ICU personnel ignorant of their risks in the interim.

According to recommendations prepared by John A. Jereb, MD, for the CDC's Division of Tuberculosis Elimination, most low-incidence state TB programs find it hard to assure reports if private medical providers and hospitals send specimens to local hospital laboratories or to out-of-state contract laboratories for testing. Jereb points out that state TB labs require substantial fixed facility and personnel investments that do not decrease even when the TB burden becomes very low.

This situation is similar in the remainder of the country. It puts the TB program at a disadvantage because these laboratories might fail to report critical results promptly to the health department. They also might discard *M tuberculosis* isolates before subsequent testing, such as DNA fingerprinting, can be done.

For instance, 21 TB cases reported in a small Maine community in 1989-1992 were traced back to a source case diagnosed after an eight-month delay. Fennelly describes a case reported by Anthony Tatandaro, MD, in which an ICU patient whose initial sputum smear was negative infected more than 75% of ICU personnel in attendance after the patient was intubated, mechanically ventilated and had a bronchoscopy procedure. That particular case was notable because the ICU was poorly ventilated, Fennelly notes, adding that the best engineering protection against TB is circulating bad air out and fresh air in. "Some hospitals have used high-efficiency particulate air filters, but they are very expensive and unproven," he says.

Old data that say that ultraviolet germicidal irradiation (UVGI) decreases the amount of viable organisms in the air, and that is supported by yet-to-be-published research in which Fennelly collaborated. It suggests that a top-of-the-line UVGI system works well. However, the best engineering control still is pollution ventilation with at least six and preferably 12 air changes per hour, he says. "We have a lot of theoretical modeling and laboratory-based work, but actual field work is impossible. You can't run an experiment in which Hospital A has protection against TB but Hospital B doesn't."

Personal Respiratory Protection

Personal respiratory protection is the most controversial measure, Fennelly says. Particulate respirators are controversial—many people think they are overkill. "There's a certain tension between traditional infection control practitioners and some of the environmental occupational health people who are relative newcomers to this field," he observes. "I think that's understandable when you realize that TB is only sporadically infectious."

Fennelly's main research interest is determining infectiousness of patients. "Many of us have been exposed to TB patients and not become infected," he notes. "That's probably due as much to the great variability among patients as sources of infection as it is to the variability and susceptibility of individuals who become infected."

Fennelly's research group, which is funded to study postdeterminants of infectiousness, is currently examining the strength and frequency of cough and viscoelastic properties of secretions to learn which parameters are the most important. Some of the group's preliminary data suggest that N95 respirators are to be recommended. One objection, he says, is that in most locales N95s cost 75 cents apiece. Though research shows that the most dangerous patients are the ones not yet identified or being treated, Fennelly says that personal respirators may be overkill with patients being treated in isolation rooms with six to 12 air changes an hour.

"I fall down on both sides of the personal respiratory question," Fennelly says. "We know that if you are treating a patient in isolation who's been on treatment for a while, the decrease in risk from personal protection is very little, but with patients not yet being treated who have a procedure such as a bronchoscopy, the risk is tremendous. With patients undergoing tracheal intubation or cough-producing procedures such as sputum induction or bronchoscopy, the staff should definitely wear some type of respiratory protection." ■

Reference

1. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health care facilities, 1994. *MMWR Morb Mortal Wkly Rep.* 1994;43(RR-13):1-132.

ED-to-ED Transfer Not Always an EMTALA Violation

State Law Must Be Followed, Unless It Conflicts

AS HOSPITALS STRUGGLE TO COMPLY WITH ASPECTS of the Emergency Medical Treatment and Labor Act (EMTALA), one thorny issue is whether patients can be transferred from an ICU of one hospital to the emergency department of another hospital, based on an accepting physician's request.

In part, the answer to this question lies with state regulations, since several states take the position that transfers to the ED from an ICU represent a transfer to a lower level of care or an abandonment of the patient, says Stephen Frew, JD, risk management consultant at Physicians Insurance Co. of Wisconsin, based in Loves Park, Ill.

Hospitals are required to comply with their state laws and regulations, to the extent that they do not conflict with EMTALA requirements, he explains. "This requirement then makes this type of transfer a violation in those states that have the rule," he says.

Frew recommends checking with your state hospital inspector to determine your state's regulations regarding transfers. However, Frew adds that EMTALA does not specifically forbid transfers to the ED. In fact, he says recent citations suggest that if there is a long transfer or deterioration, the ED should provide a medical screening examination to the transfer patient before sending patients to the floor.

EMTALA requires that the receiving hospital accept the patient, but it does not specifically indicate who the accepting person is, says Frew. "Some states require an accepting physician in addition to the EMTALA requirement," he adds. "In the absence of state standards, EMTALA does not say where or how the patient must be accepted."

Frew emphasizes that EMTALA requires that the hospital provide necessary further care and stabilization of patients who are known to have an unstable or emergency medical condition. "These terms are defined by law and are much broader than medical terminology," he notes. "It is relatively safe to state that all patients coming from an ICU in need of a higher level of care have an emergency medical condition and are unstable, as defined by EMTALA."

The Centers for Medicare & Medicaid Services will look at whether the hospital promptly and appropriately provided necessary evaluation and stabilizing care to the transfer patient, says Frew. "If that care is rendered, it is unlikely in most states that the hospital would be cited," he says. ■

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

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As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

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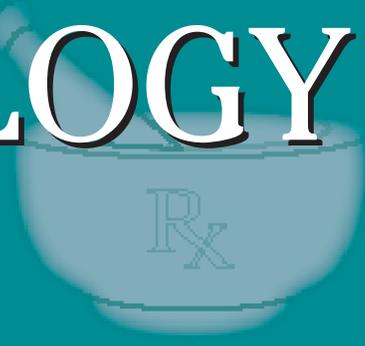
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PHARMACOLOGY WATCH



FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in

December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (JAMA. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (JAMA. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan ($P = .001$) in the intention to treat analysis ($n = 57$). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (JAMA. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant

side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (Ann Intern Med. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (N Engl J Med. 2002;347:2104-2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■