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

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INSIDE

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Incidence and Clinical Effects of Intra-abdominal Hypertension in Critically Ill Patients

ABSTRACT & COMMENTARY

By Richard J. Wall, MD, MPH

Pulmonary Critical Care & Sleep Disorders Medicine, Southlake Clinic, Valley Medical Center, Renton, WA

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

Synopsis: *This study showed that intra-abdominal hypertension is associated with increased organ dysfunction and higher ICU mortality, and two commonly used methods for measuring intra-abdominal pressure have equivalent predictive capabilities.*

Source: Vidal MG, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med* 2008;36:1823-1831.

THIS PROSPECTIVE COHORT STUDY EXAMINED THE EPIDEMIOLOGY and outcomes of patients with intra-abdominal hypertension (IAH). The study was conducted in a mixed medical-surgical ICU at a university hospital in Argentina. Patients were eligible for inclusion if they had an indwelling bladder catheter and an expected ICU stay >24 hours. The main study goals were to describe the incidence of IAH and to examine the relationship of various patient outcomes to IAH. In addition, the authors compared two different methods that are commonly used to measure intra-abdominal pressure (IAP): IAP_{max} and IAP_{mean}. Although most studies have traditionally used IAP_{max}, recent international guidelines suggest the latter may be more appropriate.[1,2]

IAP was measured using a Foley bladder catheter in the supine position. After injecting 50 mL of saline into the bladder, a pressure transducer provided measurements at end expiration. IAP was measured every 6 hours for 7 days (or until death or ICU discharge). IAH was defined as at least 3 consecutive IAP values ≥12 mmHg. The authors compared the predictive capabilities of IAP_{max} (the highest daily value) with IAP_{mean} (the average of the 4 daily values).

During a 9-month study period, data were obtained from 83 patients. Using IAP_{max}, 31% had IAH upon ICU admission and 33% developed new IAH, yielding a prevalence of 64%. Patients with IAH had higher hospital mortality (53% vs 27%, P = 0.02), longer ICU stays (10 vs 3 days, P = 0.001), and more organ dysfunction (especially respiratory and renal). Risk factors for developing IAH included acute respiratory distress syndrome, mechanical ventilation, fluid resuscitation, ileus, and various other signs of septic shock. Although only 10 patients (12%) developed full-blown abdominal compartment syndrome, their mortality was 80%. Receiver operator curves for IAP_{max} and IAP_{mean} showed similar predictive capabilities for survival, with areas under the curves of 0.70 and 0.71, respectively.

COMMENTARY

Although IAH was originally thought to be a condition of trauma patients, it is now recognized that this condition is also common among general ICU patients. With growing awareness of this entity, there has been renewed interest in developing standardized definitions and methods for measuring IAP. Recently, a detailed 2-part report from an international conference was published on the subject.[1,2]

The current study contributes to the field in several ways. First, the study confirms the high incidence (33%) of IAH in a mixed medical-surgical ICU population. In fact, only 27% of the subjects in the current study were trauma patients. Second, the study demonstrates that IAH is independently associated with longer ICU stay, worsening organ failure, and higher mortality. Third, the study shows that two common methods for measuring IAP have equivalent abilities for predicting survival. Thus, both techniques are probably comparable for the purpose of making the diagnosis. Regardless of the chosen method, however, clinicians should familiarize themselves with the numerous potential sources of error when measuring IAP.[1] Unlike the situation with blood pressure, a difference of 10 mmHg here can have enormous clinical implications.

Other studies have also shown a relationship between high-volume fluid resuscitation and IAH. The thought is that excessive fluids lead to bowel edema and impaired gut perfusion. However, such a relationship does not prove causality. For example, IAH may simply be seen in the sickest patients, and these are the individuals who require the highest fluid volumes. Any proposed relationship between IAH and mortality must also be viewed with similar caution.

Although the two measurement methods (IAP_{max} and IAP_{mean}) had "similar" abilities to predict survival, neither one performed well in this regard. In fact, the proposed values only correctly identified the patient's outcome 65% of the time. Given the many other tools available for predicting survival in ICU patients, I do not recommend using the authors' cutoff values for this purpose. Monitoring IAP as a routine "vital sign," as proposed by the authors, seems a bit more plausible. However, this approach will need to be validated before it is ready for widespread use.

Perhaps the most striking finding is that 31% of patients had IAH at ICU admission. This suggests that IAH may develop quickly and even prior to fluid resuscitation. For this reason, many experts recommend that all ICU patients be screened for IAH upon ICU admission and whenever there is new or progressive organ failure.[2] Although reasonable, I wonder how many clinicians routinely follow this advice. In general, any management decisions should be based upon serial IAP measurements and finding sustained (or rising) values over time. ■

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1. Malbrain ML, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med* 2006;32:1722-1732.

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Editorial E-Mail Address: paula.cousins@ahcmedia.com

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2. Cheatham ML, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. *Intensive Care Med* 2007;33:951-962.

Effects of Clinical Trials on Mechanical Ventilation Practice

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *Among 1675 adult patients who were mechanically ventilated for more than 12 hours in 107 ICUs, noninvasive ventilation was used more often, smaller tidal volumes were used in patients with ARDS, and spontaneous breathing trials were used more often to predict successful extubation, in comparison with findings 6 years previously in a similar patient cohort from these same ICUs.*

Source: Esteban A, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177:170-177.

In 2002, Esteban et al reported the results of an ambitious study, enrolling a prospective cohort of consecutive adult patients in 361 ICUs in 20 countries who received mechanical ventilation for more than 12 hours during the month of March 1998.[1] Although the primary purpose of the study was to determine mortality among patients requiring mechanical ventilation, and to look for variations according to geography, demographics, and ventilatory strategy, the investigators also documented how the patients were ventilated.

Of the 5183 ventilated patients in the 1998 study (33% of all patients admitted to the study ICUs during the study month), the majority (roughly two-thirds, across all diagnoses) were managed on volume assist-control ventilation, while about 15% received synchronized intermittent mandatory ventilation (SIMV), with or without added pressure support. Among the 231 patients with the acute respiratory distress syndrome (ARDS), 10% received pressure control ventilation, whereas of 522 patients ventilated because of exacerbations of chronic obstructive pulmonary disease (COPD), this mode was used in 4%. In COPD patients who received mechanical ventilation, noninvasive positive-pressure ventilation (NPPV) was used 17% of the time, while this proportion was 4% in cases of hypoxemic acute respiratory failure.

Seventy percent of all ventilated patients in 1998 underwent attempts at weaning, and these attempts consisted of once-daily spontaneous breathing trials (SBTs, in 78% of patients), multiple SBTs per day (in 14%), gradual reduction in pressure support (in 21%), and gradual reduction in SIMV, either alone (in 8%) or in combination with pressure support (in 22%). For SBTs, a T-tube was used in 52% of patients, continuous positive airway pressure in 19%, and pressure support in 28%. About 12% of patients received a tracheostomy, and 28-day mortality for the entire cohort was 31%.

Because a number of important changes have occurred both in the evidence base supporting mechanical ventilation and in prevailing practice standards since the 1998 study[1] was carried out, Esteban and colleagues in the so-called VENTILA Group undertook a second, similarly large-scale, international cohort study of ventilated patients, to assess the evolution of clinical practice during the interval. Their ambitious investigation had two parts: a descriptive study of how and why mechanical ventilation was carried out in 349 adult ICUs in 23 countries during the month of March 2004; and a comparison of various aspects of ventilatory management, in 2004 vs 1998, in the 107 ICUs from 18 countries that participated in both studies. For the second part, the authors carried out a systematic review of studies dealing with mechanical ventilation in acute respiratory failure that were published prior to the appearance of their earlier paper, and also studies appearing between 1998 and 2004. Using the results of this literature search, and before examining the data from their 2004 patient cohort, the authors generated 11 hypotheses about how the practice of mechanical ventilation might have changed as a result of the research findings. They then tested each of these hypotheses using data from the 1998 and 2004 patients studied in the same set of ICUs. The hypotheses, shown in the form of expected changes in each of 11 aspects of ventilator management, are listed in Table 1 *(see p. 52)*, along with the actual changes that were found.

Altogether, the 2004 study included 4968 patients ventilated in the 349 ICUs during the one month observation period. This represents 25% of all the patients admitted to those ICUs during that period. As in 1998, their mean age was 59 years, and 60% were men. A medical problem was the reason for admission in 59% of the patients; it was COPD in 267 patients (5%) and ARDS in 148 (3%), both of these being only about half as many as in the earlier cohort. Postoperative mechanical ventilation (in 21% of patients), pneumonia or

sepsis (20%), and coma (19%) were the most common admission diagnoses. Mortality in the ICU and in the hospital were 31% and 37%, respectively, essentially the same as in the 1998 cohort.

In the 2004 cohort, 1675 patients were managed in the 107 ICUs that had also participated in the 1998 study. As predicted *(see Table 1)*, NPPV was used substantially more often in 2004 than in 1998, although neither the need for intubation nor hospital mortality changed for such patients. For patients with ARDS, tidal volumes used during the first week decreased, and values exceeding 10 mL/kg (in 8% vs 30% of patients) were less frequently encountered. Higher levels of positive end-expiratory pressure (PEEP) were used during the first week (>10 cm H_2O in 40% of ARDS patients as compared with 28%), although the amount of PEEP used in the entire patient cohort was little changed. Volume assist-control remained the mode most often used; the use of pressure control ventilation did not increase. Prone positioning was used less often in the second study. With respect to weaning, SBTs were used more often prior to extubation, and the use of a T-piece remained the most common method for doing this. However, there was a dramatic decrease in the use of SIMV during weaning, along with a concomitant increase in the use of pressure support. The use and timing of tracheostomy did not change.

COMMENTARY

As a result of their comprehensive literature review, Esteban et al proposed 3 general areas in which the practice of mechanical ventilation might have changed since 1998: reducing the need for invasive mechanical ventilation, reducing the duration of invasive mechanical ventilation, and improving its safety. To examine these 3 areas they generated 11 specific hypotheses: increased use of NPPV, for both COPD exacerbations and acute hypoxemic respiratory failure; increased use of SBTs to assess readiness for extubation, with more use of pressure support and less use of SIMV during the weaning process; the use of smaller tidal volumes and higher PEEP levels for patients with ARDS; and no change in the use of pressure control ventilation, prone positioning, or tracheostomy. Of these 11 practice-change hypotheses *(see Table 1)*, 10 were borne out in the authors' comparisons of patients managed in the same ICUs in 1998 and 2004.

Of importance, there were 3 areas in which the observed practice change was concordant with the results of randomized controlled trials demonstrating decreased mortality and other improved patient-relevant outcomes: using NPPV for COPD exacerbations, using smaller tidal volumes in ARDS, and using SBTs to shorten the duration of intubation by identifying patients ready for weaning. Clearly, the practice of mechanical ventilation appears to be evolving in the right direction, and this study's results suggest that randomized trial results have advanced such practice internationally. However, Esteban et al found no differences in ICU length of stay, or in ICU or hospital mortality, between 1998 and 2004 among either patients treated with NPPV or patients with ARDS. Although the study

Table 1

Ventilator management in 107 ICUs in 18 countries: Hypothesized and observed changes from 1998 to 2004

Aspect of Management	Predicted Change	Observed Change
1. Use of NPPV for COPD exacerbation	Increase	Increase* (used in 44% vs 17%)
2. Use of NPPV for acute hypoxemic respiratory failure	Increase	Increase* (used in 10% vs 4%)
3. Tidal volumes in ARDS	Decrease	Decrease* (7.4 vs 9.1 mL/kg)
4. PEEP levels in ARDS	Minimal increase	Minimal increase* (8.7 vs 7.7 cm H_2O)
5. Use of pressure-control modes	No change	No change
6. Use of prone position in managing ARDS	No change	Decrease* (used in 7% vs 13%)
7. Use of SBTs to assess readiness for extubation	Increase	Trend toward increase (62% vs 58%)
8. Use of pressure support for SBTs in comparison with T-piece	Increase	Trend toward increase (14% vs 10%)
9. Use of SIMV as weaning mode	Decrease	Decrease* (1.6% vs 11%)
10. Use of decreasing levels of pressure support in weaning	Increase	Increase* (55% vs 19%)
11. Use and timing of tracheotomy	No change	No change in use (12% vs 11%) or timing (day 11 vs day 12)

* Statistically significant change

Key: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation; PEEP = positive end-expiratory pressure; SBT = spontaneous breathing trial; SIMV = synchronized intermittent mandatory ventilation.

was designed primarily to compare practice patterns in the two cohorts, and not to demonstrate outcome differences in comparable patient populations, this finding is disappointing. ■

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Special Feature

Therapeutic Hypothermia

By Saadia R. Akhtar, MD, MSc

Idaho Pulmonary Associates, Boise

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

THE AMERICAN HEART ASSOCIATION REPORTS THAT there are approximately 310,000 annual cases of out-of-hospital (OOH) cardiac arrest. In 20-38% of these persons, the initial rhythm is ventricular fibrillation or pulseless ventricular tachycardia (vfib/tach). Of those patients with return of spontaneous circulation (ROSC), approximately 80% are comatose after resuscitation. Median reported survival is 6.4%.[1] Meaningful neurological recovery (typically evaluated at 6-month follow up) occurs in ≤10-30% of survivors of OOH cardiac arrest; most studies report numbers well below 10%.[2] To date, therapeutic hypothermia is the only intervention proven in robust clinical trials to improve these outcomes.

This review will address briefly the pathophysiology of hypoxic-ischemic brain injury, the rationale for considering hypothermia, 2 large clinical studies of therapeutic hypothermia for OOH cardiac arrest, current recommendations for and some specific issues relating to implementation of therapeutic hypothermia protocols, and potential future clinical applications of hypothermia.

Pathophysiology: Time Is Brain

During cardiac arrest and loss of circulation, cerebral oxygen stores and consciousness are lost within 10-20 seconds; glucose and ATP stores are expended within ≤5 minutes.[2] It is clear that cerebral injury occurs during this initial ischemic period and as a result of subsequent reperfusion.

Global cerebral ischemia leads to ion-pump failure, depletion of ATP stores, and subsequent loss of the normal cellular calcium ion gradient. Furthermore, cerebral ischemia is associated with intracellular acidosis, glutamate release, lipolysis and accumulation of free fatty acids, activation of apoptosis, release of inflammatory cytokines, influx of leukocytes, and disruption of the blood-brain barrier (contributing to edema). Subsequent reperfusion is associated with an initial period of hyperemia followed by vasospasm with risk of secondary ischemic injury. Reperfusion allows rapid breakdown of free fatty acids (accumulated during ischemia) to oxygen free radicals that may cause further cellular damage. These are only some of the components that appear to be important in the complex cascade of hypoxic-ischemic-reperfusion cerebral injury.[3]

Hypothermia and Neuroprotection

Therapeutic hypothermia was first investigated in small clinical studies in the 1950s and 1960s. The first published report of the benefits of therapeutic hypothermia after cardiac arrest occurred in 1959.[4] Researchers applied severe hypothermia at that time. Although some positive results were noted, the work was ultimately abandoned due to the difficulty of managing cardiovascular and other side effects of hypothermia, including bradyarrhythmias, hypotension, cardiac arrest, shivering, "cold diuresis," electrolyte abnormalities, coagulopathy, and increased susceptibility to infection.

Investigation resurged during the 1990s when animal studies of mild-to-moderate (30-34° C) hypothermia for brain injury after cardiac arrest suggested benefit. Side effects were reduced, compared to those seen with severe hypothermia, and modern critical care resources greatly facilitated management of these usual complications. A greater understanding of the mechanisms of anoxic brain injury and potential neuroprotective effects of hypothermia provided further support for ongoing investigation. Hypothermia appears to slow cerebral oxygen metabolism, diminish the loss of the normal calcium ion gradient, reduce glutamate release, decrease free radical formation, and reduce markers of apoptosis and inflammation.[5]

Clinical Evidence

Two large multicenter randomized controlled clinical trials of mild-to-moderate hypothermia were published in the same issue of the *New England Journal of Medicine* in February 2002.

The Hypothermia after Cardiac Arrest Study Group, a European network, compared standard care with 24 hours of hypothermia (bladder temperature 32-34° C) for adult patients with witnessed OOH cardiac arrest, initial rhythm of vfib/tach, initiation of resuscitation within 5-15 minutes of collapse, and post-resuscitation coma. The

primary outcome measure was neurological outcome at 6 months (per the Glasgow-Pittsburgh Cerebral Performance Scale); 6-month mortality and acute complications of hypothermia were secondary outcomes. Patients were excluded for failure of ROSC within 60 minutes. The study enrolled 275 patients (median age 59 years; median time to ROSC, 20 minutes). For those in the hypothermia arm, external cooling (cooling air mattress, ice packs) was initiated in the emergency department followed by passive rewarming after 24 hours at the goal temperature. Median time from ROSC to initiation of cooling was 105 minutes and achievement of goal temperature was 8 hours. Favorable neurological outcome at 6 months was found in 55% of subjects in the hypothermia group vs 39% in the control group. Mortality was 14% less in the treatment arm. The authors found no significant differences in complications between the 2 groups, including bleeding, pressure sores, seizures, lethal or long-lasting arrhythmias, or sepsis.[6]

The second study was an Australian multicenter trial of standard care vs 12 hours of moderate hypothermia (core temperature by pulmonary artery catheter 33° C) for adult patients with witnessed OOH cardiac arrest, initial rhythm of vfib/tach, and post-resuscitation coma. The primary outcome was survival to hospital discharge with a good neurological outcome (defined as discharge to home or rehabilitation); acute complications of hypothermia were measured as secondary outcomes. The study enrolled 75 patients (median age 65 years; median time to ROSC, 25 minutes). External cooling was initiated by medics in the field, followed by active rewarming after 12 hours at the goal temperature. Median time from ROSC to achieving goal temperature was 2.5 hours. Good neurological outcome was found in 49% of patients in the hypothermia arm vs 26% in the control arm. There were no differences in adverse outcomes between the 2 groups. The authors did note higher systemic vascular resistance, glucose, and potassium, and lower heart rate in the hypothermia group.[7]

Based on this evidence, the number needed to treat to achieve one favorable neurological outcome is about 6.

Recommendations and Implementation

In 2003, the International Liaison Committee on Resuscitation's Advanced Life Support Task Force published an advisory statement recommending that "unconscious adult patients with spontaneous circulation after OOH cardiac arrest should be cooled to 32-34° C for 12-24 hours when the initial rhythm was vfib/tach." They further suggested that "Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest."[8] Subsequently, the 2005 Advanced Cardiac Life Support (ACLS) guidelines and multiple other national and international cardiology and resuscitation councils have made similar endorsements.[9]

The potential impact of these recommendations is quite substantial. One recent modeling study suggested that full implementation of this hypothermia protocol across the United States could result in 2298 additional patients annually surviving OOH cardiac arrest with good neurological outcome.[10]

However, surveys from as recently as 2006 reveal that implementation of therapeutic hypothermia has been quite limited: Only 25% of U.S. and 35% of non-U.S. specialty physicians (emergency medicine, cardiology, and critical care) use therapeutic hypothermia. These numbers and the reasons cited for not adopting the protocol are similar to what has been reported for other interventions such as low tidal volume ventilation for ARDS: not enough data, do not believe the data, protocol too difficult to implement, etc.[11,12] We see that translation of evidence-based knowledge into clinical practice remains a challenge.

On a practical level, there are some specific issues to be aware of when initiating a protocol for therapeutic hypothermia. Overly rapid cooling may induce cardiac arrest; thus, target temperatures should be achieved over a moderate time frame of about 2-4 hours. A paralytic is usually indicated for shivering, a normal response to cooling, until the goal temperature is reached; once at goal temperature, paralytics may often be stopped. (Another option for management of shivering is meperidine.) "Over-shooting" and reaching temperatures below 32° C may also increase risk of cardiac and other complications. There is a downward "drift" of temperature that may occur even when active external cooling has stopped. This is one problem that has prompted development of novel mechanisms of cooling.[13]

Cooling methods may be categorized as surface or endovascular. Traditionally, and in the cited 2 large randomized clinical trials, surface cooling with ice packs (at the head, neck, axillae, torso, and groin) and cooling blankets (relying on circulation of cool air) has been utilized. (Infusion of cold intravenous fluids may allow initiation of cooling early, such as in the field but is not appropriate for longer-term cooling.) Newer surface cooling methods use rapid water circulation through hydrogel-coated skin pads placed over the torso and thighs or similarly coated blankets combined with continuous patient core temperature monitoring to achieve and maintain goal temperatures. Although there are potential concerns about skin breakdown, skin necrosis, and the limitation of access to covered areas for examination, early experience has been positive.[13,14]

Another approach to cooling is endovascular: Most recently, specialized central venous catheters (femoral or subclavian) achieve and maintain goal temperatures by rapidly circulating water through a closed system. Because this is invasive, it presents greater potential risks (arterial puncture, bleeding, thrombosis, endovascular infection, etc).[14]

Comparison of traditional cooling methods to the newer surface cooling devices (circulating water blankets and gel pads) and endovascular cooling catheters suggests that these newer methods achieve goal temperature more quickly and maintain it more effectively (without drift).[15]

Future of Therapeutic Hypothermia

There is interest and ongoing study of therapeutic hypothermia for spinal cord injury, traumatic brain injury, and nonhemorrhagic stroke. Other potential future applications of therapeutic hypothermia that will not be addressed here include near-drowning, neonatal hypoxic-ischemic brain injury, acute encephalomyelitis, hepatic encephalopathy, and even ARDS.[13]

The case of National Football League player Kevin Everett brought a great deal of media and public attention to therapeutic hypothermia. In September 2007, Mr. Everett sustained a cervical spinal cord injury on the field with initial quadriparesis. External cooling was initiated immediately and maintained for about 48 hours. Mr. Everett has essentially had full return of spinal cord function.[16] Some animal models of spinal cord injury demonstrate improved outcomes with hypothermia. Intra-operative hypothermia has also been used to limit spinal cord damage during aortic cross-clamping in thoracoabdominal aneurysm repairs.[17] However, there are no published clinical trials of hypothermia for spinal cord injury.

Hypothermia has been used anecdotally for management of elevated ICP in acute brain injury. There have been several small randomized controlled clinical trials of prophylactic hypothermia for patients with traumatic brain injury and one larger adult multicenter trial (392 patients).[18] Although the results are not always consistent and the largest trial showed no benefit, meta-analyses of adult studies suggest that early initiation of moderate hypothermia (32-35° C) may improve neurological outcome; hypothermia for >48 hours may reduce mortality. Rewarming patients who are hypothermic at presentation may worsen outcome.[19] On the contrary, a recent large multicenter pediatric study of moderate hypothermia for severe traumatic brain injury confirmed no benefit and a trend towards worsened mortality and neurological outcomes in this population.[20]

Finally, animal studies of nonhemorrhagic stroke suggest application of hypothermia reduces infarct size.[21] Small feasibility trials in adults show safety but no apparent clinical benefit. Phase III clinical trials are now ongoing.[22]

Summary

Hypoxic-ischemic brain injury secondary to OOH cardiac arrest is common and often devastating. Therapeutic hypothermia is the only intervention to date proven (in 2 well-designed randomized controlled clinical trials) to improve neurological outcomes in these patients. Implementation of such protocols is recommended by multiple international resuscitation and medical specialty organizations and this must be a focus and priority for each of us. Ultimately, evidence may even broaden indications for therapeutic hypothermia to include spinal cord injury, traumatic brain injury, and ischemic stroke. ■

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CME / CNE Objectives

24. In the study of the prevalence of IAH, what percentage of patients were diagnosed with IAH at the time of ICU admission?
a. 12%
b. 31%
c. 48%
d. 64%
e. It was never stated.

25. Which of the following changes in mechanical ventilation practice occurred between 1998 and 2004?
a. More use of SIMV
b. Less use of spontaneous breathing trials in assessment for weaning
c. Use of lower levels of PEEP
d. Use of smaller tidal volumes in patients with ARDS
e. More use of pressure control ventilation

26. Loss of spontaneous circulation leads to which of the following change(s) in the brain?
a. Decrease in glutamate release
b. Acute atrophy
c. Accumulation of free fatty acids
d. A hypercoagulable state
e. All of the above

Answers: 24. (b); 25. (d); 26. (c).

CME / CNE 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:

A Short Written Message: Improved Satisfaction After Withdrawal of Life Support

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.

Gender Differences with Anticoagulation Discontinuation

In this issue: Some women with DVT may stop warfarin after six months; Vytorin and cancer; preventing recurrent stroke; and FDA news.

When is it safe to stop anticoagulation after an unprovoked venous thromboembolism? A new study suggests that women with minimal risk factors may safely stop anticoagulation after 6 months of therapy, although the same may not be true for men. Canadian researchers randomized 646 patients with a first, unprovoked major venous thromboembolism and followed them for 4 years. Data were collected for 69 potential predictors of recurrent venous thromboembolism while patients were taking oral anticoagulants and a multi-variable analysis of predictor variables was performed. Men had a 13.7% annual risk of recurrence after discontinuing oral anticoagulation and there was no combination of clinical predictors that could identify a low-risk subgroup of men. In women, 52% had zero or one of the following risk factors: hyperpigmentation, edema or redness of either leg, d-dimer ≥ 250 mcg/L while taking warfarin, body mass index ≥ 30 kg/m^2, or age ≥ 65 years. These women had an annual risk of recurrent thromboembolism of 1.6% (95% CI, 0.3% to 4.6%). Women who had two or more of these risk factors had an annual risk of 14.1%. The authors conclude that women with zero or one risk factor may safely discontinue oral anticoagulant therapy after 6 months of therapy following their first unprovoked venous thromboembolism; however, this conclusion does not apply to men (*CMAJ* 2008;179:417-426). An accompanying editorial points out that patients with the first episode of unprovoked venous thromboembolism have a high rate of recurrence if they stop anticoagulation therapy — about 10% in the first year. Current guidelines from the American College of Chest Physicians recommend lifetime therapy for patients with a first episode of proximal deep venous thrombosis or pulmonary embolism provided that good anticoagulant monitoring is achievable and indefinite treatment is consistent with patient preferences. This study identifies a large group of women who may safely stop anticoagulation after 6 months although the authors do recommend further validation (*CMAJ* 2008; 179:401-402).

FDA Announces Vytorin Investigation

The news keeps getting worse for Merck/Schering-Plough, the distributor of Vytorin®: The FDA has announced that it will investigate a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of the possible association between the use of Vytorin and increased incidence of cancer. The SEAS trial was designed to see if Vytorin, a combination of simvastatin and ezetimibe, would reduce cardiovascular events in patients with aortic stenosis. In a July press

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

release, the company reported on preliminary data which showed that the trial did not show benefit for the primary endpoint of aortic-valve related major cardiovascular events, but did show that a larger percent of subjects treated with Vytorin were diagnosed with, and died from, all types of cancer compared to placebo during the 5-year study. There was improvement in the secondary endpoint of ischemic events (15.7% vs 20%) but no benefit in other secondary endpoints. The number of cancers was 105 (11.1%) in the Vytorin group vs 70 (7.5%) in the control group (P = 0.01), and the number of cancer deaths was 39 (4.1%) in the Vytorin group vs 23 (2.5%) in the control group (HR 1.67; 95% CI, 1.00 to 2.79; P = 0.05). The FDA is also looking at interim data from two large ongoing trials of Vytorin, the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) which, so far, have not shown an increased risk of cancer associated with Vytorin. The SHARP trial should be completed in 2010, while the IMPROVE-IT trial should be finished in 2012. Initial data from the SEAS trial were presented in the recent news conference; full results were published at www.nejm.org (DOI: 10.1056/NEJMao0804602) on Sept. 2, 2008. The FDA says its investigation will take at least 6 months from the date of publication.

PRoFESS Trial Shows No Stroke Benefit

The recently published PRoFESS trial failed to show benefit of two strategies for preventing recurrent strokes. In the first arm of the study, the angiotensin-receptor blocker (ARB) telmisartan was compared to placebo in more than 20,000 patients with ischemic stroke. Patients were randomized to telmisartan 80 mg daily or placebo and followed for a mean follow-up of 2.5 years. Mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group; however, there was no difference in the rate of recurrent stroke (8.7% telmisartan vs 9.2% placebo [HR 0.95; 95% CI, 0.87 to 1.01; P = 0.11). The rate of new onset diabetes was 1.7% in the treatment group and 2.1% in the placebo group (P = 0.10). The authors conclude that therapy with telmisartan initiated soon after an ischemic stroke did not significantly lower the rate of recurrent stroke, diabetes, or major cardiovascular events. The second wing of the study compared aspirin plus 200 mg of extended release dipyridamole (Persantine®) twice daily vs clopidogrel (Plavix®) 75 mg daily in the same patient group. After a mean of 2.5 years of follow-up recurrent stroke occurred in 9% of patients receiving aspirin and dipyridamole and 8.8% of patients receiving clopidogrel (HR 1.01; 95% CI, 0.92 to 1.11). The secondary outcomes of stroke, myocardial infarction, or death from vascular causes occurred in 13.1% of both groups. The authors conclude that there is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke (*N Engl J Med*, published on-line at www.NEJM.org, Aug. 27, 2008).

FDA Actions

The FDA has issued a warning regarding the use of simvastatin in patients who are taking amiodarone. More than 20 mg of simvastatin plus amiodarone puts patient at higher risk for rhabdomyolysis since amiodarone inhibits CYP 3A4, one of the enzymes that metabolizes simvastatin. The simvastatin labeling has contained a warning regarding concomitant use with amiodarone since 2002; however, the FDA continues to receive reports of rhabdomyolysis associated with use of the two drugs. Physicians are also urged to tell their patients to report any unexplained muscle pain, tenderness, or weakness while taking the drugs. Other risks for rhabdomyolysis associated with statins include advanced age, uncontrolled hypothyroidism, and renal impairment.

There should be plenty of flu vaccine this fall. The FDA has announced the approval of six manufactures including GlaxoSmithKline, ID Biomedical, MedImmune, Novartis, Sanofi Pasteur, and CSL Limited. The vaccine will again be a trivalent vaccine comprised of two influenza A viruses and one influenza B virus. All three strains are new this year, an unusual occurrence as usually only one or two strains are updated each year.

The FDA issued an alert in October 2007 regarding exenatide (Byetta®) and the risk of acute pancreatitis. Since then, 6 more cases of hemorrhagic or necrotizing pancreatitis have been reported to the FDA associated with use of the drug, including two deaths. Exenatide is an injectable incretin mimetic used to treat type 2 diabetes. The FDA is recommending that exenatide should be stopped immediately if pancreatitis is suspected. Currently there is no patient profile which would predict increased risk of pancreatitis. Amylin Pharmaceuticals, the manufacture of exenatide, is working with the FDA on new labeling regarding the risk of hemorrhagic or necrotizing pancreatitis. ■