AHC Media

Vol. 19, Issue 3, June 2011
www.ahcmedia.com

Critical Care [ALERT]

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

SPECIAL FEATURE

Use of Therapeutic Hypothermia After Cardiac Arrest

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.

When patients sustain a sudden cardiac arrest, they require immediate life-saving therapies to restart cardiac function and prevent secondary anoxic brain injury. Unfortunately, resuscitative therapies in these patients are often delayed. Furthermore, even if successfully resuscitated, only 10%-30% of such patients are able to leave the hospital alive and resume an independent life. One of the key reasons many patients do not recover from such an ordeal is that they sustain severe anoxic brain injury as a result of their arrest.

The care delivered immediately after return of spontaneous circulation (ROSC) is crucial for survival and should be considered as a continuum of advanced life support. Indeed, most deaths among patients initially resuscitated after cardiac arrest occur within the first 24 hours. Thus, while the "best" care for patients after ROSC is not yet known, there is increasing interest in optimizing practices that have an increased chance of improving outcomes. In this review, I will discuss one of these interventions for adults, therapeutic hypothermia (TH).

WHAT IS THERAPEUTIC HYPOTHERMIA?

TH is a technique for preserving cerebral function in patients who are resuscitated after cardiac arrest. After patients have been stabilized from a cardiovascular standpoint, their body temperature is lowered to 32-34° C for 12-24 hours. TH benefits patients in multiple ways. During reperfusion after arrest, there is a post-resuscitation syndrome wherein free radicals, neurotransmitters, and other mediators further damage the brain. TH mitigates

Financial Disclosure: *Critical Care Alert*'s editor, David J. Pierson, MD, nurse planner Leslie A. Hoffman, PhD, RN, and peer reviewer William Thompson, MD, report no financial relationships to this field of study.

Critical Care [ALERT]

Critical Care Alert,
ISSN 1067-9502, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Critical Care Alert, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling. (Student/Resident rate: $120).

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 1-9 additional copies: $215 each; 10 or more copies: $191 each.

Back issues: $40 Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity has been approved for 13.3 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider # 14749, for 13.3 Contact Hours. This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

these effects. With hypothermia, there is also better preservation of the blood-brain barrier, cell death is lessened, and brain energy stores of adenosine triphosphate are better preserved.

WHAT IS THE EVIDENCE?

TH has been studied since the 1950s, but the first randomized controlled trial (RCT) of its use was not published until 2001.[1] This was a small feasibility study of 30 patients who sustained an out-of-hospital arrest due to asystole or pulseless electrical activity (PEA). A helmet device was used to induce mild hypothermia. No complications were noted. Since it was a feasibility study, no neurologic or clinical outcomes were reported. Shortly thereafter, however, two landmark RCTs were simultaneously published showing that induced hypothermia has a neuroprotective and mortality effect in patients resuscitated after cardiac arrest due to ventricular fibrillation (VF).[2,3]

In the first study, Bernard and colleagues randomized 77 adult patients to either hypothermia at 33° C for 12 hours within 2 hours after ROSC (n = 43) or normothermia (n = 34).[2] The initial rhythm was VF. All patients had persistent coma after ROSC. Patients assigned to hypothermia underwent basic cooling in the ambulance, followed by vigorous cooling using external packs as soon as they arrived at the hospital. Patients were sedated, mechanically ventilated, and paralyzed if necessary (to prevent shivering). At 18 hours, they were actively rewarmed using an external heated-air blanket. Overall, 49% of the hypothermia patients survived, compared with 26% in the normothermia arm (P = 0.046). Among those discharged from the hospital, the adjusted odds ratio for a good neurologic outcome in the hypothermia arm was 5.25 (P = 0.011). There was no significant difference in adverse events between the groups.

The Hypothermia After Cardiac Arrest group conducted another multicenter RCT with a similar design.[3] After screening 3551 patients with persistent coma after ROSC from VF arrest, 275 were randomized. Hypothermia patients were cooled for 24 hours using a specialized cooling mattress and, if necessary, ice packs were also added. Patients were sedated, mechanically ventilated, and paralyzed as needed (to prevent shivering). They were passively rewarmed over an 8-hour period. At 6 months follow up, 59% of the hypothermia patients were alive, compared with 45% in the normothermia arm (P = 0.02). The hypothermia group were 40% more likely to have a cerebral performance category (CPC) score of 1 or 2 (5-point scale; 1 = good cerebral performance, 5 = brain death), as compared with the normothermia group (P = 0.009). A caveat is that this study only enrolled 8% of the patients initially assessed, thus raising questions about its generalizability.

Not surprisingly, a subsequent meta-analysis of these three RCTs showed a benefit for hypothermia in terms of neurologic outcome and survival after cardiac arrest.[4] Likewise, the Cochrane investigators came to a similar conclusion when they examined the topic in 2009.[5] The Cochrane group performed a systematic review of five RCTs (4 trials and 1 abstract). They deemed study quality as "good" in the three studies described above.[1-3] Overall, they found that patients in the hypothermia group were 35% more likely to survive to hospital discharge compared to standard care. Patients in the hypothermia group were 55% more likely to achieve a favorable CPC score of 1 or 2 by the end of their hospital stay.

A recent study in 59 intensive care units (ICUs) across the Netherlands is the largest observational study ever published on TH.[6] Using a nationwide registry, the authors examined mortality rates over a 10-year period. They included all patients admitted to a Dutch ICU after any type of cardiac arrest. A key feature of this study is that more than 90% of Dutch ICUs currently use TH. Among the 5317 patients analyzed, 1547 were treated before and 3770 were treated after implementation of TH. Overall, the

adjusted odds ratio of hospital mortality for patients treated with TH was 0.80 (95% confidence interval [CI] 0.65-0.98; *P* = 0.029). Moreover, the various ICUs used different cooling techniques and protocols, suggesting that TH can be effectively implemented on a widespread basis.

WHAT ABOUT POST-INFARCT PATIENTS?

Patients surviving VF arrest often require additional therapies for treatment of their coronary disease. Case series have reported the feasibility of using TH in combination with emergent percutaneous coronary intervention. Others have described the safe use of TH in patients with cardiogenic shock after ROSC. Although there are descriptions of using fibrinolytic therapy for acute myocardial infarction after ROSC, safety data are lacking in this situation. Given the inherent risk of hypercoaguability and bleeding in TH (see below), fibrinolytics should be given with extreme caution.

WHAT ABOUT NON-VF ARREST?

No prospective RCTs have compared outcomes for patients with an initial non-VF rhythm (i.e., asystole or PEA). However, several observational studies have shown a benefit with use of TH in comatose survivors after both in-hospital and out-of-hospital cardiac arrest associated with any arrest rhythm. Curiously, a few of these studies suggested the benefit of TH is better for out-of-hospital arrest patients, even though code response times are presumably faster in the hospital. The reason for this observation is unclear, but it is probably due to the comorbidities of such patients.

Given the low survival rate in non-VF patients, it is unlikely that a clinical trial will ever be undertaken to test the efficacy of TH in this setting. Such a study would require an enormous sample size. In other words, clinicians need to rely on observational data and their own judgment in non-VF situations. If a patient appears to have a reasonable chance of survival after ROSC from a non-VF arrest, then TH should probably be undertaken.

Acknowledging these areas of uncertainty, the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation strongly recommend that "all comatose adult patients with ROSC after out-of-hospital VF arrest be cooled to 32°-34° C for 12-24 hours."[7] Induced hypothermia may also be "considered" for comatose patients with ROSC after in-hospital arrest of any initial rhythm, or out-of-hospital arrest with an initial rhythm of PEA or asystole. In addition, the guidelines state that active rewarming should be avoided in comatose patients who spontaneously develop mild hypothermia (> 32° C) during the initial 48 hours after ROSC.

METHODS OF COOLING

The optimal technique for delivering TH is unclear. In general, there are two methods — surface cooling and endovascular cooling. However, there are many nuances to these approaches: cooling pads, cooling blankets, cooling mattresses, cooling helmets, ice packs, water immersion, intravascular catheters, gastric lavage, or cold intravenous fluids. In addition, cooling can be combined with hemofiltration or extracorporeal cardiopulmonary support. RCTs have described the safe use of cooling with IV cold saline in the prehospital setting. Regardless of the cooling method chosen, clinicians must continuously monitor the patient's core temperature using an esophageal thermometer, bladder catheter in nonanuric patients, or pulmonary artery catheter (if available). Oral, axillary, and tympanic temperatures are unreliable.

The International Liaison Committee on Resuscitation identified "optimal cooling technique — internal versus external" as a knowledge gap.[8] In its 2008 consensus statement, the committee recommended that temperature control is best achieved with devices incorporating continuous temperature feedback. The committee highlighted several potential drawbacks of surface cooling (e.g., ice packs) including increased labor, greater temperature fluctuations, and inability to control rewarming. However, despite this recommendation, readers should recall that both of the landmark RCTs used external ice packs for cooling.[2,3]

Only a few small studies have compared cooling methods. Flint retrospectively evaluated endovascular cooling when used as an adjunct to a surface method in 42 patients.[9] The combined endovascular and surface cooling method provided better temperature control with less overcooling and a lower incidence of bradycardia compared to surface cooling alone. Another study compared five cooling methods in 50 patients and also found endovascular techniques more efficacious.[10] The largest study of endovascular vs surface cooling after cardiac arrest (n = 83) showed that endovascular cooling achieved more time in the target temperature range, less fluctuations, better control during rewarming, and fewer complications.[11] No studies showed differences in ventilator days, mortality, or neurologic outcomes.

A recent observational study described the safety and low cost of a combined core-surface cooling approach for achieving mild hypothermia in

65 patients with cardiac arrest.[12] Patients were cooled using a combination of rapid, cold saline infusion, evaporative surface cooling, and ice water gastric lavage. The key emphasis was on prompt hypothermia induction. Overall, the median time from induction to target temperature was 60 minutes. The authors achieved a median cooling rate of 2.6° C/hour, and 31% of patients recovered to a CPC score of 1-2.

COMPLICATIONS

Various adverse events have been reported with TH. These include coagulopathy, need for transfusions, pneumonia, sepsis, pancreatitis, renal failure, hemodialysis, pulmonary edema, seizures, arrhythmias, hyperglycemia, hypocalcemia, hypokalemia, and hypophosphatemia.[13] Although the Cochrane analysis did not find a significant difference in adverse events between groups,[5] it is well known that infections are common in post-arrest patients, and prolonged hypothermia decreases immune function. In addition, hypothermia impairs coagulation and any active bleeding must be controlled before undertaking TH. In general, clinicians need to closely monitor patients for potential complications.

FUTURE DIRECTIONS

No RCTs of TH have looked at long-term survival, dependency, quality of life, or cost-effectiveness. In addition, numerous questions remain unanswered about TH. For example, is there a "golden window" of time during which the patient must be cooled to capture the beneficial effects? Does it matter if cooling starts in the pre-hospital setting? Does cooling work equally well in every subgroup (e.g., patients with non-VF as primary rhythm, or patients with in-hospital arrest)? What is the optimal cooling protocol? What is the optimal rewarming protocol? What is the cost-benefit of TH?

In summary, there is strong evidence for the use of TH in patients who remain comatose after ROSC from VF arrest. For patients with out-of-hospital VF arrest, it is now standard of care. There is moderately robust observational evidence for the use of TH in patients who remain comatose after ROSC from non-VF arrest, albeit survival rates in such patients are usually lower and the implementation of TH should be considered in the context of the patient's overall chances for recovery. Numerous devices and protocols exist for cooling patients, but none has proven superior. Each ICU must carefully assess their available resources and expertise when choosing devices and implementing a TH program. ■

REFERENCES

1. Hachimi-Idrissi S, et al. Resuscitation 2001;51:275-281.
2. Bernard SA, et al. N Engl J Med 2002;346:557-563.
3. Hypothermia After Cardiac Arrest Study Group. N Engl J Med 2002;346:549-556.
4. Holzer M, et al. Crit Care Med 2005;33:414-418.
5. Arrich J, et al. Cochrane Database Syst Rev 2009:CD004128.
6. van der Wal G, et al. Crit Care Med 2011;39:84-8.
7. Peberdy MA, et al. Circulation 2010;122(18 Suppl 3):S768-786.
8. Nolan JP, et al. Resuscitation 2008;79:350-379.
9. Flint AC, et al. Neurocrit Care 2007;7:109-118.
10. Hoedemaekers CW, et al. Crit Care 2007;11:R91.
11. Gillies MA, et al. Resuscitation 2010;81:1117-1122.
12. Kory P, et al. Resuscitation 2011;82:15-20.
13. Nielsen N, et al. Acta Anaesthesiol Scand 2009;53:926-934.

ABSTRACT & COMMENTARY

Should We Look at the Stomach with Ultrasound Prior to Intubation?

By Andrew M. Luks, MD

Pulmonary and Critical Care Medicine, University of Washington, Seattle

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

SYNOPSIS: This single-center observational study demonstrated the feasibility of using ultrasound prior to urgent endotracheal intubation to prevent aspiration of gastric contents.

SOURCE: Koenig SJ, et al. Utility of ultrasonography for detection of gastric fluid during urgent endotracheal intubation. Intensive Care Med 2011; 37:627-631.

Bedside ultrasound is increasingly being performed in the intensive care unit (ICU) for a variety of purposes including guiding volume resuscitation, central line placement, and marking pleural fluid collections for drainage. Koenig and colleagues sought to determine whether yet another use of the technique is feasible — ultrasound of gastric contents prior to endotracheal intubation in an effort to decrease the risk of massive gastric aspiration.

To investigate this issue, the authors conducted an observational study of patients undergoing urgent endotracheal intubation (UEI) in the medical ICU at a single center. UEI was defined as a patient requiring intubation who was not in full cardiac arrest or with such severe respiratory failure that any delay for the purposes of performing ultrasound or other tasks could lead to death. Included patients underwent UEI for hypoxemic respiratory failure (defined as respiratory rate > 34 and/or $S_pO2 < 90\%$ on F_IO_2 1.0), hypercarbia ($P_aCO_2 > 45$ with altered mental status or inability to protect the airway), airway protection, septic shock, and for different procedures. Prior to sedation and intubation, a critical care attending physician scanned the left-upper quadrant (LUQ) in an effort to identify gastric fluid. In patients in whom gastric fluid was identified (several figures in the paper illustrate the typical appearance), a gastric tube was placed, tube position was confirmed with ultrasound, and the gastric contents were aspirated. The decision to place a gastric tube was made based on qualitative rather than quantitative assessment of the amount of fluid in the stomach. The patient was then sedated and endotracheal intubation was performed. All patients were monitored for aspiration of gastric contents, defined as visible regurgitation of stomach fluid into the oropharynx during intubation with subsequent penetration through the vocal cords.

LUQ ultrasonography was performed on a total of 80 patients, 19 of whom (24%) had gastric fluid identified on their scan. Gastric tubes were inserted in 13 of the 19 patients, but not placed in 5 of the remaining patients because the amount of fluid was deemed inconsequential, and not placed in another patient due to worsening clinical instability. An average of 553 ± 290 mL of gastric fluid was removed from the 13 patients (range 200-1100 mL). The patients who required gastric tube insertion had been nil per os (NPO) for several hours prior to intubation. Repeat ultrasonography following intubation showed no residual gastric fluid. The ultrasound protocol required 2 minutes to perform, although the authors do not specify whether this included time for gastric tube placement and aspiration of gastric contents. No aspiration events were witnessed in any patients in the study including the 13 who underwent gastric tube placement. The one patient in whom gastric tube placement was deferred due to clinical instability had a witnessed aspiration event.

COMMENTARY

Massive gastric aspiration at the time of intubation is not a common event but occurs frequently enough and is associated with sufficient morbidity that efforts to reduce the risk of this complication are clearly warranted. In fact, it is the primary reason why UEI is generally performed using rapid sequence intubation (RSI) in which sedative medications and paralytic agents are administered and intubation is performed without any attempt to manually ventilate the patient between these two steps. Unfortunately, the major precepts of RSI must be violated in some circumstances, such as when the oxygen saturation falls rapidly while waiting for the onset of paralysis or initial attempts at intubation are unsuccessful and the patient requires ventilation while preparations are made for subsequent attempts. Manual ventilation in these situations can lead to gastric insufflation, increasing the risk of emesis and aspiration. One might surmise that the risk of gastric aspiration would be low in patients who have been NPO prior to intubation, but the data in this paper suggest this may not be the case, as close to 25% of patients still had visible gastric contents despite being NPO for many hours.

Koenig and colleagues demonstrate that gastric ultrasound prior to intubation is both feasible and efficient from a time standpoint and may serve as a reasonable method for decreasing the risk of gastric aspiration. It is important to note, however, that their study does not prove that gastric ultrasound decreases the incidence of aspiration. Not only was the study performed at a single center but, more importantly, gastric tubes were placed in all patients in whom gastric contents were identified and no attempts were made to randomize these patients to gastric tube vs no gastric tube and then study the incidence of aspiration. While aspiration was not observed in any patient who underwent gastric tube placement, there is no way of knowing whether this was due to the gastric tube itself or conscientious application of RSI principles.

Despite these issues, gastric ultrasound seems to be a reasonable strategy when the patient's condition provides adequate time. In the hands of a trained operator, it is fast, does not appear to interrupt the overall flow of UEI, and should not add significant cost to the process, as it is performed with ultrasound units already in the ICU. We do not know from this study exactly how much gastric fluid warrants gastric tube placement but in general, the more fluid, the greater the likelihood of aspiration and the more providers should consider placing a gastric tube. The technique should not be attempted in patients in cardiac arrest or in severe acute respiratory failure; however, in those situations providers will need to remain vigilant about strict application of RSI techniques. ■

ABSTRACT & COMMENTARY

Long-Term Psychological Effects of Critical Illness

By Saadia R. Akhtar, MD, MSc
St. Luke's Idaho Pulmonary Associates, Boise

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

SYNOPSIS: This observational study noted that critically ill patients provided with clinical psychological support during their ICU stay had less anxiety, depression, and post-traumatic stress disorder at 1 year post-discharge compared to historical controls.

SOURCE: Peris A, et al. Early intra-intensive care unit psychological intervention promotes recovery from post traumatic stress disorders, anxiety and depression symptoms in critically ill patients. Crit Care 2011;15:R41.

The authors investigated whether intra-ICU clinical psychological support could impact anxiety, depression, and post-traumatic stress disorder (PTSD) rates in patients 1 year after ICU discharge. This was a single-center study focusing on patients with major trauma (defined by injury severity score > 15) as the primary reason for ICU admission. Inclusion criteria were: age 18-75 years, ICU length of stay (LOS) > 72 hours, mechanical ventilation, ability to be interviewed during ICU stay, and absence of pre-existing psychiatric illness or drug abuse. The study period spanned about 4 years from 2005 to 2009 (the first 2 for historical control data; the second 2 for intervention). The psychological interventions provided are described as "educational interventions, counseling, stress management [cognitive and emotional restructuring], psychological support, coping strategies designed to ease the management of anxiety, depression, fear, hopelessness…." These were provided several times a day by clinical psychologists who were available in-house from 12 a.m. – 4 p.m. and also by other ICU staff. Similar but separate interventions were administered to patients' family members. Validated standard questionnaires were used for assessment of PTSD (Impact of Event Scale Revised, IESR), anxiety and depression (Hospital Anxiety and Depression Scale, HADS), and quality of life.

In the 4-year study period, 376 patients met inclusion criteria and, of these, based on availability and willingness for interview and follow-up, 86 were enrolled in the control arm and 123 in the intervention arm. The two groups were well matched in demographic and diagnostic features as well as ICU course and LOS. At 1 year after ICU discharge, patients in the intervention group were less likely to have anxiety or depression by HADS score but results did not reach statistical significance. They were significantly less likely to have PTSD (21% vs 57%) or need anxiolytics or antidepressants; they also had better overall subjective assessment of quality of life. Logistic regression with some predefined variables and some selected post hoc found no clear predictors of long-term anxiety, depression or PTSD; small associations with Glasgow coma scale at admission and ICU discharge were noted.

COMMENTARY

Psychological effects of critical illness and ICU care are an extremely important — but poorly understood and studied — aspect of intensive care medicine. Rates of PTSD are high though variable, estimated at 20% in one meta-analysis of 15 studies of general ICU populations, 28% in survivors of ALI, and upwards of 60% in other reports.[1] Symptoms such as long-term anxiety and depression are similarly commonly noted. Thus, Peris et al are to be commended for considering this issue and trying to provide an intervention that may improve psychological outcomes after critical illness; they are the first investigators to do this.

The study has several limitations. One key deficiency is that the interventions provided are not clearly defined or documented in the report, either in terms of the methods or the time spent per patient and family member; this will make it difficult for others to repeat the study or apply the interventions. There are several issues with the study design that limit the accuracy, validity, and utility of the results. Some examples include use of historical controls; lack of a priori planning of sample size thus inadequate powering for assessment of outcomes and predictive factors for anxiety, depression, and PTSD; and absence of specific data about sedative and analgesic use. There are considerable differences in the rates of PTSD observed in the historical controls here compared to rates reported for trauma ICU

populations in other publications; as a result, the observed treatment effect may be exaggerated.

Despite these issues, this remains an important and at least hypothesis-generating pioneer study; it suggests that there may be some positive outcomes from early psychological support/intervention for patients and families in the ICU. It also reminds us that considerable additional work is needed to understand the factors that predispose or contribute to development, long-term, of anxiety, depression, and PTSD in critically ill patients; targeted interventions based on such data may be most effective. I can only hope that there will soon be several more robustly designed investigations into this topic that will provide clear answers and direction to guide preventive care. In the meantime, I suggest we continue to acknowledge the short- and long-term psychological side effects of critical care and provide as much general support as possible to our patients and their families. ■

REFERENCE
1. Davydow DS, et al. Gen Hosp Psychiatry 2008;30:421-434.

ABSTRACT & COMMENTARY

Does COPD Worsen Outcomes When Mechanical Ventilation is Required for Other Reasons?

By David J. Pierson, MD, Editor

SYNOPSIS: In a cohort of mechanically ventilated patients admitted with a variety of acute diagnoses, those diagnosed with COPD (but not in exacerbation) had higher ICU mortality but no difference in risk for ventilator-associated pneumonia as compared to patients without the diagnosis of COPD.

SOURCE: Rodríguez A, et al. Impact of non-exacerbated COPD on mortality in critically ill patients. Chest 2011; March 10. [Epub ahead of print.]

Rodríguez and colleagues report on a prospectively enrolled cohort of 235 consecutive patients admitted to two ICUs in Spain who required mechanical ventilation for at least 48 hours and had indications for ventilatory support other than respiratory infection or acute exacerbation of chronic obstructive pulmonary disease (COPD). The goal was to determine whether the existence of underlying COPD worsened survival of the critical illness and also whether having non-exacerbated COPD predisposed patients to ventilator-associated pneumonia (VAP).

The authors used a standard definition of COPD as characterized by chronic airflow obstruction, but they made the diagnosis using "clinical criteria" (not further described), medical records, and/or evidence of hyperinflation on chest radiograph if the patients had not had pulmonary function testing. The diagnosis of VAP required compatible findings on chest radiograph plus either purulent sputum, a leukocyte count exceeding 10,000/mL (or 20% higher than the admission value), or fever; microbiologic criteria were not used.
The 235 patients included 60 (26%) diagnosed with COPD and 175 (74%) without this diagnosis. Patients in the COPD group were more often admitted for medical (vs surgical or trauma) reasons; they were also older, had more comorbidities, and had higher APACHE II scores, all these differences from the non-COPD group being statistically significant. Overall ICU mortality was 26% and was higher in the COPD group (37%) than in the non-COPD group (23%; $P < 0.05$). The magnitude of the difference (14%) was attributed to the presence of COPD in the former group. Duration of mechanical ventilation in survivors was not different in the two groups.

The incidence of VAP as defined in this study was 11.9/1000 ventilation days in the COPD group and 16.0/1000 ventilation days in the non-COPD group ($P = 0.40$). By multivariate analysis, the statistically significant predictors of increased mortality were the presence of COPD, being in shock on admission to the ICU, and having a medical (vs surgical/trauma) diagnosis. The authors conclude that patients with underlying but non-exacerbated COPD have higher ICU mortality than patients without COPD, but no increased risk for developing VAP during their ICU stay.

■ COMMENTARY

Three aspects of this study diminish the confidence with which its findings can be accepted. First, although it was generally in line with ICU practice

in my experience, the diagnosis of COPD was imprecise and likely inaccurate in at least some patients. Airflow obstruction was acknowledged as the primary defining characteristic of the disorder, but in only 11 of the 60 "COPD" patients could severity be determined according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease. This means that only one-sixth of the patients in the COPD group had had spirometry to confirm the diagnosis and determine severity, and that in the others the diagnosis was based on vaguely stated clinical grounds. Because the history, physical exam, and chest X-ray are much less reliable for detecting the presence of COPD than spirometry, especially when it is only moderate in severity, the possibility exists that at least some of the "COPD" patients did not in fact have this disorder — or, alternatively, that if they all had COPD it was most likely severe.

The second weakness is that the patients assigned to the COPD group differed in important ways from those in the non-COPD group, apart from the presumed presence of COPD. They were older and had more comorbid conditions such as diabetes and cardiomyopathy. Their illness severity was greater on ICU admission, by APACHE II scores, and they were more likely to be admitted because of medical illness as compared to surgery or trauma. These important potential confounders make it more difficult to ascribe the observed outcome differences to the presence of COPD, despite at least some of them failing to be independent predictors by multivariate analysis.

Third, the diagnostic criteria used for VAP — purely clinical without the use of microbiologic data — were not as robust as those used in the most rigorous studies of this entity. In the methods it is stated that all patients had quantitative cultures performed on endotracheal aspirates, but the results were not used in diagnosing VAP.

These drawbacks notwithstanding, this study supports the concept that the presence of COPD as a background comorbidity in patients requiring mechanical ventilation for reasons other than an acute exacerbation predisposes patients to worse outcomes than individuals not having COPD, all other conditions being equal. It also supports the concept that VAP is primarily a complication of endotracheal intubation, and that underlying COPD is not a major determinant of its acquisition in the context of critical illness. ■

CME/CNE Questions

7. Randomized controlled studies of therapeutic hypothermia after out-of-hospital cardiac arrest have shown which of the following?

a. Improved hospital mortality

b. Improved mortality at 6 months

c. Improved neurologic outcomes at 6 months

d. Improved cardiac function

e. All of the above

8. Roughly what percentage of ICU patients who had been NPO for several hours still had gastric contents visualized on gastric ultrasound prior to endotracheal intubation?

a. 5%

b. 15%

c. 25%

d. 35%

e. 45%

9. Peris et al's study suggests that psychological support and intervention during an ICU stay may:

a. improve family members' satisfaction with the ICU stay.

b. reduce patients' risk of having PTSD 1 year after discharge.

c. decrease length of mechanical ventilation.

d. decrease length of stay in the ICU.

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

Low-tidal-volume ventilation after cardiac surgery

Sleep apnea and postoperative complications

PHARMACOLOGY WATCH

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

Women's Health Issue — Adverse Medication Effects

In this issue: Calcium supplements and MI; birth control pills and VTE; ACE inhibitors and breast cancer risk; spending on pharmaceuticals; and FDA actions.

Calcium supplements and MI risk

Do calcium supplements increase the risk of myocardial infarction (MI)? Researchers from New Zealand recently reanalyzed data from the Women's Health Initiative (WHI) in an attempt to answer this question. In 2008 the same group published a randomized, placebo-controlled trial of calcium supplements in nearly 1500 healthy postmenopausal women that showed upward trends in cardiovascular event rates with calcium use (*BMJ* 2008;336:262-266). The same group subsequently carried out a meta-analysis of cardiovascular events in randomized, placebo-controlled trials of women taking calcium supplementation without vitamin D. In that study, calcium supplementation significantly increased the risk of MI by about 30% (*BMJ* 2010;341:c3691). Although these studies garnered some interest, they were also viewed with skepticism, and most physicians, especially in this country, did not change their practice of recommending calcium supplementation for postmenopausal women. The New Zealand group then turned to the WHI data, a rather strange place to look considering that one of the main outcomes of WHI was the finding of no adverse effect of calcium and vitamin D on cardiovascular risk. However, the researchers found one major caveat: WHI did not consider whether women were taking calcium on their own prior to entry into the study. The New Zealand group got access to the original NIH data and were able to tease out women who were not using personal calcium supplements at randomization. They found nearly 17,000 women who fit that category. Women in this subgroup who were randomized to calcium and vitamin D had small but significant increased risk for cardiovascular events with hazard ratios that ranged from 1.13-1.22 ($P = 0.05$ for clinical MI or stroke, $P = 0.04$ for clinical MI or revascularization). When the WHI data were added to the previously done meta-analysis of three placebo-controlled trials, calcium and vitamin D were found to increase the risk of MI (relative risk [RR] 1.21 [95% confidence interval [CI] 1.01-1.44]; $P = 0.04$), stroke (1.20 [CI 1.00-1.43], $P = 0.05$), and the composite of MI or stroke (1.16 [CI 1.02-1.32], $P = 0.02$). Trial level data was available for more than 28,000 women who were randomly assigned to calcium plus vitamin D or placebo. Calcium or calcium plus vitamin D increased the risk of MI (RR 1.24 [CI 1.07-1.45], $P = 0.004$) and a composite of MI or stroke (1.15 [CI 1.03-1.27], $P = 0.009$). The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially MI. They suggest that a reassessment of the role of calcium supplementation in osteoporosis management is warranted (*BMJ* 2011;342:d2040 doi:1136/*BMJ*.d2040, published April 19, 2011). This study has been hotly debated and was even criticized in an editorial in the same issue of *BMJ*. Nonetheless there is a bit of irony in using WHI data, which are largely responsible for millions of women stopping hormone replacement therapy, to show a relationship between calcium and

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: neill.kimball@ahcmedia.com.

cardiovascular disease disease. There is no suggestion in any of these data that dietary calcium leads to adverse events. It is postulated that the rapid increases in calcium that occur with calcium supplementation may somehow play a role in increased cardiovascular risk.

Birth control pills and VTE risk

A progestin commonly used in birth control pills may increase the risk of venous thromboembolism (VTE). A recent report suggests that women taking oral contraceptives containing drospirenone may be at increased risk of VTE compared to women taking contraceptives containing other progestins. Two studies were recently published in *BMJ*. The first was a case-controlled study of U.S. women that showed that women taking drospirenone-containing contraceptives were twice as likely to develop nonfatal VTE compared to women taking levonorgestrel (*BMJ* 2011;342:d2151). The other study, a case-controlled study of British women, showed a three-fold higher rate of VTE with drospirenone-containing contraceptives compared to levonorgestrel (*BMJ* 2011;342:d2139). Oral contraceptives containing drospirenone include Yaz, Yasmin, and Angeliq.

ACE inhibitors and breast cancer risk

Researchers at UCLA and Kaiser Permanente in northern California recently published data suggesting that angiotensin converting enzyme inhibitors (ACEi) may increase the risk of breast cancer recurrence in breast cancer survivors. Using a database of nearly 1800 women with a history of breast cancer, there were 292 recurrences, 174 breast cancer deaths, and 323 total deaths. Twenty-three percent of the women in the study were exposed to either a beta-blocker or an ACEi. ACEi exposure was associated with breast cancer recurrence 1.5 times baseline (HR 1.56, 95% CI 1.02-2.39, $P = 0.04$) but not increased cause-specific or overall mortality. Beta-blocker exposure was associated with lower hazard of recurrence and cause-specific mortality. There was no dose-response with either medication. When a beta-blocker was combined with an ACEi, there was a lower hazard ratio for recurrence than with ACEi alone. The authors suggest that ACEis may be associated with an increased risk of breast cancer recurrence; although beta-blockers may be somewhat protective, more research is needed (*Breast Cancer Res Treat*, published online, DOI: 1007/s10549-011-1503-3). Beta-blockers have been shown to be protective against breast cancer recurrence in other studies, but the ACEi findings were unexpected.

Spending on U.S. pharmaceuticals

Spending on pharmaceuticals in the United States grew at its smallest level in years in 2010, according to a report by the IMS Institute for Healthcare Informatics. Pharmaceutical spending increased 2.3% in 2010 compared to 5.1% in 2009. Generics dominated the pharmaceutical market in 2010 making up 78% of total market share compared to 63% in 2006. Of the top 25 drugs by volume, only three were brand-name products: atorvastatin (Lipitor), clopidogrel (Plavix), and montelukast (Singulair). By spending dollars, however, Lipitor was the top grossing product at $7.2 billion in 2010, down from $7.6 billion in 2009. Esomeprazole (Nexium) was second at $6.3 billion, while Plavix ranked third at $6.1 billion. The domination of generics is of major concern to the pharmaceutical industry since there are few new drugs in the development pipeline and several high-profile drugs are due to lose protection soon. Foremost among these is Pfizer's Lipitor. Pfizer has been battling to maintain its patent protection, but generic manufacturer Watson Pharmaceuticals is expected to introduce the first generic atorvastatin in November of this year. Likewise, Merck's Singulair will likely lose its patent protection next year. The economy also has played a role in the decrease in pharmaceutical spending as the total volume of medicines consumed decreased 0.5% in 2010 along with a decrease in the number of doctor office visits of 4.2%. This extends a decline that began in mid 2009 — likely due to higher unemployment and rising health care costs.

FDA actions

The FDA has approved rituximab (Rituxan) for the expanded indication to treat Wegener's granulomatosis and microscopic polyangiitis, two rare vasculitides. The effectiveness of rituximab was demonstrated in a single control trial in which 197 patients with either condition were randomized to rituximab plus glucocorticoids or oral cyclophosphamide plus glucocorticoids. After 6 months, 64% of the patients treated with rituximab had a complete remission compared to 53% of patients treated with cyclophosphamide. Rituximab is manufactured by Genentech.

The FDA has approved gabapentin enacarbil for the treatment of moderate-to-severe restless leg syndrome. The approval was based on two 12-week clinical trials in adults showing the effectiveness of the drug vs placebo. Gabapentin enacarbil is formulated as a once a day extended-release tablet. It is marketed by GlaxoSmithKline and Xenoport as Horizant. ■