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INSIDE

Does Heliox Help in COPD Exacerbations?

ABSTRACT & COMMENTARY

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

This article originally appeared in the March 2010 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor, Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, and Dr. Thompson is Staff Pulmonologist, VA Medical Center; Associate Professor of Medicine, University of Washington; they both report no financial relationships relevant to this field of study.*

Synopsis: *In this prospective, multicenter, randomized trial, addition of a helium-oxygen gas mixture to non-invasive positive pressure ventilation in the treatment of COPD exacerbations did not decrease the need for intubation when compared to non-invasive positive pressure ventilation alone.*

Source: Maggiore SM, et al. A multicenter randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med*. 2010;38:145-151.

Previous studies have shown that addition of a helium-oxygen mixture (HeO_2) to non-invasive ventilation (NIV) in patients with COPD exacerbation improves dyspnea, work of breathing, and carbon dioxide elimination, but have yet to establish whether this approach is associated with improvements in other important clinical outcomes. Using a prospective, multicenter randomized study design, Maggiore and colleagues sought to address this gap in the literature and test the hypothesis that NIV combined with HeO_2 was associated with decreased need for intubation during COPD exacerbations when compared to NIV alone.

Patients were included in the study if they were between 18 and 85 years of age; had known or suspected COPD based on pulmonary function tests, blood gases, clinical history, or chest radiograph; had

VOLUME 5 • NUMBER 2 • APRIL 2010 • PAGES 9-16

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Financial Disclosure:

Hospital Medicine Alert's physician editor, Kenneth P. Steinberg, MD, has no relevant financial relationship related to the material presented in this issue.

worsening dyspnea for two weeks or less; had $PaCO_2$ > 45 mm Hg; and had two or more of the following: respiratory rate > 24, pH < 7.35, and PaO_2 < 50 mm Hg on room air. Patients were excluded if they had respiratory arrest or need for immediate intubation, pneumothorax, a short life expectancy (< 1 month), high oxygen requirements, and a variety of other criteria.

Enrolled patients were randomized to receive NIV plus HeO_2 or air-oxygen in addition to conventional medical treatment. All patients were treated with an FIO_2 of 0.35 and were started on an inspiratory pressure (IPAP) of 12-15 cm H_2O and an expiratory pressure (EPAP) of 5 cm H_2O with subsequent changes based on clinical status and blood gas results. NIV was not applied continuously and was, instead, applied intermittently for > 6 hours/day with clinicians free to decide how long and how often to use NIV each day. NIV was gradually discontinued when the total duration of NIV was < 6 hours/day. The decision to perform endotracheal intubation was based on pre-specified criteria that were well-defined in the study. The primary endpoint was the need for endotracheal intubation while secondary endpoints included total duration of NIV and invasive mechanical ventilation, length of ICU and hospital stay, 28-day mortality, and the incidence of adverse events.

A total of 204 patients were included in the study (102 per group). Sixty-four percent of the patients had a prior diagnosis of COPD, while the remaining 36% were suspected of having the diagnosis at the time of admission. Patients in both groups received an average IPAP of 15.1 ± 4 cm H_2O and EPAP of 3.3 ± 2.0 cm H_2O. The total duration of NIV in the first 48 hours of admission did not differ between the two groups, with the HeO_2-treated patients receiving an average of 17.7 ± 9.8 hours compared to 18.8 ± 11.3 hours in the control group. A total of 56 patients in the study (27%) required intubation. The intubation rate was lower in the HeO_2 group (24.5%) compared to the control group (30.4%), but this difference was not statistically significant ($p = 0.35$). Statistically significant differences favoring HeO_2 were seen, however, in the subgroup of patients who required NIV for < 4 days (31% vs. 53%). There were no statistically significant differences in the duration of mechanical ventilation, ICU and hospital length of stay, and mortality. Observed complications included facial skin necrosis, eye irritation, gastric distention, and nosocomial pneumonia, but there were no observed differences in the incidence of these complications between the two study groups.

■ COMMENTARY

Non-invasive positive pressure ventilation is now the standard treatment for patients who present with severe COPD exacerbations, as the treatment modality has been shown to decrease the need for intubation, shorten ICU length of stay, and improve mortality in such patients. The question is: Can we do better? The addition of HeO_2 to treatment regimens in these patients certainly makes physiologic sense — the less dense and slightly more viscous HeO_2 mixture leads to more laminar flow in obstructed airways and requires less pressure to drive ventilation — and has been shown to improve symptom-based and physiologic outcomes. Unfortunately, we still lack evidence that the therapy provides benefits over NIV alone with regard to other more important outcomes, including the need for intubation. Maggiore et al did show a trend toward improvement in this outcome measure but, as with a previous study that looked at this issue,[1] these results were not statistically significant. They did show a significant improvement in those patients who required NIV for < 4 days, but the utility of this finding is questionable, as it is very difficult to predict a priori the duration of therapy that will be required in a given patient.

Both of these studies share a problem in that they were small and likely underpowered and, as a result, potentially subject to Type II errors. The study by Maggiore and colleagues likely also suffered from their overly broad inclusion criteria that might have captured patients who did not truly have COPD (e.g., prior pulmonary function testing was not required for diagnosis and relatively young patients unlikely to have COPD were eligible for inclusion) and the fact that NIV practices and other aspects of care were not standardized across study sites. It is also unclear whether the choice of HeO_2 mixture (65% helium, 35% oxygen) was appropriate and, in particular, whether mixtures with a lower FIO_2 and, therefore, lower density, might have yielded more benefit. The choice of this mixture is somewhat odd in that the observed hypoxemia in COPD exacerbations is typically due to areas of low ventilation-perfusion

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

MANAGING EDITOR: Leslie Hamlin.
ASSOCIATE PUBLISHER: Russ Underwood.
DIRECTOR OF MARKETING: Schandale Kornegay.
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to
Hospital Medicine Alert,
P.O. Box 740059,
Atlanta, GA 30374.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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ratios rather than shunt and usually responds to only small increases in the FIO_2 well below the 35% level used in this study.

The fact that this and the prior study showed a trend toward improvement does provide a reasonable justification for conducting a larger trial to address this question, but until the results of such a trial are available, we should not be wheeling the heliox tanks to the bedsides of our COPD patients. Although the therapy is relatively benign in terms of the side effect profile, it is not cheap. At our institution, each K-sized tank costs roughly $150 and, depending on the intensity of use in a given patient, several tanks may be required each day. Granted, this expense may be offset by savings associated with decreased hospital and ICU length of stay, but before we embark on wholesale use of the therapy we should really wait for better evidence of benefit in important clinical outcomes. ■

Reference

1. Jolliet P, et al. Helium-oxygen versus air-oxygen noninvasive pressure support in decompensated chronic obstructive disease. *Crit Care Med*. 2003;31:878-884.

Stress Cardiomyopathy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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This article originally appeared in the March 2010 Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD. Dr. Weiss is Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Weiss reports no financial relationships relevant to this field of study.*

Source: Sharkey SW, et al. Natural history and expansive clinical profile of stress (Tako-Tsubo) cardiomyopathy. *J Am Coll Cardiol*. 2010;55: 333-341.

Stress-induced apical cardiomyopathy (tako-Tsubo) is a recently recognized reversible form of acute cardiomyopathy that may mimic acute myocardial infarction initially. Reported experience with this condition is limited to small observational studies with short follow-up periods. Thus, these investigators from Minneapolis and Boston assembled data on 136 consecutive cases of stress cardiomyopathy (SC) over a seven-year period. Diagnostic criteria included an acute chest pain event, typical LV contraction abnormality encompassing more than one coronary artery territory, and no significant coronary stenoses on angiography. A subgroup of 95 patients had cardiac MRI shortly after admission. Almost all the patients were women (96%), and the mean age was 68 years (range 32-94 years). In 89%, a distinct stressful event preceded the presentation within 12 hours. These events were emotional in 47% and physical (trauma, post surgical) in 42%. Among the physical triggers, use of catecholamines was common. An ECG mimicking acute ST elevation myocardial infarction was common (49%), and troponin was elevated in 92%. Ventricular wall motion abnormalities were variable, but most involved at least the apex of the left ventricle. Only one patient showed delayed enhancement on CMR consistent with scar. Acute mortality was 2%, but only one patient died of cardiogenic shock. The others died of intracranial causes. Apical ventricular thrombi were identified in five patients, two of whom had embolic events. LV function returned rapidly in 96%, although, in 5%, recovery was delayed more than two months. Nonfatal recurrences occurred in 5%. During the seven years of the study, the incidence of SC increased due to a shift to more events associated with physical trauma. The authors concluded that the clinical spectrum of SC was heterogeneous, and suggested that expanded surveillance strategies and anticoagulation should be considered.

■ **COMMENTARY**

This large observational study of patients with SC raises several interesting points about this unusual but serious condition. First, the investigators took an inclusive approach, combining those with emotionally triggered events and those with physical or pharmacologic triggers. Much has been written about the cardiomyopathy of subarachnoid hemorrhage, but it was included as another form of SC in this series. Second, in the later years of their experience, physical triggers predominated, suggesting that increased awareness led to more SC diagnoses in hospitalized patients with a variety of medical illnesses, surgical procedures, and, even, diagnostic tests (e.g., dobutamine stress echo). Third, despite the potential role of exogenous or endogenous catecholamines, beta-blocker therapy did not seem to prevent the occurrence of SC. Fourth, ventricular thrombus and systemic emboli were observed in a few patients, raising the issue of prophylactic anticoagulation. Since the majority of patients had normal LV function within a few days, perhaps prophylactic anticoagulation should be used in those with persistent apical akinesis and continued until LV function normalizes. Fortunately, mortality is low in SC and usually due to the underlying disease. ■

Aortic Stenosis — When to Operate

ABSTRACT & COMMENTARY

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This article originally appeared in the March 2010 issue of Internal Medicine Alert. It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Clinical Professor, University of California, Irvine, and Dr. Roberts is Clinical Professor of Medicine, Albert Einstein College of Medicine. Dr. Brunton is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and AstraZeneca, and serves on the speaker's bureau for McNeil, Sanofi-Aventis, and Ortho McNeil, and Dr. Roberts reports no financial relationship relevant to this field of study.

Synopsis: *Even if asymptomatic, early elective aortic valve replacement should be considered for increasingly symptomatic patients with severe aortic valve stenosis because they have a poor prognosis with a high event rate and a risk of rapid functional deterioration, especially if the peak aortic jet velocity is above 5.5 m/sec.*

Source: Rosenhek R, et al. Natural history of very severe aortic stenosis. *Circulation*. 2010;121:151-156.

The prognosis for asymptomatic patients with severe aortic stenosis is usually quite favorable and a watchful waiting approach, which has been demonstrated to be quite safe, is usually the clinical approach utilized by most physicians.[1-4] However, it must be clearly recognized that when symptoms start to develop in patients with severe aortic stenosis, a very poor prognosis can be expected unless an aortic valve replacement procedure is urgently performed.[5-7] Asymptomatic patients usually are not recommended for aortic valve replacement for many reasons, including the immediate operative risk, the long-term morbidity and mortality, and the potential need for reoperation.[8] However, many clinicians have argued in favor of an earlier intervention because of the higher operative risk that occurs as patients become increasingly symptomatic,[9] the risks of late symptom reporting by stoical patients, and the risk of sudden death even though this risk is generally quite low in asymptomatic patients.[1,2]

Rosenhek and his colleagues prospectively followed 116 consecutive, asymptomatic patients with very severe isolated aortic stenosis in an attempt to define its natural history and to determine which patients should be selected for valve replacement before they became symptomatic. They concluded that in asymptomatic patients with severe aortic stenosis, the presence of a calcified aortic valve combined with rapid hemodynamic progression identified a high-risk population in whom early elective valve replacement should be considered.[2]

■ COMMENTARY

Despite being asymptomatic, patients with very severe aortic stenosis quite often have a poor prognosis with a high event rate and a significant risk of rapid functional deterioration. This study by Rosenhek et al demonstrated that event-free survival rate for patients with severe aortic stenosis (defined by a peak aortic jet velocity of 4.0-5.0 m/sec) diminished from 82% at year 1 to 39% at year four. The survival rates were significantly worse for patients with a very severe stenosis (defined by a peak jet velocity of 5.0-5.5 m/sec): These patients had a survival rate of only 76% at year one and 17% a year four. Patients with aortic stenosis and associated coronary artery disease had a worse chance of event-free survival because a more rapid hemodynamic deterioration usually occurs.[2,8] However, the presence of coronary artery disease was not found to be of statistically significant additional prognostic importance and neither was treatment with statin drugs, renin-angiotensin-aldosterone system inhibitors, or beta blockers.

Clinicians should recognize that patients with very severe aortic stenosis (i.e., defined as those patients with a peak aortic jet velocity greater than or equal to 5.5 m/sec) tend to have more severe and rapid onset of symptoms than do those patients with a lower jet velocity. Therefore, even asymptomatic patients with very severe aortic stenosis should be considered for early elective valve replacement surgery because of the risk of rapid functional deterioration often associated with an increased event rate. All patients with aortic stenosis should be closely followed, evaluated carefully with respect to early symptom development. Additionally, they should be frequently monitored echocardiographically to determine any aortic jet velocity changes of significance. ■

References

1. Otto CM, et al. Prospective study of asymptomatic valvular aortic stenosis. *Circulation*. 1997;95:2262-2270.
2. Rosenhek R, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343: 611-617.
3. Bonow RO, et al. ACC/AHA 2006 guidelines for the management of patience with valvular heart disease. *J Am Coll Cardiol*. 2006;48:e1-e148.
4. Vahanian A, et al. Guidelines on the management of valvular heart disease. *Eur Heart J*. 2007;28:230-268.
5. Horstcotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988;9(suppl E):57-64.
6. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation*. 1968;38(1 Suppl):61-67.
7. Frank S, et al. Natural history of valvular aortic stenosis. *Br Heart J*. 1973;35:41-46.
8. Hammermeister K, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve. *J Am Coll Cardiol*. 2000;36:1152-1158.
9. STS National Database. STS US Cardiac surgery database: 1997 aortic valve replacement patients. Available at: www.ctsnet.org/doc/3031.

Cardiac Surgery in Nonagenarians

ABSTRACT & COMMENTARY

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Dr. Boyle reports no financial relationships relevant to this field of study.

This article originally appeared in the March 2010 issue of Clinical Cardiology Alert. *It was originally edited by Michael H. Crawford, MD, and peer reviewed by Ethan Weiss, MD.*

Source: Speziale G et al. Operative and middle-term results of cardiac surgery in nonagenarians. A bridge toward routine practice. *Circulation*. 2010;121:208-213.

Cardiac surgery carries greater risk in older patients. Nonagenarians are a growing part of cardiology practice as our population ages. While age > 90 years has previously been considered a contraindication to cardiac surgery, more recently, surgeons have been operating on selected nonagenarians who have high functional status. To determine the factors associated with adverse outcomes in this age group, Speziale et al present their retrospectively collected surgical data on nonagenarians undergoing cardiac surgery over a 10-year period from eight centers in Italy. In carefully selecting their patients, they routinely use the Duke Activity Status Index in all patients presenting for surgical evaluation. They considered a score less than 10 an absolute contraindication to surgery and a score of 10-15 as a relative contraindication. Furthermore, they refused surgery to those who were bed-bound and those without strong family support.

A total of 127 patients with a mean age of 92 years (range 90-103) underwent cardiac surgery — coronary artery bypass grafting (CABG), valve surgery, or both. This represented 1.2% of their total surgical volume during that time period. Importantly, over one-third of cases were non-elective. Overall 30-day surgical mortality was 13.4%. This compared favorably with the expected mortality based on the logistic EuroSCORE (21.3 6.1). Mean follow-up time was 3.6 years (range 7 months to 5 years). The total mortality at the end of follow-up was approximately 50%. Post-operative complication rates were high, occurring in 54 patients (42.5%); these included eight ICU readmissions, five surgical revisions, 17 cases of respiratory failure, 22 cases of acute renal failure, 11 neurological complications, 38 post-op arrhythmias, and two sternal wound infections. There were no differences in mortality or complication rates according to the types of surgery. Multiple logistic regression identified non-elective presentation (odds ratio 9.3, $p < 0.001$) and previous myocardial infarction (odds ratio 4.1, $p = 0.014$) as independent predictors of post-op complications. The ICU and total hospital lengths of stay were prolonged (10.2-4.1 days in ICU, 29.2-5.6 days in hospital). Despite the high mortality, complication rates, and length of stay, those who survived experienced improvement in symptoms. Comparing baseline to end of follow-up, the percentage of patients in each NYHA class were as follows: I- 10.8% vs. 44.6%; II-27.7% vs. 41.5%; III-44.6% vs. 12.3%; IV-16.9% vs. 1.5%. The authors conclude that although the complication rate is high, cardiac surgery in nonagenarians can achieve functional improvement at the price of considerable operative and follow-up mortality. Cardiac operations are supported in the very elderly if the surgery is performed early and electively.

■ **COMMENTARY**

Advanced age is associated with higher complication rates for most procedures and operations. Thus, cardiac surgery, which carries significant risk even in young healthy patients, has traditionally not been offered to the very elderly. Furthermore, many cardiac surgeries are performed to increase life expectancy, which may be unrealistic in elderly patients with other co-morbidities. However, whether cardiac surgery should be offered to those nonagenarians who are highly functional remains unknown. Studies like these, although limited by their retrospective nature and lack of control group, demonstrate that even in very rigorously selected, highly functioning nonagenarians, surgical mortality, complication rates, and length of stay are very high. As nonagenarians become a more common part of cardiology practice, which they inevitably will, discussing therapeutic options with them must include these high-mortality and complication rates. Symptomatic improvement can be seen in those who survive, but the price is high. ■

Brain Attack

SPECIAL FEATURE

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

This article originally appeared in the March 2010 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD.*

Each year, about 795,000 strokes occur in the United States; 85% of these are acute ischemic strokes. Acute stroke remains the third leading cause of death in the United States (137,000 persons yearly) and accounts for significant morbidity and disability in survivors. Risk factors for acute stroke include race (incidence is higher in African-American and Hispanic patients, compared to Caucasians), age (75% of patients are > 65 years), obesity, hypertension, atrial fibrillation, diabetes, hyperlipidemia, and tobacco use.[1]

The underlying pathophysiology of acute ischemic stroke generally involves acute intracranial arterial occlusion (thrombotic or embolic). Neurons in the area of the brain being primarily supplied by the occluded vessel die within minutes. Adjacent to and surrounding the immediate area of ischemia and infarct are further at-risk areas of diminished blood flow, the ischemic penumbra. Without rapid revascularization, these areas may infarct as well, greatly extending the injury.[2]

In the past, clinical observation and supportive care were all that could be offered for acute ischemic stroke. More recently, thrombolysis in the early hours has been shown to significantly improve outcomes. To convey the importance of early detection and intervention for stroke, the term "brain attack" (analogous to heart attack) has been advocated by some experts. This review will discuss diagnosis and initial evaluation of acute ischemic stroke, the evidence and indications for thrombolysis, and some key issues in subsequent ICU management.

Diagnosis

Acute ischemic stroke typically presents as acute onset of focal neurological deficits with or without higher cerebral dysfunction. As the term brain attack implies, these patients should be triaged with no less urgency than those with acute myocardial infarction. After assessing and stabilizing airway, breathing, and circulation, a focused history (including risk factors for ischemic stroke and potential contraindications for thrombolytics, discussed below) and examination should be performed. Determination of the exact time of symptom onset is essential for making treatment decisions.[3] It is important to consider and rule out conditions that may mimic stroke, such as severe hypoglycemia, seizure, migraine, or conversion disorder.[4] Use of a formal stroke scale is recommended by expert guidelines. There are a variety of validated assessment and scoring systems for initial diagnosis, grading of severity and subsequent monitoring of patients with acute stroke. The National Institutes of Health Stroke Scale (NIHSS) is perhaps the most commonly endorsed and utilized. It is a simple series of tests evaluating level of consciousness, comprehension, and visual, motor, sensory, and language responses, taking about 5 minutes to administer.[5]

The initial imaging study should be a noncontrast head CT scan. This will generally rule out hemorrhagic stroke, as well as mass lesions, and may give clues about the vascular distribution of an ischemic stroke. A standard brain MRI is equally useful but generally not as readily available in many centers.[6]

Additional imaging may be obtained but is not usually necessary in the initial evaluation and decision-making process about thrombolytic therapy. CT-angiography or contrast-enhanced MR-angiography can define vascular anatomy and directly identify vascular occlusions or stenoses. Diffusion-weighted MRI will demonstrate infarct within minutes of vascular occlusion and perfusion CT or perfusion-weighted MRI may help to delineate the ischemic penumbra.[6]

Thrombolysis

Stroke management changed dramatically in 1995. The National Institute of Neurological Disorders and Stroke (NINDS) undertook a randomized, double-blind, placebo-controlled clinical trial of the use of intravenous (IV) recombinant tissue plasminogen activator (tPA; 0.9 mg/kg with maximum dose of 90 mg) within 3 hours of stroke onset on neurological outcome at 3 months. Several important exclusion criteria were used: history of intracranial hemorrhage, stroke or head trauma in the past 3 months, major surgery in the past 2 weeks, GI or GU hemorrhage in the past 3 weeks, arterial puncture at noncompressible site within the past week, current use of anticoagulants or evidence of coagulopathy, BP > 185/110 mm Hg, minor or rapidly improving symptoms, symptoms strongly suggestive of subarachnoid hemorrhage, or seizure at onset of stroke. The study found that, compared with placebo, patients receiving tPA had an increase in favorable outcome; they were at least 30% more likely to have minimal or no disability at 3 months following their strokes (this benefit was later shown to extend to 1 year following treatment). This was despite an increase in symptomatic intracerebral hemorrhage in the first 36 hours following tPA administration (6.4% vs 0.6% in the placebo group). There were no differences in serious systemic hemorrhage or in 3-month mortality between the placebo and treatment groups.[7]

The findings of the NINDS trial have subsequently been replicated in large prospective observational studies of tPA.[6] More recent, robust data by Hacke et al support extension of tPA use to 4.5 hours after stroke onset, although there is a clear direct relationship between earlier time of treatment and likelihood of favorable outcome.[8] Systemic tPA is now the standard of care for acute ischemic stroke, and it is suggested that institutions develop their own protocol for this with inclusion and exclusion criteria based on those used in the above hallmark studies.[4]

There is no place in acute stroke management for other thrombolytic agents at this time: Considerably higher incidence of intracerebral hemorrhage has been seen with streptokinase and data for other agents (urokinase, desmoteplase) are insufficient.[4]

The role of intra-arterial thrombolysis directly at the occlusion site remains unclear. There is limited evidence to suggest benefit in patients with middle cerebral artery occlusions presenting within 6 hours of stroke onset, but no studies directly compare systemic IV tPA to intra-arterial thrombolysis.[9] There are some pilot studies looking at intra-arterial thrombolysis as an early "rescue" therapy if response to systemic IV tPA is limited.[6]

Finally, at this time, there is no defined role for mechanical thrombectomy/embolectomy in management of acute ischemic stroke. Small studies of endovascular devices have shown reasonable rates of vascular recanalization, but neurologic outcome has not been evaluated as a primary endpoint, and there have been no head-to-head comparisons with IV tPA.[10]

ICU Care

Airway, ventilation, and oxygenation must continue to be monitored closely once a patient is admitted to an ICU. Depressed level of consciousness and brainstem dysfunction from stroke may lead to hypoventilation, hypoxia, airway compromise, or aspiration; a low threshold must be maintained for intubation in such patients. Untreated hypoxia may worsen cerebral ischemic injury. Aspiration and other pneumonia may adversely impact outcomes. If intubation and mechanical ventilatory support are required, prognosis is guarded; half or more of patients requiring intubation in the setting of acute stroke may not survive beyond 30 days.[11]

Blood pressure management is one of the key aspects of acute stroke care in the ICU. Hypertension is common after acute stroke, and may reflect underlying chronic hypertension or acute pain or anxiety. It may also be an appropriate physiological response to maintain cerebral perfusion in the setting of loss of normal autoregulation at the area of ischemia. There is a clear U-shaped relationship between initial blood pressure and mortality from acute stroke, with adverse outcomes associated with very low and very high systolic blood pressures.[12] Very severe hypertension may increase risk of cerebral edema, hemorrhagic transformation of the ischemic stroke, or other end-organ complications (myocardial ischemia, pulmonary edema, acute renal failure); overly aggressive lowering of blood pressure may worsen cerebral perfusion and risk extension of an ischemic stroke.[6]

Therefore, current guidelines suggest not treating blood pressure in the setting of acute ischemic stroke until it exceeds 220/120 mm Hg; if patients have received thrombolytics, this parameter is lowered to 180/105 mm Hg. Beyond this, blood pressure should not be lowered more than about 15% in the first day.[4] The antihypertensive agents of choice include nonselective beta-blockers, such as labetolol, and calcium channel blockers, such as nicardipine and ACE-inhibitors; nitroprusside and hydralazine should be avoided as they may be more likely to cause cerebral vasodilation and elevation of intracranial pressure.[6]

Hypotension is uncommon in the setting of acute ischemic stroke and is a poor prognostic indicator. Intravascular volume should be maintained in these patients, using isotonic IV fluids. Clinical trials are ongoing to assess whether inducing hypertension may have benefit in patients with acute ischemic stroke and initial hypotension.[6]

It remains unclear how to best manage body temperature in patients with acute ischemic stroke. Hyperthermia (fever) is associated with worse neurological outcomes, but it has been difficult to demonstrate improvement in outcomes with treatment (or prophylaxis) with antipyretics.[13,14] Thus, the only recommendation that can be made is to consider antipyretics if fever occurs and treat the source of fever whenever possible. Similarly, although hypothermia is neuroprotective in animal models of stroke and has been shown to improve neurological outcomes after out-of-hospital cardiac arrest, further clinical trials are needed to determine whether it may benefit patients with acute ischemic stroke.[15,16]

Hyperglycemia is associated with poorer outcomes after acute ischemic stroke. It is clearly a marker of stroke severity. It worsens ischemic damage in animal models of acute stroke and is associated with increased risk of hemorrhagic transformation of acute stroke, greater infarct size on MRI, and, in some reports, less favorable neurological outcome and increased mortality. The mechanism is unclear; anaerobic glycolysis, increased free-radical formation, and disruption of the blood-brain barrier may occur. Despite these observations, there is a paucity of data to guide how best to manage glucose and whether any approach alters outcomes in patients with acute ischemic stroke. Until further evidence is obtained, guidelines recommend targeting glucose < 140-180 mg/dL.[4]

Early antiplatelet therapy with aspirin is indicated for all patients with acute ischemic stroke. Two very large randomized, placebo-controlled clinical trials (about 20,000 patients each) have shown that aspirin given within 48 hours of acute ischemic stroke reduces risk of recurrent stroke, death, and dependence.[17,18] It is recommended that aspirin be started immediately if thrombolytics are not given; if IV tPA is given, aspirin should be started 24 hours later.[19]

Finally, ICU caregivers must be vigilant for neurological complications of acute ischemic stroke: cerebral edema, hemorrhagic transformation, and seizure. Frequent examinations and monitoring with a validated stroke scale are essential for identifying neurological changes early. Cerebral edema is most common following large middle cerebral artery distribution or cerebellar strokes. Although it can progress rapidly with severe clinical deterioration within the first 24 hours, it presents most typically at about day 4. Usual treatment for elevated intracranial pressure is recommended (elevation of head of bed, hyperosmolar therapy, short-term moderate hyperventilation, CSF drainage) along with early consideration of decompressive craniotomy. Hemorrhage at the area of stroke is often limited, of little clinical consequence, and managed supportively. For more significant, symptomatic intracranial hemorrhage, particularly after tPA, fresh frozen plasma and cryoprecipitate should be administered emergently.[4,6]

Conclusion

Acute ischemic stroke is a common problem resulting in considerable morbidity and mortality. Rapid, coordinated triage/evaluation, early treatment with thrombolytics, and subsequent aggressive supportive ICU care have the potential to vastly improve outcomes. ■

References

1. Stroke Facts. Available at: www.cdc.gov/stroke/facts.htm. Accessed Feb. 2, 2010.
2. Fulgham JR, et al. Management of acute ischemic stroke. *Mayo Clin Proc*. 2004;79:1459-1469.

3. Yew KS, Cheng K. Acute stroke diagnosis. *Am Fam Physician*. 2009;80:33-40.
4. Adams HP Jr, et al. Guidelines for the early management of adults with ischemic stroke. *Stroke*. 2009;38:1655-1711.
5. Stroke Scales and Clinical Assessment Tools. Available at: www.strokecenter.org/trials/scales. Accessed Feb. 2, 2010.
6. Finley Caulfield A, Wijman CA. Critical care of acute ischemic stroke. *Crit Care Clin*. 2007;22:581-606.
7. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333:1581-1587.
8. Hacke W, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329.
9. Furlan A, et al. Intra-arterial prourokinase for acute ischemic stroke. *JAMA*. 1999;282:2003-2011.
10. Smith WS, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke. *Stroke*. 2005;36:1432-1438.
11. Bushnell CD, et al. Survival and outcome after endotracheal intubation for acute stroke. *Neurology*. 1999;52:1374-1381.
12. Leonardi-Bee J, et al. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke.* 2002;33:1315-1320.
13. Saini M, et al. Effect of hyperthermia on prognosis after acute ischemic stroke. *Stroke*. 2009;40:3051-3059.
14. Badjatia N. Hyperthermia and fever control in brain injury. *Crit Care Med*. 2009;37:S250-S257.
15. Den Hertog HM, et al. Cooling therapy for acute stroke. *Cochrane Database Syst Rev*. 2009;1:CD001247.
16. Linares G, Mayer SA. Hypothermia for the treatment of ischemic and hemorrhagic stroke. *Crit Care Med*. 2009;37:S243-S249.
17. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641-1649.
18. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;349:1569-1581.
19. Sandercock P, et al. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2003;2:CD000029.

CME Questions

1. In the retrospective, randomized trial by Maggiore et al, the use of a helium-oxygen blend, compared to an air-oxygen blend, in patients receiving noninvasive ventilation led to which of the following outcomes?

a. No statistically significant differences in mortality or ICU length of stay.

b. Increased frequency of hypoxemia.

c. Increased rates of intubation.

d. Increased rate of nosocomial pneumonia.

2. According to the descriptive case series of stress cardiomyopathy reported by Sharkey et al, which of the following interventions was associated with improved outcomes?

a. Beta-blocker therapy.

b. Catecholamine therapy.

c. Anticoagulation.

d. None of the above

3. In the recent report by Speziale et al, of a series of patients older than age 90, undergoing cardiac surgery, which of the following outcomes was observed?

a. High case fatality rate.

b. Long hospital lengths of stay.

c. Improved functional status in survivors.

d. All of the above

Answers: 1. (a); 2. (d); 3. (d)

CME / Objectives

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

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems. ■