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INSIDE

Vasopressin for Out-of-Hospital Cardiac Arrest

ABSTRACT & COMMENTARY

Synopsis: *In this randomized, controlled trial, European investigators looked at the role of vasopressin in treating out-of-hospital cardiac arrest. Although the study did not show any benefit of using vasopressin when compared to epinephrine in terms of survival to hospital, this study nonetheless makes a weak argument to use vasopressin in cardiac arrest patients with asystole.*

Source: Wenzel V, et al. *N Engl J Med*. 2004;315:105-113.

In this double-blind, randomized, controlled trial, Wenzel and colleagues evaluated the role of intravenous administration of vasopressin to patients experiencing out-of-hospital cardiac arrest. The study took place in European countries in "physician staffed emergency service units." Wenzel et al included all patients with cardiac arrest with pulseless electrical activity (PEA), asystole, or shock-resistant ventricular fibrillation. Patients younger than age 18, do-not-resuscitate (DNR) patients, pregnant patients, those with terminal illness or trauma induced cardiac arrest, and those with hemorrhagic shock or without IV access were excluded.

Randomization took place at the time of diagnosis of asystole or PEA, or after the 3rd failed countershock in patients with ventricular fibrillation. The patients were randomized in blocks of 10 by center, to receive either 2 injections of vasopressin (40 IU, intravenously) or epinephrine (1 mg, intravenously) at 3-minute intervals according to their clinical state. Subsequently, patients could receive 1 mg doses of epinephrine or other medications as the clinical condition warranted. Wenzel et al postulated that there would be no difference in survival to hospital or to discharge from hospital. Wenzel et al calculated that to demonstrate a 25% improvement in discharge from hospital with the drug and 80% power to detect such a difference with two-tailed analysis, 571 patients would be required in each group.

They enrolled 1219 patients and 1186 of them were included in their final analysis. A total of 589 patients received vasopressin and 597 received epinephrine as their initial drug of resuscitation. At baseline, the groups were comparable and equally distributed.

Overall, there was no difference in the survival to hospital admission (36.3% with vasopressin, 31.2% with epinephrine; $P = .06$) or survival to hospital discharge (9.9% both groups; $P = .99$) between the 2 groups. Spontaneous circulation was restored in 145/589 patients in the vasopressin group and 167/597 patients in the epinephrine group.

When subgroup analysis was performed, the authors did not find any benefit of using vasopressin over epinephrine in patients with ventricular fibrillation, either in restoration of spontaneous circulation (36.8% vs 42.6%), hospital admission (46.2% vs 43%), or survival to hospital discharge (17.8% vs 19.2%). Similarly, in patients with PEA as their initial rhythm, there was no difference in the ability of either drug to restore spontaneous circulation (20.2% vs 20.7%), survival to hospital admission (33.7% vs 30.5%), or survival to hospital discharge (5.9% vs 8.6%).

Wenzel et al found that in the subgroup of patients with asystole, although similar results were seen in establishing spontaneous circulation (16% vs 16.5%), more patients survived to hospital admission (29% vs 20.3% P = 0.02) and discharge from hospital (4.7% vs 1.5 % P = 0.04) when the initial treatment was with vasopressin. There was no statistical difference in the patients' cerebral function at discharge between the groups. They also looked at all patients in whom spontaneous circulation was not restored with the study drug. There was a trend toward improved survival rate if vasopressin was the initial drug used in resuscitation.

Wenzel et al conclude that vasopressin was similar to epinephrine in the management of ventricular fibrillation and PEA and was superior to epinephrine in patients with asystole. They further suggest that vasopressin followed by epinephrine may be more effective than epinephrine alone in treatment of refractory cardiac arrest.

COMMENT BY UDAY B. NANAVATY, MD

At the outset, I conclude, based on this study, that vasopressin has no advantage over epinephrine in patients with out-of-hospital cardiac arrest. This large, randomized clinical trial showed no improvement in the primary outcome, survival to hospital or survival to discharge when vasopressin was compared to epinephrine. In essence, that makes it a negative study in terms of a new therapy, where the new therapy did not improve the outcome when compared to standard treatment. This publication might add to the list of studies and publications that are used to teach clinical researchers and medical students how to read the literature. When a randomized, controlled, double-blind, clinical trial is performed, the only conclusion that has highest reliability and reproducibility is the primary end point. Subgroup analysis can best be used for hypothesis generation.

For example, in this study, the primary end point was survival to hospital admission and survival to discharge. All conclusions about that outcome are reliable, to a certain extent. The subgroup analysis requires a more cautious approach. There are random chances that one of the subgroup will show statistically significant difference. Whether that difference was due to the intervention or just a chance observation is not certain. To reduce the possibility of chance observation, one has to pay a penalty whereby, depending on the number of subgroups you look at, you raise the bar at which point an observation becomes statistically significant. Unfortunately, Wenzel et al did not adjust for these multiple comparisons. Not only that, the subgroup analysis became the major conclusion of the trial's publication.

Cardiac arrest, commonly referred as Code Blue in US hospitals, is defined as an abrupt cessation of car-

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diac pump function, which may be reversible by prompt intervention but will lead to death in its absence. In the United States, more than 300,000 people die of sudden cardiac death and, of all the mortality from cardiac causes, as much as 50% may be unexpected. Tremendous effort by large number of organizations and agencies has resulted in nearly uniform care of patients experiencing cardiac arrest. Almost all hospitals in the US use advanced cardiac life support (ACLS) algorithms to manage the cardiac arrest victims. Similar protocols are taught to emergency care providers within and outside the hospital to improve the outcome of cardiac arrest victims. For obvious reasons, patients with "In hospital" cardiac arrest are seen and treated earlier compared to "out of hospital" cardiac arrest patients.

Epinephrine, the most potent vasopressor/stress response molecule, is used to maintain perfusion or improve the circulation when the heart has stopped its pump function. With cessation of circulation and hypoxia, acidosis develops and it is shown in studies that adrenergic agents such as epinephrine and norepinephrine do not remain effective as vasopressor agents. However, larger than physiological doses of epinephrine—1 mg IV—are used, and it is a common experience that, as soon as circulation is established, the effects of intravenously administered vasopressor are seen in a large number of patients in the form of tachycardia, hypertension, and a hyperdynamic circulatory state. Epinephrine doses larger than 1 mg have been tried in randomized control trials and have not been shown to be of any additional benefit. Epinephrine itself, to the best of my knowledge, has not been tried in a placebo controlled study, but it would be unethical at this stage to perform such a study anyway.

Vasopressin, another naturally occurring hormone, has been shown to have vasopressor effects. In animal studies, it has shown promising results in improving survival and neurological outcomes in cardiac arrest models. As is usually the case, a couple of case studies in the 1990s suggested that vasopressin may improve the outcome of patients with cardiac arrest, when all else has failed. Those case series led to a randomized trial of epinephrine compared to vasopressin as an initial agent in shock resistant ventricular fibrillation in out-of-hospital settings. That small trial[1] with 40 patients in all, suggested that vasopressin might be highly beneficial in improving the survival of out-of-hospital cardiac arrest patients. A much larger trial[2] that included not only shock-resistant ventricular fibrillation but also included patients with PEA and asystole in the in-hospital setting, failed to show any benefit of using vasopressin over epinephrine. However, the American Heart Association, the organization behind the ACLS algorithm, suggested that in shock-resistant ventricular fibrillation, vasopressin, 40 IU intravenously, might be used as an alternate to the first dose of epinephrine. Although one can conclude based on the current study that vasopressin is as effective as epinephrine in all forms of cardiac arrest, the trial really was designed to prove that the drug would have a 25% improvement in outcome. To really establish that vasopressin is equally effective, a much larger study would be needed.

This study, in spite of the bold claim by Wenzel et al, further raises doubt about changing a long-established algorithm. Even though epinephrine has not been tried in randomized controlled trials against placebo, the longstanding algorithm should only be changed if there is substantial benefit from vasopressin. Although the cost per resuscitation may not change much (estimated cost of vasopressin is $14 compared to $1 for epinephrine), it would require a tremendous amount of money to change the algorithm, republish all the literature to train everyone, and then spend $28 more dollars per cardiac arrest patient, without any added benefit of doing so. ■

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Dealing with Partial DNR Orders

ABSTRACT & COMMENTARY

Synopsis: *This article points out the disadvantages of partial DNR orders—for both clinicians and patients—and offers clear steps for mitigating the problem by developing a supplemental patient care plan for patients who are less than "full code."*

Source: Berger JT. *Arch Intern Med*. 2003;163(19): 2270-2275.

In this article, Berger describes the all-too-common problems associated with use of partial "do-not-resuscitate" (DNR) orders. Partial DNR orders vary from specific refusal of a particular intervention (eg, do not intubate) to, at some institutions, an ability to pick and choose treatment components as though from a restaurant menu. Berger reviews the lack of data supporting the medical efficacy of these treatment plans.

He also discusses the ethical issues surrounding the use of these orders, including the unknown level of informed consent obtained in formulating the care plan, the frequent violation of the principle of nonmaleficence resulting from partial resuscitation, and the application of the partial resuscitation order to pre-arrest care.

Berger suggests that partial resuscitation orders should generally be avoided and recommends instead the development of a supplemental care plan for patients for whom DNR orders are being written. The elements of such a plan include:

1. Identification of patients' treatment goals;
2. Identification of specific medical interventions declined by the patient or surrogate;
3. Allowing for physician judgment and discretion in determining the use of specific treatments in particular clinical circumstances, within the context of patients' care objectives;
4. Linking the patients' or surrogates' requests for specific treatments to goals of care to avoid medically inappropriate combinations of medical interventions;
5. Making sure the plan can be readily interpreted by any physician likely to be a first responder to a medical emergency.

COMMENT BY JAMES E. McFEELY, MD

With this article Berger has certainly hit a nerve with those in the critical care community. As first responders who are frequently left dealing with the outcomes of partial DNR orders, we are often asked to perform a procedure (the partial code) for which we have no expectation of a successful outcome. Berger rightly points out the lack of data supporting even providing these types of choices to a patient or family and acknowledges the lack of informed consent that is implicit in some of these choices. What physician has the time to discuss with a patient all the ramifications of the potential combinations from the code menu? Certainly few if any patients would choose certain combinations of partial resuscitation if they knew the implied futility in the choice, yet we have all seen these combinations at times.

Often when a partial resuscitation order is written I have the feeling that the physician thought it was the "best I could get," while realizing that given the patient's overall condition, something more comprehensive would be medically appropriate.

Certainly there are clinical situations where less than a full resuscitation is appropriate, such as an end stage COPD patient who does not wish to be intubated. I think Berger's suggestion for developing a supplemental treatment plan is a good one; and when accurately reflecting a patient's treatment preferences may significantly facilitate, as Berger puts it, the "fluidity of thinking and subtlety of response" we all would prefer to provide this plan.

COMMENT BY DAVID J. PIERSON, MD

Orders directing that cardiopulmonary resuscitation (CPR) be withheld if a patient experiences cardiac arrest are appropriate when the patient (or his or her appropriate surrogate) makes the rational decision to forego it, realizing that death will likely result, or when CPR cannot benefit the patient (medical futility). CPR is a complex array of procedures, not just chest compressions and electrical defibrillation. Standards for its optimal performance are increasingly evidence-based, and undergo frequent revision. Like other invasive procedures in the ICU, CPR has major costs and complications. The whole package, promptly and skillfully applied, can save lives and enable some patients to return to health who would otherwise die.

To someone from another planet who was learning of these things for the first time, the concept that a patient (or those who loved him or her) would decide in advance to selectively withhold parts of the CPR procedure while implementing others might well appear absurd: such a strategy could not hope to achieve the full potential benefit of CPR, yet would subject the patient to the discomfort and other adverse aspects of the procedure. It would seem to this alien visitor that only someone who did not grasp the facts of the situation—what CPR involved and its potential to help the patient—could possibly agree to an order directing that only parts of the CPR procedure would be carried out.

As clinicians in the ICU know only too well, as outlandish as this scenario sounds, it plays out all too frequently. Reasons vary, but they usually include problems with communication between the patient's caregivers and the family. The product of these communication gaps may be partial DNR orders as discussed in this article.

In their book, *Managing Death in the Intensive Care Unit*, Curtis and Rubenfeld provide practical guidance for helping physicians and other caregivers to avoid the frustration and patient disservice of partial DNR orders.[1] In the institution in which Curtis and Rubenfeld (and I) work, a standardized, university system-wide ICU order form specifies each patient's code status.[2] The form identifies two possible options: full code and DNAR (do not attempt resuscitation). Although it is possible in this system for physicians and patient surrogates to construct a partial DNR "menu" type order as

discussed by Berger, this is a relatively unusual occurrence, thanks to the standardized order form and the practical guidelines on its back side to assist caregivers in approaching this issue with patients and families.

How DNR orders are handled varies substantially in different practice settings. As McFeely says, the issues discussed in the article by Berger strike a nerve for many ICU clinicians. The principles outlined in Berger's article, and the guidelines he offers for developing a supplemental care plan for patients with partial DNR orders, can go a long way toward reducing caregiver frustration and improving care for these patients. ■

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Special Feature

In Search of the Holy Grail: The Ideal Index of Hypoxemia in ARDS

By Karen Johnson, PhD, RN

Over the past 50 years, our understanding of the acute respiratory distress syndrome (ARDS) has evolved, not only with respect to the pathophysiology of lung injury and hypoxemia, but also with the definition of this syndrome and its treatment. We still have a long way to go in our understanding about the variability in pulmonary gas exchange in patients with ARDS. ARDS is characterized by severe hypoxemia,[1] which is an important element in the definition of the syndrome.[2,3] Numerous indices have been devised to describe hypoxemia and measure its severity. The search for an ideal index of hypoxemia has been like the search for the Holy Grail.

What would be an ideal descriptor of hypoxemia? Gould and colleagues offer some insight.[4] An ideal index of hypoxemia: 1) should be reliable—or, under certain conditions repeated measurements should yield similar values; 2) should measure what it's supposed to measure; 3) should be responsive to changes in the true value of the measured physiologic parameter, and should reflect the degree of these changes with acceptable sensitivity; and 4) should provide some clinically useful diagnostic and prognostic information. In addition, another criterion of an ideal descriptor, particularly for hypoxemia, should be that the index should measure physiologic function directly, rather than the therapeutic intervention employed to support pulmonary function.[5] This is particularly important when assessing hypoxemia because the index should not vary with alterations in FiO_2.

Several indices have been proposed over the past fifty years to quantify hypoxemia including intrapulmonary shunt (Qs/Qt), the alveolar-arterial gradient (PAO_2 - PaO_2), the arterial/alveolar ratio (PaO_2/PAO_2), and the PaO_2/FiO_2 ratio. The purpose of this special feature is to review these indices and identify the index that is the most ideal descriptor of hypoxemia in ARDS.

Measurement of Intrapulmonary Shunt

Intrapulmonary shunt (Qs/Qt) is often identified as the gold standard for assessing impairment of pulmonary gas exchange in critically ill patients.[6-10] The value of measuring Qs/Qt is to identify alterations in pulmonary gas exchange and to determine the degree to which the lung deviates from ideal as an oxygenator of blood. Measurements of Qs/Qt identify contributions to hypoxemia as the result of ventilation/perfusion mismatch, diffusion limitation, and true shunting.[11]

Qs/Qt can be measured by calculating the difference between the content of fully oxygenated pulmonary capillary (CCO_2) and arterial blood (CaO_2) divided by a difference between fully oxygenated pulmonary capillary blood (CCO_2) and mixed venous blood (CvO_2) according to the formula in Table 1.

Measurement of Qs/Qt has been favored by several investigators to assess hypoxemia in ARDS.[9,10,12] Information needed to calculate oxygen content in the Qs/Qt formula is available only in patients who have pulmonary and peripheral artery catheters in place for the determination of CaO_2 and CvO_2. This has forced a situation where clinicians have had to estimate arterial oxygen content difference, which is often misleading.[12] Estimation of Qs/Qt based on assumed arterial-venous difference can vary widely in ARDS.[7,9] There appears to be a good correlation between measured and estimated Qs/Qt ($r^2 = .92$) in patients with arterial-venous oxygen content differences greater than 4.5 mL/dL. However, the investigators reporting these results determined that the average estimated shunt (27.8%) was one and a half

times greater than the measured shunt (18.7%).[10]

Qs/Qt is a complex formula to calculate, although most ICU bedside monitoring systems have the capability to calculate Qs/Qt once mixed venous and arterial blood gas data are available and entered into the system. It is time consuming to obtain, complex to calculate, and costly.

Oxygen Tension-Derived Indices

Complexity of the Qs/Qt, necessity for frequent sampling of arterial and mixed venous blood, and the need for a pulmonary artery catheter led to the development of a number of indices to estimate Qs/Qt.[12,13] The indices are collectively referred to as "oxygen tension derived indices" and include: PAO_2 - PaO_2, PaO_2/PAO_2 and PaO_2/FiO_2. All relate the arterial oxygen tension to the driving force for oxygen transfer, expressed either as the FiO_2 or PAO_2. There has been some debate on the use of PAO_2 vs FiO_2 in a hypoxemia index. Some argue that PAO_2 is more advantageous because it includes the effect of CO_2.[14] Others contend that this addition has little value, adds further assumptions, and may vary somewhat with permissive hypercapnia.[15] In ARDS, PAO_2 is usually elevated as a result of increased FiO_2, and subtraction of a much smaller, relatively constant $PaCO_2$ adds little discrimination.[15]

Alveolar-Arterial PO_2 Difference ("A-a gradient")

The A-a gradient was developed based the relationship between alveolar-arterial oxygen tension: PAO_2 equals PaO_2 when ventilation and perfusion are perfectly matched. To determine this index, PAO_2 is calculated from the following alveolar gas equation:

$$PAO_2 = (FiO_2 [Pb - P_{H20}] - PaCO_2/R)$$

Where FiO_2 = Fraction of inspired oxygen; Pb = barometric pressure; P_{H20} = water vapor pressure (47 mm Hg); $PaCO_2$ = partial pressure of carbon dioxide; and R = respiratory quotient (CO_2 production/O_2 consumption in a steady state = 0.8).

In healthy conditions there is generally a small difference between PAO_2 and PaO_2. With perfect matching of ventilation to perfusion, the expected PAO_2 - PaO_2 gradient would be zero.

Several studies have compared the A-a gradient and Qs/Qt, and the 2 measures correlate moderately well in critically ill patients (r = 0.58-0.68).[9,10,16,17] However one study found that 51% of the A-a gradients did not accurately reflect Qs/Qt[17] and another actually found that in 25% of the measurements, Qs/Qt and A-a gradient varied in opposite directions.[16] The use of the A-a gradient in critically ill patients is limited because it cannot differentiate the severity of different clinical situations.[9,10,16,17] For example, a patient receiving FiO_2 70% with a $PaCO_2$ 40 mm Hg and a PaO_2 of 70 mm Hg has an A-a gradient of 379 mm Hg. Another patient receiving an FiO_2 90% with $PaCO_2$ 40 mm Hg and PaO_2 200 mm Hg has an A-a gradient of 392 mm Hg. Another limitation of the A-a gradient is that varying FiO_2 concentrations affect the measurement.[18] At increasing FiO_2, A-a gradient increases markedly, causing this index to lose clinical utility in critically ill patients. Its clinical usefulness is limited to patients with a Qs/Qt < 15% and FiO_2 < 0.50.[12]

Arterial-Alveolar Oxygen Tension Ratio ("a/A ratio")

The a/A ratio was developed based on the relationship between alveolar-arterial oxygen tension. As PaO_2 decreases relative to PAO_2, the ratio decreases and intrapulmonary shunt increases. A normal value is > 0.75 and a ratio < 0.75 indicates pulmonary dysfunction due to ventilation-perfusion abnormality, shunt, or a diffusion limitation.[19]

There are conflicting data on the accuracy with which this index reflects Qs/Qt. Cane and colleagues examined the relationship of Qs/Qt and a-A ratio in a heterogeneous group of 75 critically ill patients (50 medical and 25 surgical ICU patients) and reported a high correlation between Qs/Qt and a/A ratio (r = - 0.78).[10] Rasanen and colleagues examined the relationship between Qs/Qt and the a-A ratio in 17 critically ill patients with respiratory failure, but reported a low correlation (r = - 0.47).[20] Like A-a gradient, a-A ratio appears to be vulnerable to changes in peripheral circulation and oxygen therapy.

PaO_2/FiO_2 ("P/F ratio")

The PaO_2/FiO_2 ratio was introduced in an attempt to overcome the limitations of A-a gradient and a/A ratio and permit the evaluation of PaO_2 at varying FiO_2.[21] A normal ratio is 300-500 mm Hg, and a value less than 250 mm Hg reflects a clinically significant impairment of pulmonary gas exchange.[21]

Several studies have compared PaO_2/FiO_2 and Qs/Qt and the 2 measures have been found to be moderately to highly correlated in hemodynamically stable patients.[6, 9,10,20] Covelli and colleagues found that a PaO_2/FiO_2 < 200 mm Hg correlated with a Qs/Qt > 20% in critically ill patients with ARDS.[9] In a retrospective analysis of previously published data

Table 1

Formula for Qs/Qt Measurement

$$Qs/Qt = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

where $CcO_2 = (1.34 \times ScO_2 \times Hb) + (0.0031 \times PAO_2)$; $Ca02 = (1.34 \times SaO_2 \times Hb) + (0.0031 \times PaO_2)$; and $CvO_2 = (1.34 \times SvO_2 \times Hb) + (0.0031 \times PvO_2)$.

Making these substitutions,

$$Qs/Qt = 100 \times (1.34 \times ScO_2 \times Hb + 0.0031 \times PAO_2) - (1.34 \times SaO_2 \times Hb + 0.0031 \times PaO_2)$$
$$(1.34 \times ScO_2 \times Hb + 0.0031 \times PAO_2) - (1.34 \times SvO_2 \times Hb + 0.0031 \times PvO_2)$$

where ScO_2 = pulmonary capillary oxygen saturation (100%), and PAO_2 = alveolar oxygen tension, calculated as: (FiO_2 [Pb - P_{H20}] - $PaCO_2$/R), where FiO_2 = Fraction of inspired oxygen; Pb = barometric pressure; P_{H20} = Pressure of water vapor (47 mm Hg); $PaCO_2$ = partial pressure of carbon dioxide; R = respiratory quotient (CO_2 production/O_2 consumption in a steady state = 0.8)

of 16 patients with ARDS, PaO_2/FiO_2 in patients with moderate shunts (< 30%) varied considerably with alteration in FiO_2.[15] In all patients in this review, when the use of the ratio was restricted to FiO_2 values ≥ .50 and PaO_2 values ≤ 100 mm Hg, there was little variation in the ratio for a given patient. With low values of true shunt or with substantial perfusion of alveolar units with low ventilation/perfusion ratios, PaO_2 increased to > 100 mm Hg and diminished the value of PaO_2/FiO_2 as an index of hypoxemia.

The American-European consensus conference definition of acute lung injury and ARDS is partially based on the PaO_2/FiO_2: PaO_2/FiO_2 200-300 mm Hg defines acute lung injury and PaO_2/FiO_2 < 200 mm Hg defines ARDS.[2] PaO_2/FiO_2 has been shown to be higher in ARDS patients who survive[22] and significantly lower in non-survivors.[5] However, several studies[22,23] and a meta-analysis[24] suggest that it is an inconsistent predictor of outcome in patients with ARDS. Doyle and colleagues found no difference in mortality between patients with a PaO_2/FiO_2 ratio of 150-300 mm Hg and those whose ratio was < 150 mm Hg.[23] The Prostaglandin E_1 Study Group found that an improvement in the PaO_2/FiO_2 ratio after day one of conventional therapy predicted a favorable prognosis in their control patients.[22] This improvement in oxygenation among survivors was maintained over a 7-day period. Thus, monitoring trends over time may provide more useful information than any single measurement.

Despite these reports, PaO_2/FiO_2 remains the most important clinical physiologic variable used in the diagnosis and assessment of ARDS.[25-27] In a survey of 448 ICU Medical Directors in the United States, respondents considered the PaO_2/FiO_2 ratio to be the physiologic variable most important to determine the respiratory status of a patient with ARDS.[26]

The Ideal Index of Hypoxemia in ARDS

Which of the indices is the ideal index of hypoxemia in ARDS? Unfortunately, none of them are ideal, but the PaO_2/FiO_2 ratio appears to be the most ideal descriptor available at the present time. The Qs/Qt is considered to be the gold standard, but its measurement is limited to patients with a pulmonary artery catheter. Because it is the gold standard, it has been used as the measure to which other indices are compared. Of the 3 oxygen tension derived indices, PaO_2/FiO_2 is the most highly correlated with Qs/Qt. However, correlation is not the appropriate measure to use in these comparisons. Correlation is a poor estimate of the predictive value of an association between 2 measurements.[28]

Using criteria recommended by Gould and colleagues, PaO_2 /FiO_2 does appear to be the most ideal index of hypoxemia available at the present time: 1) The PaO_2/FiO_2 ratio appears to be the most reliable, but only under conditions when the FiO_2 is ≥ 50% and PaO_2 is ≤ 100 mm Hg. However, these conditions are frequently present in ARDS. 2) Theoretically, the ratio appears to measure hypoxemia. It relates the arterial oxygen pressure to the driving force necessary for oxygen transfer. 3) It appears to be responsive to changes in the true value of hypoxemia and it reflects the degree of the changes with some sensitivity because the ratio gets smaller with worsening pulmonary pathology. It does appear to be useful in monitoring trends in hypoxemia over time. But it does not reflect overall severity of lung injury. 4) The ratio appears to provide some clinically useful diagnostic data, but several studies suggest that it is an

inconsistent predictor of outcome in patients with ARDS. And finally, while it may be an index that measures pulmonary physiologic function, it does appear to be influenced by therapeutic interventions used to support pulmonary function. As with all the oxygen tension based indices, it is affected by changes in FiO_2. At the present time, it is the most commonly used index of hypoxemia in ARDS because of its simplicity and ease of calculation of data that are readily available. The search for the Holy Grail continues. ■

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CME / CE Questions

5. Problems with use of partial resuscitation orders include:
a. Lack of data supporting medical efficacy
b. Lack of informed consent for partial resuscitation
c. Violation of the ethical principle of nonmaleficence
d. Application of partial resuscitation to pre-arrest care
e. All of the above

6. Suggested elements of a supplemental care plan for patients with a DNR order do not include:
a. identification of the patient's treatment goals.
b. identification of the specific interventions declined by the patient.
c. minimization of physician discretion and judgment in determining the utility of specific treatments in particular circumstances.
d. making sure the plan is readily understandable to any first responder in an emergency.

7. Based on the study of vasopressin in cardiac arrest, it can be concluded that:
a. vasopressin is better than epinephrine for all forms of cardiac arrest.
b. vasopressin should not be used in any form of cardiac arrest.
c. vasopressin should be used prior to first attempt at defibrillation.
d. vasopressin does not improve survival compared to epinephrine in out of hospital cardiac arrest patients.
e. vasopressin should replace epinephrine in all cardiac arrest scenarios.

Answers: 5 (e); 6 (c); 7 (d)

CME / CE Objectives

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

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

In Future Issues:

Decision Analysis of Treatment Strategies for Ventilator-Associated Pneumonia

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Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Migraine and Subclinical Brain Lesions

Source: Kruit MC, et al. *JAMA*. 2004;291:427-434.

The data on the relationship between migraine and other vascular events such as stroke have been conflicting, although in some populations (such as young women smokers who suffer migraine with aura) the adverse association is more clear-cut. Because such a high proportion of women, and a not-insubstantial population of men suffer migraine, any important association with other major morbidities becomes epidemiologically compelling.

Using MRI scans in a population of migraine sufferers without history of prior stroke or TIA, infarcts and white matter lesions were defined, all by the same neuroradiologist who was blinded to the clinical data about the patients (n = 435, inclusive of 140 controls). Most patients (71%) were female, the mean age was 48 years, and patients were equally divided between migraine with and without aura.

Although the absolute number of infarcts demonstrated only a trend towards being more frequent in migraneurs, it was the posterior circulation infarcts which were markedly more common (7-fold increase in migraine population vs controls), an effect which was even more exaggerated in the migraine with aura category (odds ratio = 13.7). In the total unselected population, no difference in white matter lesions between migraine sufferers and controls was discerned; however women migraneurs had an increased odds ratio (OR = 2.1) for white matter lesions compared to controls.

None of these patients had any prior evidence of cerebral ischemic events. The relationship between migraine and increased risk of cerebral ischemia prompts consideration of whether more vigorous prevention of migraine might reduce risk of subsequent tissue damage. ■

Memantine Treatment in Alzheimer Disease

Source: Tariot PN, et al. *JAMA*. 2004;291:317-324.

Memantine (MEM) is the first clinically available NMDA receptor antagonist with demonstrated clinical efficacy and an acceptable adverse event profile for persons with Alzheimer disease (ALZ). Cholinesterase inhibitors like donepezil (DON) might work in a complementary fashion, hence this MEM + DON trial.

Subjects with ALZ (n = 404) who had been on a stable dose of DON for at least 6 months, and were free of known secondary etiologies for dementia, were randomized in a double-blind fashion to MEM titrated from 5 mg/d up to 20 mg/d (administered as 10 mg b.i.d.) for 6 months, vs placebo. DON was continued in both the placebo and the MEM treatment arm.

Changes in cognitive function, functional capacity, and global outcome were measured throughout the trial, the primary outcome being based upon scores on the Severe Impairment Battery and Activities of Daily Living Inventory.

There was a statistically significant positive effect of MEM when added to DON, complemented with a very favorable adverse effect profile: more patients in the placebo group withdrew due to adverse events than in the MEM group. Only headache and confusion were more common in the MEM group, both of which occurred in less than 10% of recipients. In addition to being useful as ALZ monotherapy, there may be additional clinical benefits from combining MEM with DON in ALZ therapy. ■

Casual Postprandial Glucose Levels in Type 2 Diabetes Management

Source: El-Kebbi IM, et al. *Diabetes Care*. 2004;27:335-339.

Tight control of type 2 diabetes (DM2) has been proven to reduce microvascular complications. Use of the hemoglobin A1c to assess long-term control is standard, but for modulation of treatment, timed specimens (eg, fasting, 1-2 hours postprandial) obtained by patient self-monitoring of blood glucose are often the information clinicians use to make choices about therapy modification.

Unless instructed otherwise, most DM2 patients are 1-4 hours postprandial at the time of an office visit. El-Kebbi, et al, investigated whether casual glucose levels obtained at the office visit might function as an adequate barometer of glucose control to

help modify treatment.

Established DM2 patients (n = 1827) at the Grady Diabetes Clinic (Atlanta) underwent simultaneous A1c and casual glucose measurement during their regular visit. The correlation between casual glucose measurement and A1c was strong (correlation coefficient = 0.63). The presence of a casual glucose > 150 predicted an A1c > 7.0 with a sensitivity of 78% (positive predictive value = 80%).

El-Kebbi and colleagues suggest that a casual plasma glucose greater than 150 mg/dL may serve as a surrogate for A1c; results above this level should prompt an intensification of therapy. ■

Exemestane after Tamoxifen Therapy in Breast Cancer

Source: Coombes RC, et al. *N Engl J Med*. 2004;350(11):1081-1092.

Tamoxifen (TAM) is well established to reduce, over 5 years, both risk of breast cancer (BCA) recurrence (47%) and mortality (26%) among women who have undergone surgery for BCA and who have estrogen-receptor positive tumors. Exemestane (EXE) is classified as an irreversible steroidal inactivator, and works by blocking the enzyme (aromatase) which is responsible for converting androgens to estrogens, ultimately inhibiting aromatization by about 98%. Although TAM is of remarkable positive benefit, it is not without risks, including increased likelihood of endometrial cancer attributed to endometrial stimulation. EXE is not known to induce endometrial proliferation, or increase proclivity for endometrial cancer.

The Intergroup Exemestane Study (IES) investigated whether substituting EXE for TAM after 2-3 years would provide better outcomes than simply treating with TAM continuously for 5 years. Study subjects were postmenopausal women (n = 4742) who remained free of recurrence during sustained TAM treatment. EXE (25 mg p.o. q.d.) was substituted for TAM in one half of the subjects.

After a median followup of 30.6 months, the risk of recurrence, contralateral BCA, or death was reduced by 32% in the EXE group compared with TAM. The adverse effects seen more frequently with EXE than TAM included diarrhea and arthralgia, but thromboembolisms was almost twice as common in the TAM group. Coombes and colleagues suggest that switching women from TAM to EXE at the 2-3 year point in treatment may provide more favorable outcomes. ■

An Analysis of How Long Patients Remain on Various Antihypertensive Therapies

Source: Esposti LD, et al. *J Clin Hypertens*. 2004;6:76-84.

The term 'drug efficacy' is technically intended to reflect impact of an agent on a designated end point in a study population participating in a clinical trial. 'Drug effectiveness,' on the other hand, refers to the 'real life' effects drug treatment produces as seen separately from a clinical trial; ie, what impact might be seen when 'typical patients' use a medication in, for instance, the community setting.

As many as half of patients who begin antihypertensive drug therapy (HTN-Rx) discontinue treatment within a few months of initiation. Study subjects from the area in and around Ravenna, Italy comprised this hypertensive patient population (n = 14,062). All were first time recipients of a new HTN-Rx. 'Persistent patients' were defined as either maintaining, combining with, or switching from their initial HTN-Rx to another HTN-Rx, for a duration of > 273 days from the day of enrollment.

Discouragingly, 48% of patients discontinued treatment after a single prescription! Medication choices were similar to those commonly used in the United States (ACE/ARB/HCTZ/CCB/Beta Blocker). Angiotensin Receptor Blockers demonstrated the highest continuation rate, followed by ACE inhibitors, CCBs, and Diuretics.

Cost of treatment decreased as age increased, and increased for persons who switched or combined agents. Angiotensin receptor blockers were the most expensive single agents. Overall, specific individual drug cost and pattern of drug persistence correlated best with total cost for hypertension treatment. These data suggest that although drug cost is important, aspects of the drug treatment which affect persistence patterns ultimately have a substantial effect on overall cost. ■

Association of Endothelial Dysfunction with Insulin Resistance and Carotid Wall Thickening in Hypertension

Source: Suzuki M, et al. *Am J Hypertens*. 2004;17:228-232.

Endothelial dysfunction (END) is a fundamental defect in essential hypertension (HTN) and is closely associated with carotid wall thickening (CWT), a consistent marker for early atherosclerotic change. Insulin resistance (IR) is also associated with both HTN and CWT, suggesting a potential relationship between IR and END.

HTN subjects (n = 41) were studied if they met inclusion criteria including HTN, no diabetes, no suggestion of secondary HTN, no major cardiovascular, renal, hepatic, or other endocrine disease, no smoking, and no medications which modulate carbohydrate or lipid metabolism (eg, statin, steroids) for at least 12 months. All subjects underwent measurement of endothelial function, carotid interomedial thickness by ultrasound, and insulin sensitivity as defined by insulin/glucose infusion.

END was found to be associated both with IR and CWT. The changes in CWT and END were strongly associated, suggesting a close correlation between functional (END) and structural (CWT) atherosclerotic changes. The confirmed association between END, CWT, and IR may prompt consideration of investigation to seek causality between, eg, IR and CWT ■

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.*

Atherosclerosis Reversed With Lipid-Lowering Drugs

When it comes to treating lipids in patients with heart disease, the mantra may be, "The lower the LDL, the better." Data from the multicenter Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial indicate that aggressive reduction of atherogenic lipoproteins prevents progression of disease. The study randomized 654 patients with coronary disease to pravastatin 40 mg/d (moderate lipid-lowering regimen) or atorvastatin 80 mg/d (intensive lipid-lowering regimen). After 18 months of therapy, 502 patients were evaluable with baseline and post-treatment intravascular ultrasounds. The primary outcome was percentage change in atheroma volume. Intensive lipid-lowering therapy with atorvastatin resulted in a decrease of LDL cholesterol from an average of 150 mg/dL to 79 mg/dL, while pravastatin therapy resulted in a decrease to 110 mg/dL. C-reactive protein decreased 36.4% with atorvastatin and 5.2% with pravastatin ($P < .001$). Progression of coronary atherosclerosis did not occur in the atorvastatin group, while coronary atherosclerosis progression did occur in the pravastatin group compared with baseline. The authors suggest that the data support aggressive lipid lowering, below the current national guidelines for secondary prevention in patients with coronary atherosclerosis (*JAMA*. 2004;291:1071-1080). It is of note that this study employed the relatively new technology of coronary ultrasound, which more effectively measures plaque volume as opposed to coronary angiography, which merely quantifies the lumen. Still, this technology is relatively new, as pointed out in an accompanying editorial, but the results appear to be valid. The editorial also points out that the moderate lipid-lowering regimen in the study did not achieve levels of LDL lowering recommended by national guidelines, which suggest lowering LDL below 100 mg/dL for secondary prevention. The authors recommend focus on all risk factors in patients with coronary disease, including LDL lowering at least to levels recommended in national guidelines (*JAMA*. 2004;291:1132-1134).

Positive Alendronate Data in Osteoporosis

Does alendronate prevent fractures after 10 years of therapy? According to a new multicenter placebo-controlled trial, the drug is effective and safe over 10 years in women with osteoporosis. Data from the study are from a follow-up of 2 identical 3-year trials of alendronate therapy followed for an additional 7 years. In this follow-up study, women were randomized to 3 daily doses of alendronate or placebo. The 3 active treatment groups included women who took alendronate 5 mg or 10 mg daily for the entire 10-year study. A third group took 20 mg of

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alendronate daily for 2 years and 5 mg daily in years 3, 4, and 5 followed by 5 years of placebo. This last group was called the "discontinuation group." Women in the original placebo group ended up receiving alendronate in years 4 and 5 and then were discharged. There were 247 women who participated in all 4 phases of the study. Treatment with 10 mg of alendronate daily for 10 years resulted in statistically significant increases in bone mineral density at the following sites: 13.7% increase, lumbar spine; 10.3%, trochanter; 5.4%, femoral neck; and 6.7%, proximal femur as compared with baseline values ($P < .001$; 95% CI for all groups). The percentage increases for the 5 mg group were 9.3%, lumbar spine; 4.8%, trochanter; 2.8%, femoral neck; and 2.9%, proximal femur. Alendronate also resulted in fewer fractures and lower rates of loss of stature over the 10-year period. Discontinuation of alendronate resulted in a gradual loss of bone density. The authors conclude that continued treatment with 10 mg of alendronate daily for 10 years was associated with a sustained therapeutic effect on bone density and bone remodeling. Concern over increase fracture rates with bisphosphonates over time was not validated by the study (*N Engl J Med*. 2004;350:1189-1199).

NSAIDs For Myocardial Infarction

Nonaspirin NSAIDs, especially ibuprofen and naproxen, may protect against myocardial infarction in patients who are not taking aspirin. Researchers from Pennsylvania conducted a case-control study with cases of first, nonfatal MI identified prospectively with random controls from the community. The use of a nonaspirin NSAID was associated with a significant reduction in MI compared to those not using aspirin (OR 0.53; 95% CI). The adjusted odds ratio for ibuprofen was 0.52 and for naproxen was 0.48. The odds ratio for aspirin alone in this study was 0.79. The combination of aspirin with a nonaspirin NSAID trended toward increased risk of MI and worsened as the frequency of nonaspirin NSAIDs use increased; however, the confidence intervals for this determination were very wide. The authors conclude that in patients who are not taking aspirin, a nonaspirin NSAID is associated with a reduced risk of MI. The concomitant use of aspirin for cardioprotection along with a nonaspirin NSAID needs further study (*J Am Coll Card*. 2004;43:985-993).

Four-Hour Window for CAP Patients

Medicare patients with community-acquired pneumonia (CAP) fare better if they receive their first dose of antibiotics within 4 hours of hospitalization, according to new study. The records of nearly 14,000 Medicare patients admitted for CAP, who had not received antibiotics as outpatients, were reviewed. The administration of an antibiotic within 4 hours of arrival to the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR] 0.85; 95% CI, 0.74-0.98), reduced mortality within 30 days of admission (11.6% vs 12.7%; AOR 0.85; 95% CI, 0.76-0.95), and reduced length of stay as measured by hospitalization exceeding the 5-day median (42.1% vs 45.1%; AOR 0.90; 95% CI, 0.83-0.96). Early administration of antibiotics also resulted in a 0.4-day shorter length of stay. The study did show that the majority of patients (60.9%) received antibiotics within 4 hours of arrival (*Arch Int Med*. 2004;164:637-644). Current CAP guidelines generally recommend initiation of an antibiotic within 8 hours of arrival, but this study suggests that those guidelines may not be aggressive enough.

FDA Actions

Rofecoxib (Vioxx) has been approved for the treatment of migraine attacks with or without aura in adults. The approval was based on a large study that showed that the single dose of rofecoxib, either 25 or 50 mg, effectively reduced migraine pain at 2 hours and reduced the use of rescue medications.

The FDA has issued a Public Health Advisory about the need for physicians, patients, and families to closely monitor adults and children with depression when beginning treatment certain antidepressants and has asked the manufacturers of these drugs to include new warnings in their labeling about the potential for increased suicidality. The antidepressant drugs are the serotonin reuptake inhibitors fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro); and the non-SSRI antidepressants bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). ■