

Blood glucose variability in critical illness: Is it time to cast a wider net?*

Alterations in glucose homeostasis are common in critical illness, even in the absence of underlying diabetes mellitus (1). In the past, this was largely ignored or considered to represent an adaptive response to critical illness. It is becoming increasingly obvious that stress hyperglycemia of critical illness is associated with poor outcomes (2, 3). More recently, evidence has emerged that hypoglycemia in critical illness may also be independently associated with poor outcomes (4, 5). A new paradigm that is being explored is the impact of blood glucose variability on outcomes from critical illness (6, 7), a concept that attempts to describe the complex temporal fluctuation of blood glucose concentrations between extremes of high and low levels during the evolution of critical illness.

Why might blood glucose variability be an important consideration when evaluating the impact of blood glucose concentrations on outcomes from critical illness? During states of health, blood glucose concentrations are closely regulated via homeostatic mechanisms in the body. During the acute phase of illness, variability in blood glucose concentrations may initially represent an allostatic or adaptive state involving changes in the neuroendocrine axis as well as cell signaling machinery to prolong survival (8). However, in chronic critical illness, the stressors may overwhelm these compensatory mechanisms. Consequently, the allostatic load rapidly progresses to allostatic overload, resulting in greater fluctuations in blood glucose concentrations, in-

volving both hyperglycemia and hypoglycemia (8). In such circumstances, blood glucose variability may very well serve as a more discriminating marker of poor outcomes, a fascinating paradigm that deserves greater scrutiny.

In this issue of *Pediatric Critical Care Medicine*, Dr. Hirshberg and colleagues (9) add to the growing body of literature on the impact of altered glucose homeostasis on outcomes in critically ill children. The authors describe the association of hyperglycemia, hypoglycemia, and blood glucose variability with mortality, hospital length of stay, and nosocomial infections in critically ill children in the absence of insulin therapy. The authors retrospectively analyzed data for 863 children admitted to the pediatric intensive care unit (PICU) over a 12-month period for ≥ 24 hrs with at least one blood glucose measurement in the PICU. The authors excluded children with preexisting disorders of glucose metabolism, such as diabetes mellitus, primary hypoglycemia, and fatty acid oxidation defects. The authors also specified that no blood glucose management protocols were in place in the PICU during this period. Thus, they attempted to correlate the "wild landscape" of blood glucose concentrations with outcomes in critically ill children, in an effort to gain important insights into the natural patterns and variations in blood glucose concentrations during critical illness.

The authors observed that hyperglycemia (blood glucose ≥ 150 mg/dL [≥ 8.3 mmol/L]) was extremely common during PICU stay, occurring in approximately 56% of subjects, similar to previously published studies (3). In addition to confirming the association between hyperglycemia and mortality (odds ratio 9.6; 95% confidence interval, 1.2–77.2), the authors observed a trend between hyperglycemia and nosocomial infections. Hypoglycemia (blood glucose ≤ 60 mg/dL [≤ 3.3 mmol/L]) occurred in approximately 10% of all patients, in the absence of insulin therapy and blood glu-

cose management protocols, and was more common in younger children. Interestingly, blood glucose variability (defined by the authors as hyperglycemia and hypoglycemia occurring in the same patient) was more strongly associated with mortality (odds ratio 40.5; 95% confidence interval, 4.6–358.7) and nosocomial infections (odds ratio 4.9; 95% confidence interval, 1.9–12.7) than was either hyperglycemia or hypoglycemia alone.

Blood glucose variability may have a much bigger role to play in critical illness than hitherto recognized and may serve as an important marker of poor outcomes. Egi et al. (10) observed that blood glucose variability (expressed as SD or coefficient of variation) was independently associated with intensive care unit and hospital mortality in adults after adjustment for potential confounders. Similarly, Wintergerst et al. (11) reported an association between index of glucose variability and mortality rates in critically ill children. Recent data from patients with diabetes indicate that fluctuations in blood glucose concentrations increase cellular damage via oxidative stress, with toxicity being most pronounced when the concentrations changed rapidly from normal to elevated (12). Children in the PICU are at increased risk for significant fluctuations in blood glucose concentrations due to numerous stressors, such as mechanical ventilation, vasoactive infusions, sedation, neuromuscular blockade, steroids, and parenteral nutrition, several of which were not accounted for in the present study. The authors defined blood glucose variability rather simplistically and did not examine more widely used definitions, such as average daily risk range or mean amplitude of glycemic excursion, to capture more subtle variations (13). The authors also acknowledge detection bias in blood glucose measurement resulting from intermittent sampling that might have underestimated the true extent of fluctuation of blood glucose concentrations. Newer techniques of continuous sampling can potentially de-

*See also p. 361.

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fect significant blood glucose variability that might be missed with intermittent measurements in children with diabetes (14). Nevertheless, the authors highlight an important association between blood glucose variability and outcomes from critical illness in children.

While intensive insulin therapy to normalize blood glucose concentrations to 80–110 mg/dL (4.4–6.1 mmol/L) has been observed to significantly reduce mortality and morbidity in selected critically ill adults, more recent studies have not demonstrated the same degree of benefit and, indeed, have raised several important questions and controversies regarding the timing, duration, and extent of glycemic control (15). None of these studies analyzed the impact of blood glucose variability, which may have played an important role in influencing outcomes. Future studies of glycemic control in critically ill children may need to incorporate algorithms that account for blood glucose variability and maintain blood glucose concentrations within a narrow range. The time has come to cast a wider net.

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Extracorporeal membrane oxygenation in immunocompromised patients: Avoiding the incurable or missing opportunities?*

When routine mechanical ventilation becomes inadequate to support gas exchange in patients with immune compromise, adjunct therapies are often added. Most commonly, high-frequency oscillation, inhaled nitric oxide (iNO), and prone positioning are applied in an attempt to improve oxygenation, limit ongoing ventilator-induced lung injury, and improve survival (1–3). Surfac-

tant has also been promoted recently as an effective tool (4). It is interesting to note, however, that the benefit of these therapies in overall survival has been poorly established, and none of these therapies have been compared between immune-deficient and immune-competent patients in randomized trials (although *post hoc* attempts have been made to assess this difference). Nonetheless, these tools are commonly used to support patients with severe respiratory failure. So too it is with extracorporeal life support. The few attempts at randomized trials of extracorporeal membrane oxygenation (ECMO) in the pediatric population have failed from recruitment or design issues, but this has not stopped many of us from using this technique when all else seems to fail (5, 6). Conversely, avoiding the use of ECMO in im-

mune-deficient patients has also been a conscious choice in many centers.

In this issue of *Pediatric Critical Care Medicine*, Dr. Gupta and colleagues (7) reviewed data from the Extracorporeal Life Support Organization (ELSO) registry regarding immunocompromised patients and found that ECMO has been used in 6% of pediatric respiratory failure cases (7). While the overall survival of patients with immunocompromise was lower than those without (31% vs. 57%), the fact that a third of such patients survived provides some degree of optimism. Certainly, similar survival rates have not eliminated the use of ECMO as a supportive tool for postoperative single-ventricle patients or those with refractory cardiac arrest. Indeed, the use of ECMO in these groups is increasing, despite few data on long-term outcome or randomized trials demonstrating efficacy. It also seems that

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the use of ECMO in other ill-defined groups, such as sepsis with multiple organ failure and even disseminated intravascular coagulation, has increased, and ECMO is now part of the algorithm of care in catecholamine-resistant septic shock (8). The same story does not apply to immunodeficient patients—across all six categories assessed in the review by Dr. Gupta and colleagues, <25 patients combined received ECMO support in any 1 year, which makes it extremely difficult to draw any meaningful conclusions from the data presented. Why is this? It seems unlikely that patients with immune deficiencies are not entering the intensive care unit (ICU) in increasing numbers, given our medical advancements in treatment of disorders like human immunodeficiency virus (HIV) and cancer. It also seems unlikely that such patients do not develop severe enough illness to meet ECMO candidacy. In several reviews of cancer patients in the pediatric ICU (PICU), even though survival has improved over the past few years, death still occurs in >40% of patients requiring mechanical ventilation and vasoactive agents (9–11). Similarly, HIV patients who require ICU care for *Pneumocystis carinii* pneumonia or other respiratory disease have a mortality rate of 40%, much better than years ago, but still much less than “average” ICU patients, who leave the PICU alive >95% of the time (12). The continued reluctance to apply ECMO to immunodeficient patients highlights the need to continue striving for predictive models that can establish risk of death and guide therapies. Recent reports of the use of the oxygenation index, Pediatric Index of Mortality, organ failure scores, and the like have also demonstrated that these markers may be helpful in decision making, not only in immunocompromised patients but in general ICU patients as well (13).

The finding that a commonly used adjunct therapy, iNO, was associated with adverse outcome is interesting. Such techniques are often used to improve oxygenation as a means to avoid ECMO, even if only effective temporarily. This has raised concerns that such treatments only delay the time to ECMO initiation and adversely affect outcome if ECMO is ultimately performed. In several analyses of the effects of iNO or high-frequency ventilation on outcome in neonates, no adverse outcome effects from ECMO in infants exposed to these modalities before ECMO were noted (14, 15). In the current

report, however, the finding that iNO in particular was associated with worse outcomes in pediatric patients receiving ECMO is bothersome. A similar unpublished review of the ELSO database between 1995 and 2003 noted that pediatric patients receiving both high-frequency ventilation and iNO had decreased survival (49% vs. 59%, $p = .002$) compared with those patients without exposure to these techniques (16). This analysis also found that exposure to iNO was associated with decreased survival (52% vs. 57%), although this was not statistically significant ($p = .07$). Of interest, exposure of neonates to iNO before ECMO was associated with improved outcome (75% vs. 72%, $p = .02$). Whether this reflects a difference between mechanism of respiratory failure and response to iNO between infants and children (pulmonary hypertension vs. parenchymal disease) seems likely but unproven. One exciting issue regarding iNO is the development of a new patient registry, developed and maintained by ELSO, which will collect more specific data on what types of patients are receiving iNO support and outcome details. A similar iNO database has also recently been devised in Europe. From this type of effort, a control group of patients receiving iNO both without and with ECMO support can be established. Factors associated with response rates and outcome may thus become available to help guide use of this medication.

One final concern raised from review by Dr. Gupta and colleagues (7) is illustrated by the dismal outcome of patients with bone marrow transplant (BMT). The 0% survival rate listed in the ELSO registry is concerning not only for obvious reasons but also for that fact that several case reports presented at ELSO-related conferences or published in the literature have reported survival in BMT patients receiving ECMO (17). Where are these patients? An analysis would only need to miss one or two survivors to dramatically change the outcome rates and perhaps the perception of ECMO for BMT, given the few patients listed in this category. One problem with databases in general is that they are limited in the data collected and are only as good as the data provided to them. The ELSO registry undergoes periodic validation to ensure that the data supplied are consistent. The database collects a primary diagnosis and up to four secondary diagnoses. As pointed out by Dr. Gupta and colleagues, however, how

these diagnoses are derived is up to the ECMO center to determine and rank. If BMT (or another immune diagnosis) was not listed as the primary International Classification of Diseases–Ninth Revision or Current Procedural Terminology code, it is possible that these patients could have been missed. This could dramatically skew data and make conclusions inaccurate. Fixing such problems is difficult, but the current redesign of the ELSO database, which will collect more specific data over time instead of just at the beginning and end of ECMO, may help to eliminate some problems. Coders and data abstractors must be educated about the importance of identifying diagnoses like those associated with immune disorders.

There are no definitive factors that can predict what patients should receive ECMO and what the outcome will be. ELSO is currently implementing guidelines for candidacy and care in various patient groups that may help unify approaches and enhance data collection. Until the day (if ever) that “clinical decision rules” offer an algorithm of risk of death that can be followed easily over time, clinicians are left with their own interpretation of evidence-based medicine to determine what patients in their own centers warrant ECMO exposure and when it should be applied. The current review gives us a little more information but still cannot answer these difficult questions.

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Decreasing pneumothorax in very low birth weight infants on ventilation: An issue of quality control*

Pneumothorax is predominantly seen in very low birth weight (VLBW) infants who require assisted ventilation for hyaline membrane disease (HMD), although the frequency of pneumothorax has steadily decreased since the introduction of surfactant therapy and other improved modalities of neonatal ventilation. In a study conducted before the use of surfactant (1), pneumothorax was found in 3.5% of infants with HMD who were not ventilated, 11% who were on continuous positive airway pressure alone, and 24% of those treated with continuous positive airway pressure who later required positive end-expiratory pressure (PEEP) on a ventilator. The frequency was much higher (33%) in infants who required PEEP from the outset. Addition of PEEP to ventilation doubled the frequency of

pneumothorax (2). Association of pneumothorax in HMD doubled the mortality (1). Horbar et al. (3) reported a decrease in mortality and morbidity in VLBW infants during a 10-yr period of study (1991–1999). The decrease was pronounced during the first half of the decade, but starting in 1995 there was no additional improvement. The data regarding pneumothorax varied by birth weight. In the weight group of 501–750 g, pneumothorax decreased from 16% in 1991 to 10% in 1994. Then the rate increased to 14% in 1999. But for weight groups of 751–1000 g and 1001–1500 g, pneumothorax continued to decrease from 11% to 7% and from 6% to 4%, respectively. The increase in pneumothorax in the lowest birth weight group was thought due to misuse use of respiratory interventions by unskilled, inexperienced personnel.

Pneumothorax in a critically ill VLBW infant is associated with the far more serious long-term complications of intraventricular hemorrhage and bronchopulmonary dysplasia, as noted by authors. Therefore, it is important to prevent the occurrence of pneumothorax.

In this issue of *Pediatric Critical Care Medicine*, Dr. Klinger and colleagues (4) report a retrospective analysis of 679 VLBW infants admitted to their neonatal

intensive care unit during a 6-yr period. The authors studied the frequency and the factors affecting pneumothorax. Eleven percent of the 679 infants developed pneumothorax. To study antecedent factors associated with pneumothorax, the authors matched these infants for gestational age, birth weight, and gender with an equal number of control infants who did not develop pneumothorax. Information on variables related to ventilation was analyzed. Univariate analysis was performed to identify differences between the study and control groups. Stepwise logistic regression analysis was performed on treatment variables only.

No differences in baseline data on day 1 between the groups were found. But the treatment variables, maximal peak inspiratory pressure (PIP) and minimal F_{IO_2} , on the day of occurrence of pneumothorax were significantly higher in the study group. Another interesting observation was the association of decreased risk with maximal PEEP. However, this finding needs cautious interpretation. The mean maximum PEEP was not different between the groups on day 1 or on the day of pneumothorax (Tables 2 and 3 in the article by Dr. Klinger and colleagues). But the mean maximal PIP was significantly higher in the pneumothorax group. The relatively low frequency of

*See also p. 398.

Key Words: neonatal; very low birth weight; pneumothorax; hyaline membrane disease; bronchopulmonary dysplasia; intraventricular hemorrhage; assisted ventilation; continuous positive airway pressure; positive end-expiratory pressure; quality control

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pneumothorax among the infants with high PEEP can be explained on the basis of lower effective inspiratory pressure (maximal PIP – maximal PEEP) (calculated from Tables 2 and 3) delivered in the non-pneumothorax group. Another major finding was the association of pneumothorax with endotracheal suction (Table 4 in the article by Dr. Klinger and colleagues). While the total number of suctionings did not differ, the number of suctionings at 8 hrs and 24 hrs before pneumothorax was significantly higher in the study group. The number of intubations and fixations before the event of pneumothorax was also high: three times higher in the pneumothorax group than in controls (mean of 17 vs. 6).

Although endotracheal suction is a necessary procedure in infants and adults on ventilator care, the association of suction with increased pneumothorax also is well known (5). As shown in this study, of all the ventilator variables that preceded pneumothorax, the procedure of suctioning can be modified through a quality control process. Important steps in endotracheal suction include frequency, intervals between suction size and depth of the tube, and pressure used during suction. In the early 1970s, the dictum was to carry out tracheal suction every 4–6 hrs to keep the airway patent (6). Today the standards for respiratory care are different (7).

How does endotracheal suction make the lungs vulnerable to develop pneumothorax? Many years ago, Brandstater and Muallem (8) showed that endotracheal suction leads to loss of lung volume and consequent atelectasis. When ventilation is resumed, sudden inflation causes stress on uncollapsed alveoli, causing rupture. A recent study by Morrow et al. (9) showed that endotracheal suctioning frequently caused an immediate drop in dynamic compliance and loss of expired tidal volume. This is due to derecruitment and collapse of alveoli during suctioning. Recruitment of alveoli can be pronounced in the VLBW infant in whom the lung is unstable to begin with. When ventilation is reinstated with the same high PIP, there is the likelihood of suddenly overdistingending the uncollapsed alveoli and causing rupture. This phenom-

enon is likely to occur more often if open suction is used (10). In open suction, the infant is disconnected from the ventilator and then suction is applied to the endotracheal tube. Following suction, the ventilator is reconnected to the infant. In closed suction, ventilation continues during the suction period, and the suction tube is passed through the side port of the endotracheal connection. Closed-system suctioning causes less volume change and so also less PIP change, therefore causing minimal alteration in dynamic compliance. Increased frequency of suction with shorter intervals in between, as shown by Dr. Klinger and colleagues (4), will lead to increased episodes of derecruitment of alveoli with each suction and increased risk of developing pneumothorax.

Following their analysis, Dr. Klinger and colleagues (4) instituted a policy of “minimal handling” in their unit with a resultant decrease in the occurrence of pneumothorax. The details of the minimal handling protocol instituted are not provided. It is understood that the suction procedures were minimized and personnel were well trained in minimizing PIP to achieve better fixation of the endotracheal tube.

Important considerations in safe endotracheal tube suction for neonatal patients include understanding the pulmonary dynamics associated with suctioning and skills of healthcare personnel. Because of associated complications of endotracheal tube suctioning, the procedure is used only when infants manifest moist lungs, thick secretions, or alterations in breath sounds. Scheduled suctioning may be used specifically for infants who manifest excess secretion. Improved technology for delivering high humidity of gases during ventilation has significantly reduced recurrent accumulation of thickened secretions.

What do we learn from this study? Mortality alone does not quantify quality of care in the intensive care unit. There is a need to analyze the associated morbidities vigorously to find the root cause. Then only can one develop standardized practice protocols. Quality control is a continuous process (11). There is a dire

need for similar studies to evaluate neonatal ventilator practices. Only through appropriate modification of clinical behavior can we achieve better short-term and long-term outcomes.

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Is it time to put procalcitonin to the (randomized, controlled) test?*

Since the association between elevated procalcitonin and bacterial infection was reported in a study of 79 hospitalized children in 1993 (1), hundreds of studies have been published examining its association with infection, organ failure, and mortality. As has been summarized in multiple meta-analyses on the topic (2–4), studies have examined a myriad of populations, time points in the course of illness, cutoff values indicating a positive test, and properties in comparison with other biomarkers. All studies have been challenged by the limited ability to definitively rule in or rule out bacterial infections in a considerable minority of patients, a limitation that is unlikely to change substantially in the near future.

What do we know so far? In sum, procalcitonin is a good, but far from perfect, marker of bacterial infection. It usually performs better than commonly used tests, such as white blood cell count or C-reactive protein (CRP) (5, 6). Its sensitivity is lower for some types of infection (mycoplasma, yeast, and well-localized infections) (7–9). Sicker patients tend to have higher procalcitonin levels, and an increasing level usually portends a poor outcome (9).

What good is a good, not great, biomarker? Ultimately, a biomarker's usefulness is related to whether it provides information that improves clinical decision making, has prognostic value, or enhances research subject selection. Other less-than-perfect biomarkers (e.g., superior vena cava oxygen saturation) have proven to be useful, if not invaluable, tools in improving diagnostic and treatment decisions for patients (10). Despite its limitations, procalcitonin also has been found to be useful in enhancing clinical decisions in studies of adults. Procalcitonin-guided treatment strategies safely decreased unnec-

essary antibiotic use in three single-center, randomized trials: in adults with lower respiratory infections (11), community-acquired pneumonia (8), and chronic obstructive pulmonary disease exacerbations (12). Several multicenter trials are currently being conducted or planned to expand on these findings (13, 14).

Findings from the study by Dr. Simon and colleagues in this issue of *Pediatric Critical Care Medicine* (15) suggest that procalcitonin may be able to help us make better clinical decisions for critically ill children as well. In this well-done, single-center study, the authors screened all patients in their tertiary pediatric intensive care unit for the presence of systemic inflammatory response syndrome (SIRS) daily for >6 months. Of the 224 patients who developed SIRS, 66 (29%) were enrolled in the study, and 64 had complete data collection. Enrolled patients had weight, age, and severity of illness similar to those of patients with SIRS who were not enrolled. At enrollment, soon after the onset of SIRS, procalcitonin and CRP were measured, and the patient's attending physician was asked her opinion on the likelihood of bacterial infection in the patient. A panel of three investigators subsequently used culture and other clinical data to determine retrospectively whether subjects had bacterial infections. Attending physicians and the investigator panel were kept unaware of procalcitonin and CRP results.

By themselves, procalcitonin and CRP were not more accurate than clinical judgment alone. However, the combination of the tests with clinical judgment enhanced the ability to correctly identify patients with and without bacterial infection. Nearly all patients with an elevated procalcitonin in whom the attending suspected a bacterial infection were subsequently found to be infected. Conversely, infection was found in almost none of the patients with a negative CRP in whom infection was not suspected (surprising, as CRP increases more slowly than procalcitonin in response to infection (5)).

How useful is a test that merely corroborates physician opinion? One of the study's most remarkable findings was

that the use of procalcitonin and CRP results could have potentially altered physician behavior in nine of the 64 patients. Seven patients received antibiotics who were believed by their attending to be at low risk of infection and had a negative CRP, none of whom were found to have a bacterial infection. Perhaps more important, two patients whom attendings believed likely to have bacterial infections were not started on antibiotics at the onset of SIRS, had elevated procalcitonins, and were subsequently found to be infected.

Unfortunately, the authors did not report the infection status in the face of discrepant results (e.g., elevated procalcitonin and low clinical suspicion), so we do not know if the tests could have been useful in altering physician opinion regarding the likelihood of bacterial infection. Nor do we know whether values of procalcitonin and CRP changed over time in ways that could have influenced therapy. The authors point out that serial tests would likely have been more informative than a single test at the onset of SIRS, and other studies have borne this out (8, 16, 17).

What else do we need to know? While it is still premature to incorporate routine use of procalcitonin into pediatric critical care practice, the time is right to embark on a series of studies that can produce generalizable results defining how procalcitonin can be used at the bedside of our patients. The current study asks the question in an important group of patients: those with SIRS in the pediatric intensive care unit, in whom risks of under- or overtreatment of bacterial infection are high. Larger, multicenter observational studies would certainly provide more robust estimates of test characteristics and clinician behavior.

Stronger still would be studies that focus on specific clinical decisions. Does an increasing procalcitonin indicate that a patient is infected with a resistant organism? Does a postoperative patient with increasing procalcitonin have inadequate source control? Randomized controlled trials, although challenging and expensive to conduct, could address more difficult questions. Can we avoid or shorten courses of antibiotics in the face of a low procalcitonin (or CRP)? Even

*See also p. 407.

Key Words: sepsis; infection; biomarkers; procalcitonin; C-reactive protein; critical care; pediatrics

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better, could procalcitonin facilitate a strategy of early, goal-directed antibiotics, with an elevated procalcitonin motivating more rapid antibiotic administration and serial levels guiding antibiotic duration? I would posit that thanks to Dr. Simon and colleagues (15) and other investigators who have so well laid the groundwork, now is the time to find out.

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Cum hoc ergo propter hoc (“With this, therefore because of this”)*

Springfield had just spent millions of dollars creating a highly sophisticated “Bear Patrol” in response to the sighting of a single bear the week before.

Homer Simpson: *Not a bear in sight. The Bear Patrol is working like a charm!*

Lisa Simpson: *That’s specious reasoning, Dad.*

Homer: *Thanks, honey.*

Lisa: *By your logic, I could claim that this rock keeps tigers away.*

Homer: *Hmm. How does it work?*

Lisa: *It doesn’t work. It’s just a stupid rock!*

But I do not see any tigers around, do you?

Homer: *Lisa, I want to buy your rock.*

Diabetic ketoacidosis is a complex disorder with derangements affecting many organ systems. While the most ominous has been cerebral edema, many of the other complications have been attributed to severe dehydration with decreased end organ perfusion. In this issue of *Pediatric Critical Care Medicine*, Dr. Quiros and colleagues (1) sought to determine the clinical and biochemical characteristics associated with patients with amylase and lipase increases by analyzing data from a primary study of diabetes ketoacidosis-related cerebral edema. They postulated that pancreatic enzyme elevations would be associated with biochemical markers of hypoperfusion. To achieve this goal, they conducted a multivariate analysis in

67 patients with amylase and lipase elevations. They found mildly elevated (less than twice normal) amylase in 24% of children and lipase in 31%. They found that these elevations were statistically related to elevations in the admission blood urea nitrogen but not to serum Na, pH, bicarbonate, lactate, triglyceride, or glucose, or to the presence of abdominal pain. Although half of the children were new diabetics, it is not stated whether the relationship was stronger in these new diabetics, who usually are cachectic and more severely and chronically dehydrated.

Other than creatine phosphokinase isoenzymes, serum enzymes are measured as enzyme units per liter (U/L) One enzyme unit is defined as that amount of the enzyme that catalyzes the conversion of 1 mol of substrate per min. Thus, unlike electrolyte measurements, enzyme measurements record activity rather than concentration. Amylase (from the Greek

*See also p. 418.

Key Words: diabetic ketoacidosis; amylase; lipase; pancreas

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word *amylone*, meaning starch) and lipase are just two of the >20 enzymes synthesized by the endoplasmic reticulum of the pancreatic acinar cells and sorted in the trans-Golgi network. Under cholinergic or hormonal stimulation, zymogen granules transport and release the digestive enzymes into the acinar lumen by exocytosis. The enzymes are transported into the duodenum and are activated by brush-border enterokinase in the small intestine (2). Rapid calcium release in response to hormonal stimulation is a signaling mechanism, which regulates pancreatic secretions (3). Amylase is primarily derived from the salivary glands (55%–60% S-isoamylase) and pancreas (40%–45% P-isoamylase). Lipases are mainly from pancreatic origin, but are contained in other organs including the stomach, duodenum, small bowel, colon, heart, and tongue. More than 99% of pancreatic lipase is excreted from the apical pole of the acinar cells into the ductal system of the gland; 1% diffuses from the basilar pole of the acinar cell directly into the lymphatics and reaches the circulation (4).

Removal of serum pancreatic enzymes is through the kidneys (25%), reticuloendothelial system, and liver. Unlike amylase, lipase can be reabsorbed in the kidneys, causing it to have a substantially longer serum half-life (6.9 to 13.7 hrs) than amylase (5). Increased levels of pancreatic enzymes may be secondary to an imbalance between pancreatic release and renal or hepatic clearance. Both obstructive and nonobstructive elevations of pancreatic enzymes probably are related to physical disruption of the acinar cells or alteration of the normal exocytosis process resulting in enzyme release into the interstitial space and reabsorption by the lymphatics into the bloodstream (6).

Conditions associated with high serum levels of pancreatic enzymes include:

Pancreatic: trauma, surgery, cancer, manipulation, and pancreatitis;

Salivary: infection, trauma, obstruction, and radiation;

Gastrointestinal: perforation, obstruction, infarction, celiac disease, and gastroenteritis (which can have amylase levels up to 2.2 times normal);

Gynecologic: pregnancy, perforation, cysts, and infection (S-isoamylase);

Neoplasms: of the ovary, prostate, esophagus, breast, and thymus, as well as pheochromocytosis and myeloma.

Other conditions include renal failure, burns, acidosis, acquired immune deficiency syndrome, critical illness, bulimia (62% had elevated S-amylase), head trauma (P- and S-isoamylase), diabetic ketoacidosis (raises both S-isoamylase and P-isoamylase), familial hyperamylasemia, dyslipidemia, and a large number of drug exposures (7, 8). Isolated elevations of lipase are not from pancreatic sources (9). Conversely, pancreatitis caused by hypertriglyceridemia or ethanol may have normal amylase.

As mentioned by the authors, many studies have noted mild elevations in amylase and lipase during diabetic ketoacidosis. Some have correlated the increases with osmolarity, acidosis, serum glucose, triglycerides, trypsinogen, and leukocyte elastase (an early predictor of pancreatitis) (10, 11). Increases in both P-isoamylase and S-isoamylase are present, with most studies finding a greater percentage of S-isoamylase (12, 13). The authors also noted a decrease in phosphate. Respiratory alkalosis moves phosphate into cells by activating phosphofructokinase, which stimulates intracellular glycolysis. Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced. Any cause of hyperventilation (e.g., sepsis, anxiety, pain, heatstroke, alcohol withdrawal, diabetic ketoacidosis, hepatic encephalopathy, salicylate toxicity) can precipitate hypophosphatemia (14).

There is no doubt that children with diabetic ketoacidosis are intravascularly, interstitially, and intracellularly dehydrated. One would expect that new diabetics, often with weeks of presenting symptoms, would be most affected. Blood urea nitrogen is certainly an indicator of intravascular hydration, but is highly influenced by renal function and protein metabolism. The hematocrit and corrected serum sodium also are indirect measures of intravascular volume. A better measurement is osmolarity as measured by freezing point depression. Atrial filling on echocardiogram is another noninvasive technique for estimating intravascular volume. Other noninvasive measurements of splanchnic hypoperfusion include measurements of serum transaminases, alpha-glutathione S-transferase, serum D-lactate levels, gastric tonometry, and Doppler flowmetry.

Considering the complexities of the metabolic derangements during diabetic ketoacidosis, with the inability for sub-

strate to enter the Krebs cycle thus producing adenosine triphosphate deficiency in the face of increased metabolic demands, it is no wonder that measurements of enzyme systems are difficult. Suffice it to say that amylase and lipase levels often are elevated in children with diabetic ketoacidosis and rarely are related to clinically significant pancreatitis. Whether this observation is owing to generalized metabolic derangements, gastric and pancreatic trauma from abdominal breathing, or emesis or splanchnic hypoperfusion will be best determined by specific studies aimed directly at this issue. Meanwhile, we are grateful to these authors for reassuring us that mild elevations in amylase and lipase during diabetic ketoacidosis rarely require any additional evaluation and evoking us to undertake a more rigorous study to unravel the cause of these elevations.

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Measuring cardiac output in critically ill infants and children: Are we still “talking the talk” or can we now “walk the walk”?*

We dare say that not a single day in the pediatric intensive care unit goes by without the words *cardiac output* (CO) being mentioned or addressed in nearly every critically ill patient, and yet it is rare to actually measure CO in these patients. We, as pediatric intensivists, have relied on our clinical acumen in assessing the hemodynamic status of critically ill patients despite the well-known and documented limitations of such clinical variables and the known adverse outcomes of inadequately treating abnormal hemodynamic states (1–6). There are invasive (pulmonary artery flotation catheter, pulse contour CO, lithium dilution) (7, 8) and noninvasive (echocardiographic, impedance cardiography, partial carbon dioxide rebreathing) (9–13) methods of measuring CO, either continuously or intermittently. All have variable limitations with regard to accuracy, bias, complications, instrumentation for neonates and pediatric patients, and user expertise. For these reasons, we continue to “talk the

talk” about measuring CO in critically ill infants and children.

In this issue of *Pediatric Critical Care Medicine*, Dr. Krivitski and colleagues (14) assess the accuracy of a novel ultrasound-measured blood velocity method for measuring CO and three novel hemodynamic variables—central blood volume (CBV), total end-diastolic volume (TEDV), and active circulation volume (ACV)—in an *in vitro* model of circulation in infants and children. In this study, CO is estimated using the Stuart-Hamilton principle by measuring changes in blood velocity after saline (dilution) injection. The potential utility of this new diagnostic tool is reviewed using a modified evidence-based medicine approach (15).

Was there an appropriate comparison with a reference standard?

The authors compared the ultrasound-measured blood velocity method of CO with a volumetric measurement (reference) that has a high degree of accuracy (1%). CBV, TEDV, and ACV were simulated, although there are no reference standards.

Did the model include an appropriate spectrum of clinical conditions in which the diagnostic test will be applied in clinical practice?

The study compared CO: 1) over a wide range of flows (100–1200 mL/min) typical of neonatal and pediatric patients; 2) over a wide range of simulated hematocrit values (25% to 55%); 3) with and without a venous capacitor (simulated preload); and 4) by varying user inputs into the measurement (volume, rate, and temperature of saline injection). TEDV was not simulated in the neonatal model. Hypertonic saline (a newtonian fluid) was used to simulate blood (a non-newtonian fluid), which will affect the measured velocity profile even though other additives (starch) have been used in models of the circulatory system. The effect of turbu-

lent flow (i.e., from blood clots) in the arteriovenous loop was not addressed although it is likely to be present in the clinical setting.

Were the methods for performing the test described in sufficient detail to permit replication?

The characteristics of flow through the simulated circulation are not described, which concerns us in regard to its ability to simulate (pulsatile) blood velocity profiles seen in neonates and children in altered hemodynamic states, including those with cardiac lesions that produce turbulent flow (i.e., coarctation of the aorta). Also, the bubble traps used to simulate end-diastolic volumes in the model are not described with regard to their volume or composition (presumably a nonelastic material).

Is the statistical analysis of the test results appropriate?

The authors compare their new method to the gold standard using a mean absolute error but, more appropriately, using the Bland-Altman methodology (in their Figure 5) (16). This analysis indicates that the measurements performed very well with reasonable accuracy (12% for neonatal flows and 10% for pediatric flow), typical of other clinically useful measures of CO and without significant bias (–2 mL/min for neonatal flow and +6 mL/min for pediatric flow).

Will the reproducibility of the test result and its interpretation be satisfactory in my setting?

The reproducibility of the metrics in this study is very good and acceptable for clinical use in the pediatric intensive care unit. CO is a hemodynamic variable well known by pediatric intensivists, who will be able to easily interpret and act upon these values. The other derived variables (CBV, TEDV, and ACV) are novel and potentially useful, for which the utility in clinical practice will need to be determined.

*See also p. 423.

Key Words: pediatric intensive care unit; cardiac output; hemodynamic status

Dr. Kocis is the cofounder and major stockholder of a new medical device company, REALTROMINS, Inc. This device has no apparent conflict with this cardiac output device. In addition, Dr. Kocis is a co-author of a manuscript that is in final review by *Pediatric Critical Care Medicine*, reporting the results of study of the pulse contour cardiac output device (PiCCO, Pulsion Medical Systems, Germany) in an animal model of hemorrhagic shock. The lead author (Mark Piehl, MD) was a fellow under Dr. Kocis' supervision during this study and received catheters and the central monitor for the study from Pulsion. Finally, another coauthor, Bruce Cairns, MD, was an invited speaker at two national meetings for which his travel expenses were paid by Pulsion. Dr. Olson has not disclosed any potential conflicts of interest.

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Will the results change my management and will my patients be better off as a result of the test?

This is often the most important question clinicians must answer as new diagnostic technology is taken from the bench to the bedside. Whether the immediate availability of these hemodynamic variables will provide more useful information that will improve the outcome of critically ill patients remains unknown, although we strongly believe that it will.

The ultrasound-measured blood velocity in an extracorporeal arteriovenous loop approach is a very good step forward in accurately measuring CO in neonatal and pediatric intensive care unit patients. This study provides a strong basis for further *in vivo* testing in an animal model followed by well-controlled clinical trials in pediatric patients (which have apparently begun) before the introduction of the technology into clinical practice. The invasiveness of the technique is a major limitation of the technology, so if it is used, it will be done so in a select group of high-risk pediatric intensive care unit patients in whom the decisions to place central venous catheters and to provide arterial access has been made, knowing the attendant risks and potential complications. The intermittent nature of the measurements is also problematic considering the rapid swings that can occur in the hemodynamic state of these critically ill patients. Unfortunately, this technology will not be available to children with intracardiac shunt lesions in whom the measurement of CO would be extremely valuable. The clinical utility of three new hemodynamic variables (CBV, TEDV, and ACV) awaits further evaluation. This persuasive *in vitro* study speaks volumes, but we do not believe that we

are ready to “walk the walk” quite yet with this promising new technology.

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