CLINICAL INVESTIGATIONS

End-tidal Carbon Dioxide Predicts the Presence and Severity of Acidosis in Children with Diabetes

Deirdre M. Fearon, MD, Dale W. Steele, MD

Abstract

Background: Patients with diabetic ketoacidosis (DKA) hyperventilate, lowering their alveolar (PaCO₂) and arterial carbon dioxide (PaCO₂). This ventilatory response lessens the severity of their acidemia in a predictable way. Because end-tidal CO₂ (ETCO₂) closely approximates PaCO₂, measured ETCO₂ levels should allow for predictions about the presence and severity of acidosis in diabetic patients. Objectives: 1) To evaluate the relationship between measured serum bicarbonate (HCO₃⁻) and ETCO₂ measured via nasal capnography in children with suspected DKA; and 2) to assess the ability of capnography to predict DKA. Methods: Children being evaluated in a pediatric emergency department for suspected DKA (known or suspected diabetes presenting with hyperglycemia with or without ketonuria) were enrolled in a cross-sectional, prospective, observational study. Prior to the availability of venous HCO₃⁻ results, ETCO₂ values were measured using a Nellcor NPB-70 Handheld Capnograph. Results: Forty-two patients were enrolled. Linear regression analysis revealed a significant relationship between HCO₃⁻ and ETCO₂ (R² = 0.80, p < 0.0001). Mean ETCO₂ was 37 torr (95% CI = 35.5 to 37.9 torr) in the children without DKA and 22 torr (95% CI = 17.4 to 26.9 torr) in the children with DKA (p < 0.0001). An ETCO₂ cut-point of <29 torr correctly classified the most patients (95%), with a sensitivity of 0.83 (95% CI = 0.52 to 0.98) and a specificity of 1.0 (95% CI = 0.88 to 1.0). No patient with an ETCO₂ of ≥36 torr had DKA, for a sensitivity of 1.0 (95% CI = 0.74 to 1.0). Conclusions: End-tidal CO₂ is linearly related to HCO₃⁻ and is significantly lower in children with DKA. If confirmed by larger trials, cut-points of 29 torr and 36 torr, in conjunction with clinical assessment, may help discriminate between patients with and without DKA, respectively. Key words: diabetes; ketoacidosis; capnography; end-tidal carbon dioxide.

By definition, patients in diabetic ketoacidosis (DKA) have hyperglycemia, ketonuria, and a metabolically acidosis. Therapeutic decisions depend upon which of these laboratory values are abnormal and to what degree. For the treating physician, rapid acquisition of accurate laboratory results is essential for the initiation of definitive patient care. Glucose levels can be obtained at the bedside with a hand-held glucometer. The presence or absence of urine ketones can be measured with a dipstick. Yet, rapid determination of acid–base status remains a challenge. In practice, venous blood is sent to the hospital laboratory for analysis. Serum bicarbonate (HCO₃⁻) and venous pH values are used to assess the degree of acidosis. Arterial sampling is commonly reserved for critically ill patients. Unless point-of-care testing is done, specimen transport and other delays may impede timely availability of these results to the treating clinician.

The normal physiologic compensation for metabolic acidosis is to increase minute ventilation, thereby decreasing arterial carbon dioxide tension (PaCO₂). Prior studies using arterial blood gas analyses have shown that patients with metabolic acidosis demonstrate a predictable decrease in PaCO₂ such that

$$\text{PaCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8$$

The partial pressure of CO₂ at the end of an exhaled breath (ETCO₂) closely approximates arterial CO₂ (PaCO₂). This relationship has been confirmed in normal children using nasal capnography. The close agreement between ETCO₂ and PaCO₂ also holds true for children who are severely hypocarbic as a result of DKA.

Given the near equivalence of ETCO₂ and PaCO₂ and the known relationship between PaCO₂ and HCO₃⁻, measured ETCO₂ should allow for predictions about the presence and severity of metabolic acidosis. Thus, nasal capnography may enhance the clinical recognition of compensatory hypocarbia, much as pulse oximetry aids in the assessment of hypoxemia.

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The purposes of this study were 1) to evaluate the relationship between HCO₃ and ETCO₂ measured via nasal capnography and 2) to assess the ability of capnography to predict DKA, defined as HCO₃ <15 mEq/L in the presence of hyperglycemia and ketonuria.

METHODS

Study Design. A convenience sample of children evaluated for suspected DKA was enrolled in a cross-sectional, prospective, observational study. The study was approved by our institutional review board. Written informed consent was obtained from parents of all subjects.

Study Setting and Population. The study was conducted in an urban, university-affiliated pediatric emergency department (ED). Patients were eligible for enrollment if they had known or suspected new-onset diabetes and presented to the ED with hyperglycemia. Attendings and fellows were trained in nasal capnography and encouraged to enroll all eligible patients.

Study Protocol. All eligible children were enrolled unless 1) the parent or child refused participation, 2) the child was unable to tolerate the cannula without crying, or 3) the child had been previously enrolled. End tidal CO₂ measurements were made prior to obtaining serum laboratory studies to ensure that investigators were blinded to these results while recording ETCO₂. A consistent waveform was noted prior to recording a single numeric ETCO₂ value from a digital display.

Measurements. End tidal CO₂ values and respiratory rates were measured using a Nellcor NPB-70 Handheld Capnograph with an appropriately sized Microstream Nasal Filterline (Mallinckrodt Inc., St. Louis, MO). Serum glucose levels were measured using a Surestep Pro glucometer (Lifescan, Inc., Milpitas, CA) at the bedside. The presence or absence of urine ketones was evaluated using Chemstrip urine dipsticks (Roche Diagnostics Corporation, Indianapolis, IN). Electrolytes, blood urea nitrogen, and creatinine levels were measured in the hospital laboratory with a Beckman Coulter LX20 analyzer (Beckman Coulter Inc., Fullerton, CA). Venous pH was determined using a Bayer blood gas analyzer, Model 865 (Bayer, East Walpole, MA). Ketonuria was defined as the presence of any ketones by urine dipstick and acidosis as a venous HCO₃ of <15 mEq/L.

Data Analysis. Analyses were performed using Stata 6.0 (Stata Corp., College Station, TX). We calculated means and 95% confidence intervals (95% CIs) for all measurements. Linear regression analysis was used to assess the relationship between HCO₃ and measured ETCO₂. Diabetic ketoacidosis was defined as a serum HCO₃ of less than 15 mEq/L with a serum glucose of >250 mg/dL and the presence of ketones on urine dipstick.²

Because of the non-normal distribution of ETCO₂ in patients with DKA, the non-parametric Kruskal-Wallis test was used to compare ETCO₂ values between groups with and without DKA. A receiver operating characteristic (ROC) curve analysis was performed to evaluate ETCO₂ as a predictor of DKA.³

RESULTS

Forty-four patients were approached for enrollment. Two children were excluded from analysis: one refused consent, and one could not tolerate the cannula without crying. Thus, the final sample consisted of 42 patients. Subjects ranged in age from 2 to 18 years. Overall, 23 patients (55%) had new-onset diabetes. Of these, six presented with DKA. Thirty-seven patients (88%) had ketonuria. Twelve patients (29%) had a serum HCO₃ <15 mEq/L. All 12 patients with HCO₃ <15 mEq/L had ketonuria (sensitivity = 1.0; 95% CI = 0.74 to 1.0). Twenty-five of the 30 patients with HCO₃ ≥15 mEq/L also had ketonuria (specificity = 0.17; 95% CI = 0.06 to 0.35). Mean laboratory values, with their ranges and standard deviations, are shown in Table 1.

TABLE 1. Mean Laboratory Values with Standard Deviations and Ranges for Subjects without and with Diabetic Ketoacidosis (DKA), Defined as Serum Bicarbonate (HCO₃) <15 mEq/L

<table>
<thead>
<tr>
<th></th>
<th>Without DKA (n = 30)</th>
<th>With DKA (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>426 ± 247</td>
<td>160–1,249</td>
</tr>
<tr>
<td><strong>HCO₃ (mEq/L)</strong></td>
<td>21.3 ± 3.6</td>
<td>15–28</td>
</tr>
<tr>
<td><strong>Anion gap (mEq/L)</strong></td>
<td>14.8 ± 5.0</td>
<td>7–27</td>
</tr>
<tr>
<td><strong>Venous pH</strong></td>
<td>7.36 ± 0.05</td>
<td>7.23–7.45</td>
</tr>
<tr>
<td><strong>End-tidal CO₂ (torr)</strong></td>
<td>36.7 ± 3.2</td>
<td>30–42</td>
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Figure 1 is a scatterplot of our data with the least squares regression line. The line represents the predicted serum HCO3 for any given ETCO2. The slope of the regression line is significantly greater than zero, indicating that there is a non-chance relationship between HCO3 and ETCO2 (slope = 0.68; 95% CI = 0.58 to 0.79; p < 0.0001; HCO3 = 0.68 [ETCO2] - 4.2; r² = 0.80).

Mean ETCO2 was 37 torr in the children without DKA, and 22 torr in children with DKA (p < 0.0001). Figure 2 shows the ETCO2 values in patients with and without DKA.

To find the ETCO2 values that best predicted DKA, a ROC curve was plotted and analyzed (Fig. 3). The area under the curve was 0.95 (95% CI = 0.89 to 1.0). An ETCO2 cut-point of <29 torr correctly classified the most patients (95%), with a sensitivity of 0.83 (95% CI = 0.52 to 0.98) and a specificity of 1.0 (95% CI = 0.88 to 1.0). No patient with an ETCO2 of >36 torr had DKA. Values between 30 and 35 torr did not consistently predict presence or absence of acidosis. These cut-points have the potential to be applied clinically. In practice, initial therapy is partially determined by severity of acidosis. Diabetic children without ketoacidosis can often be treated with oral fluids and subcutaneous insulin, without the need for intravenous catheter placement or blood gas analysis. Alternatively, those children with DKA are often treated with intravenous insulin and parenteral fluids. Nasal capnography, combined with a thorough clinical evaluation, may help to quickly categorize patients into one of these two groups.

If our results are confirmed in future trials and reliable cut-points are established, initial therapeutic decisions for children with DKA may be facilitated by measurement of ETCO2. Until then, predictions based on ETCO2 should be confirmed by performing serum electrolyte and blood gas analyses.

For equal degrees of acidosis, the subjects in our study exhibited different degrees of hyperpnea.
Figure 2. A graphic representation of end-tidal carbon dioxide (ETCO₂) values in patients with and without diabetic ketoacidosis (DKA). Value labels different levels of serum bicarbonate.

0: HCO₃⁻ ≥ 19 mEq/L
1: HCO₃⁻ = 15–18 mEq/L
2: HCO₃⁻ = 10–14 mEq/L
3: HCO₃⁻ < 10 mEq/L

Figure 3. Receiver operating characteristic curve illustrating end-tidal carbon dioxide (ETCO₂) cut-points as predictors of diabetic ketoacidosis.

While some of this variation may be due to measurement error, it is likely that there are physiologic explanations. In an animal model of induced metabolic acidosis, the ventilatory response was shown to be mediated by both peripheral and central nervous system (CNS) chemoreceptors. There was an immediate increase in ventilation in response to acidemia and a further increase as CNS acidosis developed. For a given blood pH, our subjects may have had different degrees of CNS acidosis, which could account for the observed variability in their measured ETCO₂ values.

There are possible prognostic uses for capnography. In a recent multicenter, retrospective, case–control study, investigators found that a low partial pressure of arterial carbon dioxide is associated
with an increased risk of cerebral edema in diabetic children.\textsuperscript{13} Because ETCO\textsubscript{2} approximates PaCO\textsubscript{2}, nasal capnography may help identify those children who are at higher risk for cerebral edema.

**LIMITATIONS**

Our sample size is relatively small. As a result, the confidence intervals around the sensitivity and specificity of our proposed cut-points are wide. A larger sample size will allow a more precise estimate of the usefulness of our proposed cut-points.

We were unable to enroll all eligible patients. Thus, the possibility of selection bias exists. For example, one toddler was excluded after enrollment. Others may not have been approached due to anticipated intolerance of the nasal cannula. Although we enrolled patients with a broad range of severity of acidosis, our convenience sample may not reflect the overall spectrum of illness of all patients seen in our ED with diabetes.

The definition of DKA is necessarily arbitrary. As Figure 2 illustrates, patients with mild acidosis (serum bicarbonate between 15 and 18 mEq/L) demonstrate an increase in ventilation while not meeting published criteria for DKA.

A few patients in our series presented in a hyperglycemic, hyperosmolar state. These children had only mild acidosis, despite severe dehydration and extreme hyperglycemia. As expected, their ETCO\textsubscript{2} values were only slightly low. In most patients, the degree of acidosis predicts severity of illness. Hyperglycemic, hyperosmolar patients are an important exception. In these patients, ETCO\textsubscript{2} values in isolation may underestimate the severity of the metabolic derangement.

End tidal CO\textsubscript{2} reliably predicts PaCO\textsubscript{2} only in patients with normal lungs. Caution must be used in interpreting ETCO\textsubscript{2} in patients with diabetes and co-existing pulmonary disease.

Compensatory increases in ventilation are not specific to ketoacidosis. Other important causes of metabolic acidosis such as uremia, increased serum lactate, and methanol toxicity should also result in decreases in ETCO\textsubscript{2}. Capnography predicts acidosis, but cannot distinguish between different etiologies.

The use of capnography as a screen for metabolic acidosis assumes that patients are able to appropriately compensate for their metabolic acidosis by increasing their minute ventilation. Individuals who are obtunded may lose the ability to compensate in this way. These patients might have ETCO\textsubscript{2} values in the “normal” range, despite severe acidosis, which would be falsely reassuring if taken out of context. On the other hand, if continuous capnography is used in conjunction with intermittent measurement of arterial blood gases, trends in ETCO\textsubscript{2} become useful. An acute rise in ETCO\textsubscript{2} despite unresolved metabolic acidosis may serve as an early warning to clinicians of progressive obtundation and/or impending herniation.

**CONCLUSIONS**

Children with DKA require rapid, definitive treatment. The aim of our study was to evaluate the utility of ETCO\textsubscript{2} measurement as a screening tool to predict the presence and severity of ketoacidosis in diabetic children. Nasal capnography is easy to perform at the bedside, provides continuous and almost instantaneous information, and is well tolerated by patients. We were able to demonstrate a predictable, linear relationship between ETCO\textsubscript{2} values and serum bicarbonate levels (HCO\textsubscript{3}) in diabetic children. We have also shown that a significant difference exists between the ETCO\textsubscript{2} measurements of patients who are in DKA and the ETCO\textsubscript{2} measurements of those who are not. If confirmed by larger trials, cut-points of 29 torr and 36 torr in conjunction with clinical assessment may discriminate between patients with and without DKA, respectively.

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**References**


