Capnography as a tool for triaging and diagnosis of diabetic ketoacidosis in the emergency department: A prospective observational study

Suhrith Bhattaram¹, Varsha Sambhaji Shinde¹*, Princy Panthoi Khumujam², Anjeeth Puthoor Anilkumar¹, Dhruva Kumar Reddy¹

¹Department of Emergency Medicine, Dr. D. Y. Patil Medical College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra, India, ²Department of Obstetrics and Gynaecology, NEIGHRIMS, Shillong, Meghalaya, India

*Corresponding author

Abstract:
OBJECTIVES: The cornerstone of management of acidosis in a patient with diabetic ketoacidosis (DKA) has traditionally been carried out by blood gas analysis, which is expensive and associated with significant risk. It is against this background that the correlation between end-tidal carbon dioxide (EtCO₂), blood pH, and EtCO₂ bicarbonate levels was analyzed. The predictive value of EtCO₂ was also analyzed in the diagnosis of DKA. Finally, we aimed to determine the value of EtCO₂ as a screening test for the exclusion of DKA.

MATERIALS AND METHODS: This was a prospective cohort study carried out in the emergency department of a tertiary care teaching hospital from September 2020 to September 2021. Patients with suspected DKA underwent simultaneous blood gas collection and EtCO₂ analysis.

RESULTS: A total of 123 patients with blood sugar levels >250 mg/dl and moderate-to-large (≥2+) urine ketones were studied. A cut-off value of EtCO₂ ≤24 was determined to rule in DKA with a sensitivity of 93.02% and specificity of 91.9%. EtCO₂ >26 could effectively rule out the diagnosis of DKA with sensitivity of 98.8% and specificity of 75.7%. A significant linear correlation between pH and EtCO₂ (P < 0.0001, r = 0.82) and HCO₃⁻ and EtCO₂ (r = 0.896, P < 0.0001) was found.

CONCLUSIONS: EtCO₂ values ≤24 can accurately identify patients with DKA in the presence of elevated blood sugar and urinary ketones and must be considered a valuable addition to the diagnostic criteria. EtCO₂ values >26 can be an effective triaging tool for ruling our DKA. A significant linear correlation between pH and EtCO₂ and pH and HCO₃⁻ was observed. EtCO₂ can be considered a surrogate marker for the degree of response to the treatment in DKA.

Keywords: Capnography, diabetic ketoacidosis, end-tidal carbon dioxide

Introduction

Diabetic ketoacidosis (DKA) is one of the most significant and life-threatening complications of diabetes mellitus. The impact of diabetes on mankind has seen a steady increase over the past 25 years, with India being a major contributor. Known as the world’s capital of diabetes, India is close to touching the alarming mark of 69.9 million by 2025 and 80 million by 2030.[1] There is a global variation in mortality associated with DKA and diabetes. In developed countries, the overall mortality rate among children...
BOX-ED section
What is already known on the study topic?
• Diabetic ketoacidosis (DKA) is diagnosed by a combination of blood glucose, ketones, and blood gas analysis
• Monitoring the degree of acidosis during treatment requires multiple pricks for blood sampling.

What is the conflict on the issue? Has it importance for readers?
• Blood gas analyses are painful, complex, expensive, and associated with significant risk to the patient
• Blood samples are also prone to preanalytical errors due to improper collection, handling, or transportation.

How is this study structured?
• This was a single-center prospective observational study carried out in the emergency department of a tertiary care teaching hospital and includes data from 123 patients.

What does this study tell us?
• EtCO₂ values can accurately identify patients with DKA in the presence of elevated blood sugar and urinary ketones. It can also be used to measure the degree of response to treatment. It is also a valuable triage tool for ruling out DKA.

In a hospital’s emergency department (ED), DKA is traditionally diagnosed based on the laboratory values of blood sugar, urinary or blood ketones, and arterial or venous blood gases (ABG or VBG). While the first two can be determined by rapid, painless, and inexpensive laboratory tests, ABGs are painful, complex, expensive, and associated with significant risk to the patient. For obvious reasons, closely monitoring the degree of acidosis and response to therapy by performing serial blood gas analyses is simply not sustainable. Blood samples are also prone to preanalytical errors due to improper collection, handling, or transportation. About 70% of all the errors occur in the pre-analytical phase, i.e., while collecting the blood sample and transporting it to the laboratory. In this situation, capnography is an alternative, noninvasive, and inexpensive method of assessing the metabolic acidosis of DKA by studying the ventilatory response to the latter. The reason for measuring end-tidal carbon dioxide (EtCO₂) in metabolic acidosis is that as the pH decreases, a compensatory increase in respiratory rate leads to alkalosis and a fall in EtCO₂. The greater the severity of acidosis, the lower the HCO₃⁻ which in turn results in lower EtCO₂. When a patient is found to have a high blood glucose value, they are often triaged to the high acuity area for further management. This process often leads to overcrowding in the critical area and is distressing to the medical team.

For this subset of patients, we had aimed to investigate the utility of EtCO₂ as a diagnostic criterion and a screening tool for DKA.

The availability of a rapid, noninvasive, sensitive screening tool that has the ability to rule out DKA in those with severe hyperglycemia will avoid unnecessary and expensive treatments.

A highly specific test may expedite the diagnosis and, by extension, the monitoring of the degree of acidosis in DKA.

Materials and Methods

Study design and setting
A prospective cohort study was conducted to evaluate the role of EtCO₂ in patients presenting with suspected DKA to a tertiary health-care center between September 2020 and September 2021. The Institutional Ethics Committee of Dr. D.Y. Patil Medical College and Hospital, Pune approved the study protocol (Approval Date: November 8, 2019; Approval No: IESC/PGS/2019/177).

Selection of participants
Subjects were chosen from a 40-bedded ED in a large tertiary care university hospital in western India, which has a fully functional emergency medicine (EM) department and is well equipped to handle all emergencies. The annual patient load ranges between 40,000 and 45,000 patients. As soon as a patient fitting the inclusion criteria was identified, an informed consent was taken to enroll the patient in the study. All patients were preliminary assessed by residents of the ED with the oversight of attending physicians. The final diagnosis of the patient was established by the attending EM physician. The patients were treated in the EM-intensive care unit or EM-ward and later referred to internal medicine and shifted as per hospital protocol.

Definitions
DKA – a blood glucose level >250 mg/dL, an anion gap >10–12 mEq/L, a bicarbonate level <15 mEq/L, and a pH <7.3 with moderate (≥2+) ketonuria, or ketonemia.

Suspected DKA – patient with clinical features of DKA, with blood sugar level (BSL) >250 mg/dL, moderate and large ketonuria (≥2+), and pending blood gas analysis.
Inclusion criteria
1. Patients ≥ 12 years
2. Patients presenting to the ED with suspected DKA.

Exclusion criteria
1. Patients <12 years of age
2. Pregnant women
3. Patients unwilling to give consent for the study
4. Patients with incomplete or missing data
5. Patients with clinical or radiological suspicion of lung infiltrates.

Sample size
Assuming a sensitivity of 90% at an acceptable error of 10% with confidence interval (CI) of 95%, the number of DKA cases required was 35. Assuming a prevalence[^1] of 34.4%, the minimum sample size required was 101.

Formula used was:
\[
\text{Sample size} = \frac{(1.96)^2 \times \text{Sensitivity} \times (1 - \text{Sensitivity})}{(\text{Deviation})^2}
\]

Total sample required = No. of patients with disease / prevalence

Patient recruitment
All patients with hyperglycemia and moderate and large ketonuria (≥2+) who presented to the ED during the study period were first identified in the triage. Patient demographic variables and their clinical and laboratory parameters and EtCO₂ values were documented. Serum glucose levels were measured using a CareSens™ N EcoGlucometer (i-SENS, Inc.,) at the bedside. The presence or absence of urine ketones was evaluated using Keto-Diastix® (Ascensia Diabetes care India Private limited). EtCO₂ values were recorded with patient in supine position with mainstream EtCO₂ monitor (Mainstream EtCO₂; Philips Capnostream M2501A, Germany) attached to a Silicone Ambu® face mask, ensuring a good seal in nonintubated patients and to the endotracheal tube in intubated patients.

All patients underwent simultaneous blood gas collection and EtCO₂ analysis to avoid changes in patient physiology. All data were collected before the initiation of treatment and entered into the data sheet by the primary investigator. Blood gases were analyzed using an ABL 90 FLEX blood gas analyzer (Radiometer, Denmark) within 2 min of collection and without any delay. All silicone masks were subject to thorough sterilization procedures after every use as per hospital protocol. Patients with clinical or radiological suspicion of lung infiltrates were not included in the study due to the COVID-19 pandemic. Selection bias may have occurred because individuals with lung infiltrates that seemed to be clinically or radiologically suspect were not included in the trial; nonetheless, this was unavoidable given the COVID-19 pandemic that was still on-going at the time.

Statistical analysis
The collected data (patient variables, serum blood glucose, urine ketones, EtCO₂, pH, bicarbonate, and other data) was recorded and managed using numbers (Apple Inc. Cupertino, California, United States) version 11.1. All the entries were double checked for any possible error. Descriptive statistical approaches (domains, frequency, percentage, mean ± standard deviation [SD], and variance) were used for each category. Qualitative data was compared using either the Chi-square test or Fisher’s exact test. For the quantitative variables, approximate normality of the distribution was assessed using Kolmogorov–Smirnov test. If normal distribution was seen, the data were compared using Welch’s t-test or Student’s t-test and nonnormal data were further analyzed by nonparametric Mann–Whitney U-test. Variables following normal distribution were summarized by mean and SD; the remaining variables were summarized as median (interquartile range). All tests were two tailed; a P < 0.05 was considered as statistically significant. Receiver operating characteristic curve was used to determine the accuracy of the EtCO₂ value in diagnosing or eliminating DKA. All tests results are reported with 95% CI. Statistical software IBM SPSS (IBM SPSS Statistics, Somers NY, USA); Systat 12 (Systat Software, Inc., Chicago IL, USA); and MedCalc for Windows 2000/XP/Vista/7 (MedCalc Software BVBA, Belgium) were used for statistical analysis.

Results
A total of 138 patients with BSLs >250 mg/dl and moderate-to-large (2+) ketones on urine dipstick testing were considered for enrolment. 15 patients were excluded from analysis due to the lack of consent or unavailable EtCO₂ values. The final sample consisted of 123 patients. A flow diagram of our study is presented in Figure 1.

Overall 86 patients (69.9%) were diagnosed with DKA and the remaining 37 were diagnosed as having diabetic ketosis without acidosis.

Out of the total 123 patients, 104 were previously diagnosed diabetics. Males constituted 66.7% (n = 81) of the study population. The mean age of the participants was 42.30 ± 17.03 years. Table 1 shows a statistically significant difference between the two groups (DKA and non-DKA) regarding age, EtCO₂, pH, bicarbonate, PaCO₂, and urinary ketones. A spearman’s
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Table 1: Demographic and biochemical data of patients with diabetic ketoacidosis and nondiabetic ketoacidosis

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>Non-DKA</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>39.88±17.31</td>
<td>47.94±15.12</td>
<td>1.56–14.55</td>
<td>0.0114*</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>32 females/54 males</td>
<td>10 females/27 males</td>
<td></td>
<td>0.3067†</td>
</tr>
<tr>
<td><strong>Blood sugar (mg/dL)</strong></td>
<td>483±187</td>
<td>403±128</td>
<td>13.21–146.79</td>
<td>0.0075*</td>
</tr>
<tr>
<td><strong>EtCO₂</strong></td>
<td>14.51±6.45</td>
<td>29.89±5.69</td>
<td>12.95–17.80</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.11 (6.9–7.25)</td>
<td>7.39 (7.35–7.42)</td>
<td>0.24–0.41</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td><strong>Bicarbonate</strong></td>
<td>7.74±4.99</td>
<td>19.49±3.63</td>
<td>10.09–13.40</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td><strong>PaCO₂</strong></td>
<td>22.66±6.92</td>
<td>34.05±7.05</td>
<td>8.86–14.09</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Urinary ketones (n)</strong></td>
<td>58</td>
<td>17</td>
<td></td>
<td>0.0285†</td>
</tr>
<tr>
<td>Large</td>
<td>28</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Welch’s t test, †Fisher’s exact test, ‡Mann–Whitney U-test, §Median (IQR). All values in DKA, DK columns are mean±SD unless specified otherwise. DKA: Diabetic ketoacidosis, CI: Confidence interval, EtCO₂: End-tidal carbon dioxide, PaCO₂: Partial pressure of carbon dioxide, SD: Standard deviation, IQR: Interquartile range.

Bhattaram, et al.: Capnography in diabetic ketoacidosis

A value of EtCO₂ ≤12 was 100% specific for the diagnosis of DKA and an EtCO₂ >28 was a 100% sensitive in ruling out DKA.

The positive predictive value of EtCO₂ ≤24 as a diagnostic test for DKA was 0.96, 95% CI (89.9–98.8) and the negative predictive value was 0.85, 95% CI (72.3–92.5) with an accuracy of 92.68%, 95% CI (86.6–96.6).

The posterior probability (odds) for a positive test (i.e., EtCO₂ ≤24) diagnosing DKA was calculated as 96% (25.6), 95% CI (90–99) and the posterior probability (odds) for a negative test was 16% (0.2), 95% CI (7–28).

In short, the results of this study show that approximately 1 in 1 patient with a positive test (EtCO₂ ≤24) are diagnosed as DKA and 1 in 1.2 patients with a negative test (EtCO₂ >24) are diagnosed as non-DKA. Table 2 shows sensitivities and specificities of various values of EtCO₂ for diagnosis of DKA.
End-tidal carbon dioxide as a screening test for ruling out diabetic ketoacidosis (>26)

A value EtCO$_2$>26 was analyzed as a screening test to rule out the diagnosis of DKA. The sensitivity and specificity of the test were found to be 98.84%, 95% CI (93.6–99.9) and 75.68%, 95% CI (58.8–88.2), respectively [Table 3].

The percentage of misclassification with this test is only 8.13%.

The positive predictive value of EtCO$_2$>26 as a test for ruling out DKA was 0.90, 95% CI (84.3–94.3) and the negative predictive value was 0.96, 95% CI (79.8–99.5) with an accuracy of 91.87%, 95% CI (85.6–96).

The posterior probability (odds) for a positive test (i.e., EtCO$_2$>26) ruling out DKA was calculated as 90% (9.4), 95% CI (2.30–7.18) and the posterior probability (odds) for a negative test was 4%, 95% CI (0–0.11).

Hence, EtCO$_2$ >26 can be used as a screening test for ruling out DKA.

Discussion

DKA is one of the life-threatening complications of diabetes mellitus. It occurs both in type I and type II diabetes. The acidosis of DKA was traditionally diagnosed and monitored through blood gas analysis, which is both time-consuming and expensive and comes with a risk of serious complications.

The need for repeated arterial punctures has reduced following the acceptance of venous blood gas monitoring. We suggest going further down this road and opting for less invasive procedures like EtCO$_2$ monitoring instead of VBG analysis. While numerous studies have explored the association of metabolic acidosis with capnography, most have targeted the pediatric population or had small sample sizes.[8-11] The present study, in contrast, recruited all its participants from the adult population and had...
Table 3: Data table of EtCO₂ >26 as a screening test to rule out DKA

<table>
<thead>
<tr>
<th>TEST (EtCO₂)</th>
<th>DISEASE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (DKA)</td>
<td>Absent (non-DKA)</td>
</tr>
<tr>
<td>(EtCO₂ ≤26)</td>
<td>85</td>
<td>9</td>
</tr>
<tr>
<td>(EtCO₂ &gt;26)</td>
<td>1</td>
<td>28</td>
</tr>
</tbody>
</table>

| Total       | 86      | 37     | 123  |

a comparatively large sample size. The study assessed three possible roles of EtCO₂: (a) its role as a triage tool for excluding DKA; (b) as an additional diagnostic criterion for DKA; and (c) its role in monitoring the treatment (degree of acidosis).

To the best of our knowledge, this is the first study carried out in an ED in India to analyze the relationship between EtCO₂ and DKA.

When the EtCO₂ values were measured and compared between the two groups, the average EtCO₂ was significantly lower among those with acidosis than among those without (14.51 ± 6.45 vs. 29.89 ± 5.69, P < 0.0001). As expected, significant differences in values for bicarbonate and pH were noted between the two groups. There was a significant linear correlation between EtCO₂ and bicarbonate (r = 0.896, P < 0.0001) and EtCO₂ and pH (r = 0.825, P < 0.0001). These results are in accordance with similar studies conducted in pediatric and adult patients.[5,12]

This preliminary evidence shows that EtCO₂ monitoring during the course of treatment is a modality for monitoring the degree of acidosis in patients with DKA. Noninvasive EtCO₂ monitoring would act as a surrogate marker for variations in pH or bicarbonate. This would improve patient comfort by removing the need for repeated blood gas analysis and also decrease the potential complications of repeated venipuncture. The inclusion of EtCO₂ as a criterion for monitoring patients’ response to treatment might have the additional benefit of reducing health-care costs.

The close relationship of EtCO₂ with pH and bicarbonate further prompted the analysis of EtCO₂ as a diagnostic criterion for DKA. The cut-off determined for the diagnosis of DKA was EtCO₂ ≤24, with a sensitivity and specificity of 93.02% and 91.89%, respectively. The positive and negative predictive values were 96.4% and 85.0% with an accuracy of 92.7%. The compelling predictive value of capnography in detecting diabetic ketoacidosis (DKA), as observed not only in this study but also in prior studies[5–10], strongly suggests the inclusion of end-tidal carbon dioxide (EtCO₂) measurements in the diagnostic criteria for DKA.

Similar studies have shown a significant difference between DKA and non-DKA groups with regard to EtCO₂ values. They have concluded that capnography values of more than 24.5 mmHg could rule out the diagnosis of DKA with a sensitivity and specificity of 0.90.[5,6]

This study also assessed the utility of EtCO₂ as a screening tool for ruling out DKA in the ED. EtCO₂ >26 was found to be 98.84% sensitive in ruling out DKA. This highlights the potential of EtCO₂ as an additional tool in the armament of an ED physician to discriminate between those who would require floor admission and those that would require higher care. A similar study carried out on 58 pediatric patients (1–18 years old) with type 1 diabetes stated that EtCO₂ >30 could rule out DKA with 100% sensitivity.[9]

The authors of this study are of the opinion that EtCO₂ monitoring in a patient with DKA should become routine practice as there are several potential benefits with almost no chances of harm. There is enough precursory data to also indicate that EtCO₂ levels should be analyzed for inclusion in the diagnostic algorithm for DKA. Monitoring EtCO₂ during the course of the treatment seems to accurately reflect the changes in acidosis (pH and bicarbonate). The authors of this study firmly believe that monitoring EtCO₂ would only improve the quality of treatment and patient comfort.

Unfortunately, there is a large amount of heterogeneity in the available literature using capnography in the assessment of DKA. Further studies looking at confounding factors in EtCO₂ would help determine more definitive recommendations in the future.

Limitations

The main limitation of this study is that it is a single-center study with a relatively smaller sample size. A more precise estimate of these cut-off points could be obtained with a larger sample size. Furthermore, the patient group consisted of a high male-to-female ratio.

Furthermore, although mainstream capnometry was used for this study, the possibility of variation in results with sidestream capnometry also exists and must be evaluated. Finally, potential confounders of EtCO₂ were also not assessed.

Conclusions

EtCO₂ values can accurately identify patients with DKA in the presence of elevated blood sugar and urinary ketones. Capnography values ≤24 must be considered a valuable addition to the diagnostic criteria of DKA. EtCO₂ should be used as a tool to measure the degree of response to treatment (changes in acidosis) in a patient with DKA as a surrogate to blood gas analysis. EtCO₂
>26 can be used as a screening test for ruling out DKA. EtCO₂ is highly sensitive in ruling out DKA and should be considered a formidable additional tool to help in triaging patients. Supplemental studies are needed to find more data in support of these recommendations.

Author contributions statement
Authorship provides credit for a researcher’s contributions to a study and carries accountability. Authors are expected to fulfill the criteria below:
• SB - Writing - original draft (lead), formal analysis (lead), final draft (lead)
• VS - Conceptualization (lead), supervision (lead), methodology (lead)
• PK - Writing - original draft (supporting), Writing - original draft preparation (supporting)
• DR - Data curation (supporting)
• AP - Data curation (lead).

Conflicts of interest
None Declared.

Ethical approval
Ethical approval has been obtained from the university ethics committee:
• Name - Institutional Ethics Committee of Dr. D. Y. Patil Medical College and Hospital
• City - Pimpri, Pune
• Country - India
• Approval No - IESC/PGS/2019/177
• Approval Date – November 8, 2019.

Consent to participate
Informed consent was taken. Informed consent for publication has been granted by the patient and/or next of kin in both the cases.

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References