ORIGINAL RESEARCH

Comparison of End-Tidal Carbon Dioxide (ETCO2) Gradient and Vena Cava Collapsibility Index (VCCI) in Response to Intravenous Fluid Therapy in Patients with Moderate and Severe Dehydration and Acute Gastroenteritis

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Abbreviations:
ABP: arterial blood pressure
AGE: acute gastroenteritis
DBP: diastolic blood pressure
ETCO2: end-tidal carbon dioxide
HCO3: bicarbonate
IV: intravenous
IVC: inferior vena cava
IVC_{exp}: inferior vena cava expirium
IVC_{insp}: inferior vena cava inspirium
MAP: mean arterial pressure
NEWS: National Early Warning Score
NPV: negative predictive value
PaCO2: partial pressure of carbon dioxide
POAC: Primary Options of Acute Care Scale
PPV: positive predictive value
ROC: receiver operating characteristic curve
SBP: systolic blood pressure
SpO2: oxygen saturation
USG: ultrasonography
VCCI: Vena Cava Collapsibility Index
VCIE: vena cava inferior expirium
VCII: vena cava inferior inspirium

Abstract

Introduction and Objective: Acute gastroenteritis (AGE) is one of the most common clinical diagnoses globally, and dehydration in severe AGE cases can cause severe morbidity and mortality. Depending on the metabolic acidosis that occurs in dehydration, the respiratory rate per minute is increased, and the carbon dioxide pressure in the arterial blood is decreased. This condition correlates with end-tidal carbon dioxide (ETCO2). Therefore, this study primarily aims to evaluate whether ETCO2 measurement has a role in detecting metabolic fluid deficit, dehydration level, and regression in dehydration level after fluid replacement and its correlation with Vena Cava Collapsibility Index (VCCI).

Material and Method: This study included spontaneously breathing patients admitted to the emergency department of a tertiary training and research hospital with symptoms of AGE and were thought to be moderately (6.0%-9.0%) and severely (>10.0%) dehydrated according to the Primary Options of Acute Care (POAC) Clinical Dehydration Scale. After the first evaluation, the patients' vital signs, ETCO2 values, diameters of the inferior vena cava (IVC) in inspiration and expiration, and VCCI were measured and recorded. These measurements were repeated after intravenous (IV) fluid replacement, and finally, a comparison was made between the measurements.

Results: A total of 49 patients, as 16 male (32.7%) and 33 female (67.3%), were included in the study. The mean fluid replacement value was calculated as 664.29 (SD = 259.41) ml. The mean increase in ETCO2 was 3.653 (SD = 2.554) mmHg (P <.001). The mean increase in inferior vena cava expirium (IVC_{exp}) was calculated as 0.402 (SD = 0.280) cm (P <.001) and the mean increase in inferior vena cava inspirium (IVC_{insp}) as 0.476 (SD = 0.306) cm (P <.001). The VCCI (%) decreased by 12.556 (SD = 13.683) (P <.001). Post-replacement vital signs, ETCO2, and VCCI correlations of the patients were examined and no significant correlation was found between ETCO2 and VCCI (%). As a result of this study, a receiver operating characteristic (ROC) curve was established for the ETCO2 values predicting the level of dehydration and fluid response, and the area under the curve was calculated as 0.748. However, to classify the patient as moderately dehydrated, the ETCO2 cutoff value was determined as 28.5mmHg.

Conclusion: The sensitivity and specificity of ETCO2 levels were 71.43% and 74.29% in evaluating the level of dehydration, and no correlation was found with VCCI, which is known to have high sensitivity and specificity in previous studies in determining the level of dehydration and fluid response. Hence, VCCI measurement made through ultrasonography (USG) is a method that should be preferred more in determining the level of dehydration.

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Nevertheless, as per the results of this study, swift ETCO2 measurements may be helpful in monitoring the change in the degree of dehydration with treatment in patients who were admitted to the emergency department with dehydration findings and were administered IV fluid replacement therapy.

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Introduction

Acute diarrhea in adults is one of the most common admission complaints in general practice, and acute dehydration is responsible for a significant proportion of deaths world-wide. In the United States, which has a population of approximately 360 million, there is an average of 99 million cases of acute diarrhea in adults each year. In the United States, acute diarrhea is the cause of hospitalizations in the elderly at 25% and the rate of diarrhea-related deaths is 85% in geriatric patients.[1–3]

Rapid and reliable identification of severe dehydration in patients with acute diarrhea and determining when patients with acute diarrhea without dehydration can be discharged safely are a challenge for the clinician.[4] Although treatment guidelines are based on the severity of dehydration, the accuracy of the clinical dehydration scale is suboptimal, and more objective methods should be used to manage treatment and predict the clinical course.[5–8]

Respiratory alkalosis is a normal physiological response to metabolic acidosis, which is common in children with gastroenteritis. By increasing the number of respirations per minute, patients can lower the partial pressure of carbon dioxide (PaCO2) to correct the underlying acidemia. Among patients with normal lung functions, it was shown that PaCO2 is correlated with the PaCO2 during exhalation, known as end-tidal carbon dioxide (ETCO2).[9]

Although studies have shown that ETCO2 and Vena Cava Collapsibility Index (VCCI) measurements, which are noninvasive methods, are useful in determining the response to fluid therapy and the level of dehydration, most of these studies have been performed in intubated, mechanically ventilated patients, children, and intensive care units. Therefore, these data on the usability of these methods in emergency services in adult patients with spontaneous breathing are limited. The primary aim of this study is to evaluate whether ETCO2 measurement has a role in determining metabolic fluid deficit and response to fluid replacement in patients with acute gastroenteritis (AGE) who were admitted to the emergency department, have spontaneous breathing, and are clinically predicted to be dehydrated, by comparing it with VCCI.

Materials and Methods

Study Design

This research was a single-center, cross-sectional, and prospective clinical study. The study's center is the emergency department of a tertiary training and research hospital with 688 service beds and 50 emergency beds. The study was initiated after the approval of the ethics committee (Health Sciences University Bozyaka Training and Research Hospital Clinical Research Ethics Committee; İzmir, Turkey; 17.07.2019; Decision Number: 02). Patients who volunteered for the study were included in the study and their written consent was obtained.

Study Population, Groups, and Definitions

The eligibility of patients to the study was determined according to the exclusion and inclusion criteria in patients: who admitted to the emergency department of the University of Health Sciences Bozyaka Training and Research Hospital with the complaint of diarrhea on August 1, 2019, and within four months afterward; who were determined as urgent according to the triage classification of the Ministry of Health; who received intravenous (IV) fluid treatment indication; and who were moderately dehydrated (with signs of thirst, oliguria, weakness, dizziness, collapsed eyeballs, postural hypotension, and dry mucous membranes) or severely dehydrated (with signs of thirst, tachycardia, low pulse volume, cold extremities, decreased skin turgor, marked hypotension, and confusion) according to the Primary Options of Acute Care (POAC) Dehydration Scale. Patients over the age of 18 who volunteered for the study were included in the study. The exclusion criteria of the study were determined as: being under the age of 18; not giving consent to participate in the study; or having concomitant chronic kidney disease, pulmonary hypertension, congestive heart failure, liver cirrhosis, chronic obstructive pulmonary disease, being pregnant, having a history of abdominal surgery that would affect the anatomy of the inferior vena cava (IVC), having a psychiatric illness, being in shock, intubated patients, being resuscitated, being under positive airway pressure support, or failure to visualize the IVC during ultrasonographic (USG) studies (ie, obesity, chest wall anomalies, congenital anomalies, and communication problems with the patient).

Study Protocol

After the triage, vital measurement results and symptoms of the patients who met the inclusion criteria for the study were recorded, and the patient's primary physician informed the researcher who conducted the study before any treatment method was applied. The clinical findings and demographic characteristics of the patients included in the study according to the POAC Dehydration Scale were recorded in the standard survey form. The systolic and diastolic blood pressures (SBP, DBP), mean arterial pressure (MAP), heart rate, oxygen saturation (SpO2), and ETCO2 values were measured and recorded by the primary physicians of the patients before IV fluid therapy. The amount of IV fluid replacement to be administered to the patients according to NICE 2017 "Intravenous Fluid Therapy in Adults in Hospital – Clinical Guideline" was calculated. Pre- and post-replacement inferior vena cava expirium (IVC_{exp}) and inferior vena cava inspirium (IVC_{insp}) values were measured and recorded by the researcher who was blinded to ETCO2 values. Ultrasonographic measurements were made by a single observer.

Arterial blood pressure (ABP) and SpO2 measurements were made by GE Healthcare B40 (GE MedicalSystems; Milwaukee, Wisconsin USA) patient monitors. When the ABP measurement was completed, the SBP, DBP, and MAP values monitored on the monitor were recorded in the data form for each patient.

The ETCO2 measurements were made using the side-stream method using the GE HEALTHCARE B125 E-miniC Module (GE MedicalSystems; Milwaukee, Wisconsin USA) connected to patient monitors and a standard, non-reservoir oxygen mask that can be connected to this module. During the

	Mean Difference	Standard Deviation	Standard Error	95% Confidence Interval		P Value
				Lower Bound	Upper Bound	
Systolic Blood Pressure†-Systolic Blood Pressure‡	-4.184	10.653	1.522	–7.244	-1.124	**.008**
Diastolic Blood Pressure†-Diastolic Blood Pressure‡	–4.020	10.355	1.479	-6.995	–1.046	**.009**
Mean Blood Pressure†-Mean Blood Pressure‡	–4.020	8.355	1.194	-6.420	-1.620	**.001**
ETCO2†-ETCO2‡	-3.653	2.554	0.365	–4.387	–2.919	<**.001**
IVCexp†-IVCexp‡	–0.402	0.280	0.040	–0.483	–0.321	<**.001**
IVCins†-IVCins‡	–0.476	0.306	0.043	–0.565	-0.388	<**.001**
VCCI (%)†-VCCI (%)‡	12.556	13.683	1.955	8.626	16.486	<**.001**

Table 1. Pre- and Post-Replacement Change Level of Vital Signs
Note: Wilcoxon Test, † pre-replacement, and ‡ post-replacement. A total of 49 patients, 16 male (32.7%) and 33 female (67.3%), admitted to the emergency department with symptoms of AGE met the inclusion criteria and were included in the study. The mean value of fluid replacement administered to the patients was calculated as 664.29ml (SD = 259.41).
Abbreviations: AGE, acute gastroenteritis; ETCO2, end-tidal carbon dioxide; IVCexp, inferior vena cava expirium; IVCinsp, inferior vena cava inspirium; VCCI, Vena Cava Collapsibility Index.

measurement, when the values on the patient monitor were stabilized, the value read was recorded in the data form.

The IVC_{exp} and IVC_{insp} measurements were made using PHILIPS HD11 XE (PhilipsMedicalSystems; Bothell, Washington USA) ultrasound device and S4-1 Broadband Sector Array Probe (PhilipsMedicalSystems; Bothell, Washington USA). The right atrium, IVC, and hepatic veins were visualized in the subxiphoid window, longitudinal axis to measure the diameter of the IVC. The IVC diameters measured in M-Mode, 2-3cm distal to the right atrium and approximately 2cm below the junction of the IVC and hepatic vein, were recorded in the data form as IVC_{exp} (diameter during expiration) and IVC_{insp} (diameter during inspiration). The VCCI was calculated manually by substituting the recorded values in the formula: $VCCI = (IVC_{exp} - IVC_{insp})/IVC_{exp} \times 100$.

Outcome Measures
The primary endpoint was determined to collect ETCO2 and VCCI measurements for four months to evaluate the degree of dehydration in patients with AGE and fluid replacement indication after the ethics committee's approval.

Data Analysis
Statistical analyzes were performed with the help of the SPSS version 17.0 program (SPSS Inc.; Released 2008. SPSS Statistics for Windows, Version 17.0; SPSS Inc.; Chicago, Illinois USA). The compliance of the variables to normal distribution was examined using histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation (SD), median, and minimum-maximum values were used when presenting descriptive analyzes. The pre- and post-replacement values were examined with the Wilcoxon Test. Pearson Correlation Test analyzed the measurement data with each other. The effect of ETCO2 on the detection of fluid response was investigated by receiver operating characteristic (ROC) curve analysis. The situations where the P value was less than 0.05 were determined as statistically significant results.

Informed Consent/Ethical Approval/Human Rights
This study was conducted on healthy adult volunteers and written informed consent was obtained from all healthy adult volunteers participating in this study. This study has been approved by the Health Sciences University and Health Sciences University Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2019-7/02) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Results
A total of 49 patients, 16 male (32.7%) and 33 female (67.3%), admitted to the emergency department with symptoms of AGE and met the inclusion criteria were included in the study. The mean value of fluid replacement administered to the patients was calculated as 664.29 (SD = 259.41) ml. Statistical evaluation of pre- and post-replacement vital signs, ETCO2, and VCCI values are presented in Table 1.

After the dehydration level was determined, the mean ETCO2 level was found to be 25,857 (SD = 4.735) mmHg in the measurements made before the fluid replacement, while the ETCO2 level was 29.510 (SD = 4.287) mmHg in the repeated measurements after the replacement. The mean increase in ETCO2 after replacement therapy was calculated as 3.653 (SD = 2.554) mmHg and a statistically significant difference was observed (P <.001). After the dehydration level was determined, VCCI was 48.333% (SD = 12.301) in the measurements performed before fluid replacement, and it decreased to 35.777% (SD = 11.425) after fluid replacement. It was observed that there was a decrease of 12.556 (SD = 13.683) in the VCCI (%) value (P <.001). A weak correlation in the same direction (r: 0.390) was found between ETCO2 and VCCI % (P <.005; p: 0.006). That is, as VCCI % increased, ETCO2 also increased.

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Area	Standard Error	P Value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.748	0.074	.007	0.604	0.892

Table 2. ROC Analysis Results for the Effect of ETCO2 in Determining the Degree of Dehydration

Note: The effect of ETCO2 on the determination of the degree of dehydration was investigated by ROC analysis, and as a result of the analysis, the threshold value was determined as 28.5 mmHg to classify the patient as moderately dehydrated.

Abbreviations: ETCO2, end-tidal carbon dioxide; ROC, receiver operating characteristic curve.

	Sensitivity	Specificity	PPV	NPV
ETCO2< 28.5	71.43%	74.29%	52.63%	86.67%

Table 3. Sensitivity, Specificity, PPV, NPV Rates found for ETCO2 >28.5

Note: It was thought that patients with an ETCO2 value above this value could be considered mildly dehydrated or normovolemic with statistical sensitivity of 71.43%, specificity of 74.29%, PPV of 52.63%, and NPV of 86.67%.

Abbreviations: ETCO2, end-tidal carbon dioxide; PPV, positive predictive value; NVP, negative predictive value.

The effect of ETCO2 on the determination of the degree of dehydration was investigated by ROC analysis, and as a result of the analysis, the threshold value was determined as 28.5mmHg to classify the patient as moderately dehydrated (Table 2).

It was thought that patients with an ETCO2 value above this value could be considered mildly dehydrated or normovolemic with statistical sensitivity of 71.43%, specificity of 74.29%, positive predictive value (PPV) of 52.63%, and negative predictive value (NPV) of 86.67% (Table 3).

Discussion

To the best of the authors' knowledge, there is no study determining the accuracy of noninvasive ETCO2 in evaluating the volume status and response to IV fluid therapy in dehydration in an adult with spontaneous breathing by comparing it with the VCCI. Therefore, this study primarily aimed to evaluate the ETCO2 measurement by comparing it with the VCCI, whether it had a role in determining the metabolic fluid deficit, the degree of dehydration according to clinical findings, and the response to fluid replacement.

In this study, as patients received fluid replacement therapy, vena cava inferior expirium (VCIE) and vena cava inferior inspirium (VCII) measurements decrease, and the index decreased. These findings, which revealed an increase in vena cava measurements after fluid VCCI compared to before fluid replacement, were compatible with the literature compared with previous studies.[10–12]

The mean VCCI (%) was 48.333 (SD = 12.301) in the measurements performed in all moderately dehydrated (6.0%-9.0%) patients before replacement. In the study of Orso, et al in which they evaluated the effectiveness of VCCI and VCIE measurements in detecting dehydration, it was found to be compatible with the threshold value of 48% for VCCI in predicting the patient's dehydration.[13]

In the study conducted by Freedman, et al which included 195 children aged three months to ten years who were admitted to the emergency department due to vomiting and/or diarrhea, 116 children were able to complete acceptable ETCO2 measurements, ETCO2 values of five percent or more were recorded before and after IV, and oral fluid therapy and ETCO2 values, which predict the level of dehydration, were investigated. As a result of the study, the ROC curve was created for ETCO2 values predicting five percent or more dehydration level, and the area under the curve was calculated as 0.34. Accordingly, the accuracy of ETCO2 to predict five percent or more dehydration level is limited, and it is not capable of identifying these patients. Due to the limited accuracy of ETCO2 in predicting dehydration, a threshold value that could classify patients with dehydration level of five percent and above could not be determined.[7] Over against, in this study, the area under the curve for ETCO2 was found to be 0.748 to predict the level of dehydration. Besides, the effect of ETCO2 on the determination of the degree of dehydration was investigated by ROC analysis, and as a result of the analysis, the threshold value was determined as 28.5mmHg (sensitivity: 71.43%; specificity: 74.29%) to classify the patient as moderately dehydrated. In this study, the POAC Clinical Dehydration Scale was used to determine the dehydration level of the patients. Per this scale, all of the patients included in the study were in the moderate dehydrated class, and the percentage of dehydration was between 6.0% and 9.0%. The total body fluid amount of children covers a larger part of their total body area than adults. Hence, it was thought that the response of children and adults to fluid loss may not be the same, that five percent or more dehydration may not present with the same symptoms in clinical situations, and that they may respond with different physiological capacities at the same degree of dehydration.

The study of Nagler, et al aimed to determine the correlation between ETCO2 levels and serum bicarbonate (HCO3) concentrations before and after IV and oral hydration therapy in pediatric patients admitted to the emergency department due to gastroenteritis. In this study, serum HCO3 values were used as a measure of dehydration. Measurements were completed in 130 of 146 children included in the study, and the correlation between ETCO2 measurements and serum HCO3 levels before and after fluid therapy was examined. Finally, ROC curves were created to determine the accuracy of ETCO2 in predicting metabolic acidosis. According to ≤13, ≤15, ≤17mmol/L HCO3 levels, the areas under the curve were calculated as 0.94, 0.95, and 0.90, respectively. Accordingly, capnography is an objective and noninvasive measurement method that shows the severity of acidosis in patients with gastroenteritis.[9] However, in this study, the area under the curve may have been calculated more since the patient population consisted of the pediatric age group, and the metabolic responses of the body in case of dehydration were different. Nevertheless, in the study of Nagler, et al, the amount of fluid therapy administered compared to the current study was unclear. This may explain the difference in results.

Uzunosmanoğlu, et al aimed to test the use of ETCO2 levels to evaluate the severity of dehydration in adult patients admitted to the emergency department with AGE symptoms, and 87 patients were included in the study. Patients were divided into mild and moderate severity per the National Early Warning Score (NEWS) at their first admission, and the ETCO2 levels of these patients were recorded. Mean ETCO2 levels were higher in the mildly severe group than in the moderately severe group. In the ROC analysis performed to compare both groups, the area under the curve was calculated as 0.988. The threshold value for

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separating mild and moderately dehydrated patients is 33.5mmHg (95% sensitivity; 93% specificity).[14] In this study, the two groups whose ETCO2 levels were compared did not receive any hydration therapy. In the current study, pre- and post-fluid replacement ETCO2 values were measured and compared. The fact that the patients who were initially considered dehydrated in this study had not yet received any fluid therapy may have caused these results to be different. Unlike the NEWS used in that study, the POAC Clinical Dehydration Scale used in this study includes clinical parameters, such as fatigue and thirst, as well as the vital signs. All patients included in the current study were considered moderately dehydrated, and moderate and mildly dehydrated patients were included in this study. The lower threshold value (28.5mmHg; sensitivity: 71.43%; specificity: 74.29%) calculated in the current study can be attributed to this reason.

The results of the current study revealed that VCII, VCIE, and ETCO2 values increased and VCCI (%) values decreased with fluid replacement therapy. On the other hand, in correlation analysis between VCIE, VCII, and VCCI (%) with ETCO2, there was a weak inverse (r: -0.282) correlation between ETCO2 and VCII before replacement (p: 0.050; P <.005). That is, while the VCCI value increased, the ETCO2 value decreased. There was a weak positive correlation (r: 0.390) between ETCO2 and VCCI (%) (p: 0.006; P <.05). That is, while the VCCI % was high, ETCO2 was also high. While VCII, VCIE, and ETCO2 values were found to change in the same direction and the opposite direction with VCCI in the correlation analysis performed with single parameters, the opposite result was obtained in the correlation analysis in pairwise comparisons. However, according to single analysis, it was predicted that ETCO2 values should be high in patients with low VCCI (%) and low ETCO2 values in patients with high VCCI (%).

As per the dehydration levels determined according to the POAC Clinical Dehydration Scale, the sensitivity of ETCO2 was 71.43%, the specificity 52.63%, PPV was 52.63%, and NPV was 86.67% in detecting moderately dehydrated patients (6.0%-9.0%). However, no statistically significant results were found in correlation analysis in which VCCI (%) values were compared to ETCO2 values, which is a more advanced and objective method used in clinical practice. In previous studies, considering the high sensitivity and specificity values of VCCI (%) in determining the level of dehydration, it is thought that the primary method of detecting dehydration is the measurement of VCCI (%).[14] However, the tendency of ETCO2 values such as VCII and VCIE to increase in response to fluid therapy may still guide the clinician.

In the light of current literature data, there is no study evaluating the degree of dehydration, the adequacy of fluid therapy in case of dehydration, by comparing it with ETCO2 and VCCI. In this respect, the current study may be a leading study in this regard, but further studies are needed due to the limited number of patients.

Limitations

The study was performed in a single-center, and the number of patients included in the study was low (n: 49). The gender distribution was unequal (16 men [32.7%] and 33 women [67.3%]). The patient enrollment period (four months) was short. These reasons limit the relevance of the results of the study to the general population.

The patients included in the study did not have any history of comorbid diseases and drug use. Since it is thought that ETCO2 levels due to metabolic processes of existing diseases may be affected in patients with comorbidity, in the study design, almost completely healthy individuals were included in the study, except for the complaints of applying to the emergency department. Therefore, it is suggested that there may be differences in the use of ETCO2 levels in people with comorbidities in detecting dehydration and evaluating the response to fluid therapy.

Conclusion

When the sensitivity and specificity values of VCCI (%) in previous studies investigating the use of VCCI as an indicator of dehydration status were compared with the sensitivity and specificity values obtained here for ETCO2 in the current study (Table 3) which evaluated the use of ETCO2 for the same purpose, VCCI was found to have higher sensitivity and specificity (sensitivity, specificity, PPV, and NPV were, respectively 99.3%; 100%; 100%; and 99.2%).[13] Hence, VCCI measurement made through bed-side USG is a method that should be preferred more in determining the level of dehydration.

However, as per the results of this study, swift ETCO2 measurements may be helpful in monitoring the change in the degree of dehydration with treatment in patients who were admitted to the emergency department with dehydration manifestations and were given IV fluid replacement therapy.

Author Contribution

Gİ, HPK, and HG contributed equally to this study. All authors participated in the design, data collection and analysis, drafting of the manuscript, and approval of the final version.

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