BRIEF REPORT

OPEN

Change in End-Tidal Co_2 After Mini-Fluid Challenge to Determine Fluid Responsiveness

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OBJECTIVES: Distributive shock is a major cause of morbidity and mortality in the ICU. IV fluid resuscitation is a vital intervention to improve cardiac output and end-organ perfusion during the initial resuscitation and for those who remain fluid responsive. Noninvasive measures of fluid responsiveness are lacking. The aim of this study is to assess whether changes in end-tidal co_2 after mini-fluid challenge, or 250 mL bolus, can predict fluid responsiveness in mechanically ventilated patients with distributive shock.

DESIGN: Single-center prospective study.

SETTING: Patients were enrolled from 2019 to 2021 from the medical ICU within a single academic hospital.

PATIENTS: Thirty-eight patients with paired measurements of fluid responsiveness as determined by bioreactance who were admitted to the ICU with a diagnosis of distributive shock and on mechanical ventilation.

INTERVENTIONS: Stroke volume index (SVI), cardiac index, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and $ETco_2$ were measured before and after completion of a mini-fluid challenge. Test characteristics of change in $ETco_2$ ($\Delta ETco_2$) greater than or equal to 2 after mini-fluid challenge to determine fluid responsiveness were calculated with percentage change in SVI greater than or equal to 10% used as the reference standard.

MEASUREMENTS AND MAIN RESULTS: The sensitivity and specificity of a $\Delta ETco_2$ greater than or equal to 2 mm Hg as a predictor of a change in SVI greater than or equal to 10% following a mini-fluid challenge were 20.0% and 91.3%, respectively. The area under the receiver operating characteristic curve was 0.62.

CONCLUSIONS: A $\Delta ETco_2$ greater than or equal to 2 mm Hg after mini-fluid challenge has limited test performance for determining fluid responsiveness in intubated patients with distributive shock.

KEY WORDS: bioreactance; end-tidal carbon dioxide; fluid responsiveness; medical intensive care unit; shock

Patients with distributive shock require judicious administration of IV fluids since both inadequate and excess fluid resuscitation are associated with poor outcomes (1, 2). Instead of a uniform dose, the specific amount of fluid that a patient requires could be determined by an individual patient's change in cardiac index (CI) after a preload challenge, also called fluid responsiveness (3). Pre-existing methods that can help to determine fluid responsiveness are limited by their invasiveness and need for specialized equipment (3). Monitoring change in end-tidal Co_2 ($\Delta ETco_2$) after preload change is a promising way to determine fluid responsiveness and uses routine ICU monitors (4). In situations where alveolar ventilation and tissue Co_2 production remain stable, $\Delta ETco_2$ is

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KEY POINTS

Question: Can a change in end-tidal Co_2 ($ETco_2$) greater than or equal to 2 mm Hg after a mini-fluid challenge predict fluid responsiveness for intubated patients with distributive shock?

Finding: Paired measurements from 38 intubated patients with distributive shock yielded a sensitivity of 20%, specificity of 91%, and area under the receiver operating characteristic 0.62 for change in $ETco_2$ greater than or equal to 2 mm Hg to predict fluid responsiveness.

Meaning: Change in $ETco_2$ greater than or equal to 2 mm Hg after a mini-fluid challenge is insufficient to determine the fluid responsiveness status for intubated patients with distributive shock.

then determined by changes in cardiac output (4). Prior studies have identified that a $\Delta ETco_2$ greater than or equal to 2 mm Hg after a preload challenge can identify those patients who remain fluid responsive (4, 5). Our study investigated whether $\Delta ETco_2$ greater than or equal to 2 mm Hg after a mini-fluid challenge could identify patients who are fluid responsive.

METHODS

Our study was a single-center prospective study of patients admitted to the medical ICU at the University of Virginia in 2019–2021 and was approved by the Institutional Review Board as study 21461 in June 2019. Our study was titled "Changes in end-tidal carbon dioxide as a marker of fluid responsiveness in distributive shock as determined by noninvasive cardiac output monitoring." Our study was in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975. Consent was deferred as the clinical data were generated from routine clinical care. Patient data were collected and stored in a REDCap (Research electronic data capture) (6) database.

Patients and Study Protocol

We included patients who were at least 18 years old, intubated with continuous waveform capnography, ventilated with volume or pressure control, had a temperature between 36.0°C and 37.9°C, and met clinical criteria for the diagnosis of distributive shock of any etiology. Patients could be enrolled in the study if the primary team elected to determine if the patient was fluid responsive using the Starling Fluid Management Monitoring System (Baxter International, Deerfield, IL) as part of routine clinical care. Fluid responsiveness was then assessed by placing proprietary chest wall electrodes to obtain baseline bioreactance determined stroke volume index (SVI) and CI. Simultaneously, a baseline end-tidal Co_2 ($ETco_2$) value and noninvasive hemodynamic measurements were recorded (CARESCAPE, GE Healthcare, Chicago, IL). The patient then received a mini-fluid challenge or a standardized 250 mL bolus of 0.9% normal saline. After completion of the mini-fluid challenge, repeat SVI and CI per bioreactance, $ETco_2$ value, and noninvasive hemodynamic measurements were recorded. After enrollment, study personnel collected patient demographic information and clinical data.

Definition of Fluid Responsiveness and Reference Measurement

Determining fluid responsiveness status by $\Delta ETco_2$ greater than or equal to 2 mm Hg after a mini-fluid challenge was the outcome of interest. The reference standard for fluid responsiveness was an increase in SVI greater than or equal to 10% by bioreactance (7). Bioreactance has been established as an accurate and precise noninvasive measurement of cardiac output as compared to invasive gold standard (8). SVI is calculated by bioreactance measures as previously described (8). Prior studies demonstrate that an increase in SVI greater than or equal to 10% can distinguish fluid responders from nonresponders (7, 9).

Statistical Analysis

Statistical analysis was completed in Excel (Microsoft Corporation, Redmond, WA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under receiver operating characteristic (AUROC) were calculated for $\Delta ETco_2$ greater than or equal to 2 mm Hg after mini-fluid challenge.

Median values and interquartile ranges of heart rate, blood pressure, pulse pressure, SVI, CI, and $ETco_2$ were

calculated. Comparisons for these indices were made pre and post mini-fluid challenge for both responder and nonresponder groups. p value was set at 0.05 for statistical significance for two-sided comparisons.

RESULTS

Patient Characteristics

Paired measurements were obtained from 38 patients (**Table 1**). The median patient age was 68, with a median body mass index of 29.8. The majority of patients had acute respiratory distress syndrome, and the median Simplified Acute Physiology Score II score was 50. Preexisting chronic pulmonary conditions were present in 12 patients with chronic obstructive pulmonary disease (COPD) being the most common pulmonary diagnosis. Thirty-five patients were receiving vasoactive medications when measurements were obtained. Most patients were on a single vasoactive agent of which norepinephrine was the most commonly used. Our cohort had a 39.5% fluid responder rate as determined by bioreactance.

Hemodynamic Variables

The absolute value of SVI was significantly different after the mini-fluid challenge in the responder group (35.2 ± 8.8 vs 42.8 ± 10.6 mL/m^2; $p < 0.05$) (Table 1). No other hemodynamic variable was different when comparing within groups or between groups. Absolute value of $ETCO_2$ was not different before or after mini-fluid challenge in either group and was not different at baseline or after mini-fluid challenge when comparing groups.

Test Characteristics

The sensitivity and specificity of a $\Delta ETCO_2$ greater than or equal to 2 mm Hg as a predictor of an SVI increase greater than or equal to 10% after mini-fluid challenge was 20.0% and 91.3%, respectively. The AUROC for $\Delta ETCO_2$ to predict an SVI increase of greater than or equal to 10% was 0.62.

DISCUSSION

Our study enrolled a cohort of patients from a single ICU with distributive shock who were undergoing invasive mechanical ventilation. Static hemodynamic measurements and absolute values of $ETCO_2$ did not differ for responders and nonresponders before or after the mini-fluid challenge. The test characteristics of $\Delta ETCO_2$ greater than or equal to 2 mm Hg after mini-fluid challenge were comparable with prior studies, and our AUROC of 0.62 demonstrates that $\Delta ETCO_2$ measurement after mini-fluid challenge overall lacks discriminatory power when determining who is fluid responsive (10, 11).

The change in $ETCO_2$ after other preload challenges has demonstrated superior test characteristics. Studies measuring change in $ETCO_2$ after fluid boluses of 500 mL have demonstrated AUROC 0.80–0.82 (11, 12). Studies measuring change in $ETCO_2$ after passive leg raise (PLR) have demonstrated AUROC 0.80–0.94 (4, 5, 10).

Our study used a patient-centered approach by using a noninvasive form of CI monitoring and mini-fluid challenge. Although the mini-fluid challenge does not appear to sufficiently distinguish between fluid responders and nonresponders, given the concerns about volume overload with larger fluid boluses and logistical challenges with PLR, it was prudent to investigate the utility of a mini-fluid challenge.

Our study has several limitations. First, our cohort was a convenience sample of patients identified by study members and bedside providers familiar with the aims of the study. This may have unduly impacted the responder rate in our cohort. Prior studies have reported comparable percentages of fluid responders irrespective of whether consecutive or convenience enrollment was used (4, 11–13). Second, our study used single measurements of $ETCO_2$ at time points prespecified by the fluid responsiveness assessment done by the bioreactance device used in our ICU. Changes in $ETCO_2$ after a mini-fluid challenge may occur at a different time point than changes in SVI as determined by bioreactance. A more granular quantitative analysis of the CO_2 waveforms may yield a more robust measure of fluid responsiveness. Third, our cohort, although comparable in size to other published studies, may have lacked sufficient size to most accurately assess the test characteristics of $\Delta ETCO_2$. Fourth, 16% of our cohort had COPD and a disproportionate number were present in our nonresponder cohort. This may cause variation in alveolar variation and impact $ETCO_2$ measurements. Other studies have had notably fewer patients with COPD or other chronic lung disease in their cohorts or do not specifically identify this within their cohort descriptions (4, 12, 13); however, one study had a cohort with 40% of

TABLE 1.
Cohort Characteristics and Assessment of Hemodynamic Variables Before and After Mini-Fluid Challenge

Characteristics	Responders (*N* = 15)	Nonresponders (*N* = 23)
Age, yr, median (IQR)	63 (52–74)	68 (55–73)
Sex, *n* (%)		
Female	4 (27)	4 (17)
Male	11 (73)	19 (83)
Body mass index, median (IQR)	29.4 (26.5–34.05)	29.1 (24.9–32.1)
Simplified Acute Physiology Score II, median	55.8	45
Acute respiratory distress syndrome, *n* (%)	12 (80)	21 (91)
Chronic pulmonary conditions, *n* (%)		
Chronic obstructive pulmonary disease	1 (6)	5 (22)
Asthma	2 (12)	2 (9)
Other	0	2 (9)
Ventilator settings, *n* (%)		
Volume control	14 (93)	18 (78)
Pressure control	1 (7)	5 (22)
Quantity of IV fluid in 24 hr prior to fluid responsiveness assessment, L, median (IQR)	2.8 (1.7–4.3)	2 (0.9–2.9)
Vasoactive medications		
Patients on vasopressors, *n* (%)	14(93)	21 (91)
Number of vasopressors, mean (± SD)	1.29 (± 0.69)	1.21 (± 0.74)

Hemodynamic Variables, Mean ± SD	Responders (Pre)	Responders (Post)	Nonresponders (Pre)	Nonresponders (Post)
Heart rate (beats/min)	89±25	88±23	95±25	93±25
Systolic blood pressure (mm Hg)	108±15	115±19	106±15	121±28
Diastolic blood pressure (mm Hg)	55±11	56±10	53±7	54±7
Mean arterial pressure (mm Hg)	73±8	76±9	73±7	76±8
Pulse pressure (mm Hg)	54±19	59±22	62±28	66±32
Stroke volume index (mL × m^{-2})	35.2±8.8	42.8±10.6[a]	36.7±13.5	36.3±13.8
Cardiac index (L × min^{-1} × m^{-2})	3.1±0.7	3.52±0.8	4.8±7.9	4.3±5.4
Absolute $ETCO_2$ (mm Hg)	35±9	35±10	36±9	35±8
Change $ETCO_2$ (mm Hg)		−0.2±2.7.		−0.7±1.9

$ETCO_2$ = end-tidal Co_2, IQR = interquartile range.
[a]$p < 0.05$ for comparisons between before and after mini-fluid challenge.

patients having COPD but still demonstrated a robust AUROC for $\Delta ETCO_2$ after PLR.

CONCLUSIONS

In summary, for our cohort, a $\Delta ETCO_2$ greater than or equal to 2 mm Hg after a mini-fluid challenge did not adequately distinguish between fluid responders and nonresponders. Since this is only the second study to investigate $\Delta ETCO_2$ after a mini-fluid challenge in a medical ICU population undergoing mechanical ventilation, additional studies would be needed to determine whether there is clinical utility in this proposed test of fluid responsiveness. However, since more

robust evidence exists for measuring $\Delta ETCO_2$ after larger fluid boluses and/or PLR, it may be prudent for future studies to focus on the clinical application of this fluid responsiveness assessment.

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Dr. Kadl had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors made substantial contributions to the study design, data acquisition, data analysis and interpretation, figure design and creation, and article writing. All authors have all given final approval for publication of this version of the article and are accountable for all aspects of the work.

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