Original Article

End-tidal carbon dioxide's change to fluid challenge versus internal jugular vein dispensability index for predicting fluid responsiveness in septic patients: A prospective, observational study

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ABSTRACT

Background and Aims: The prediction of fluid responsiveness is crucial for the fluid management of septic shock patients. This prospective, observational study was conducted to compare end-tidal carbon dioxide (ETCO2) change due to fluid challenge (FC-induced ΔETCO2) versus internal jugular vein distensibility index (IJVDI) as predictors of fluid responsiveness in such patients. **Methods:** Septic hypoperfused mechanically ventilated patients were classified as fluid responders (Rs) and non-responders (NRs) according to the improvement of left ventricular outflow tract-velocity time integral (ΔLVOT-VTI) after fluid challenge (FC). The receiver operating characteristic (ROC) curves of FC-induced ΔETCO2, pre-(FC) IJVDI and their combination for prediction of fluid responsiveness were compared to that of ΔLVOT-VTI% as a gold standard. **Results:** Of 140 patients who completed the study, 51 (36.4%) patients were classified as Rs and 89 (63.6%) patients as NRs. With regard to the prediction of fluid responsiveness, no significant difference (*P.* 0. 384) was found between the diagnostic accuracy of FC-induced ΔETCO2 >2 mmHg (area under the ROC curve [AUC] 0.908, $P < 0.001$) and that of pre-(FC) IJVDI >18% (AUC 0.938, $P < 0.001$), but a prediction model combining both markers, ΔETCO2 ≥3 mmHg and IJVDI ≥16%, achieved significantly higher accuracy (AUC 0.982, $P < 0.001$) than each independent one ($P < 0.05$). **Conclusion:** Under stable ventilatory and metabolic conditions, the predictivity of FC-induced ΔETCO2 >2 mmHg can be comparable to that of pre-(FC) IJVDI >18%. A predictive model combining both FC-induced ΔETCO2 ≥3 mmHg and IJVDI ≥16% can provide higher accuracy than that recorded for each one independently.

Key words: Carbon dioxide, fluid responders, resuscitation, sepsis, shock, internal jugular vein dispensability index, end-tidal carbon dioxide, fluid challenge

INTRODUCTION

Prediction of fluid responsiveness is essential for the haemodynamic management of septic patients without the risk of fluid overloading and mortality.[1,2] Internal jugular vein distensibility index (IJVDI) is a non-invasive, effective predictor of fluid responsiveness as shown in many studies.[3] End-tidal carbon dioxide (ETCO2) variation (ΔETCO2) was shown to reflect cardiac output (CO) changes after fluid challenge (FC) during acute circulatory failure.[4,5] Compared to IJVDI, FC-induced ΔETCO2 can be a simpler, continuous, feasible alternative for prediction.[6] The objective of this study was to compare the predictivity of FC-induced ΔETCO2 and pre (FC) IJVDI for fluid responsiveness in septic patients.

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METHODS

This prospective, observational study was performed in the department of anaesthesia and surgical intensive care unit (SICU), Faculty of Medicine, Zagazig University, after approval was obtained from the Institutional Review Board (IRB) (ZU-IRB #6522 dated 15-12-2019) and informed consent was obtained for participation in the study and use of the patient data for research and educational purposes from patients' first-degree relatives during the period February–December 2020. All study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration of 2013.

Patients aged 18–75 years, diagnosed to be septic shock and showing signs of sustained hypoperfusion after initial resuscitation were included in the study. Hypoperfusion was considered if systolic arterial pressure (SAP) was <90 mmHg, heart rate (HR) was >100 beats/min, capillary refill time was >2 s or urine output was <0.5 ml/kg/h for 1 h. Exclusion criteria included bronchial asthma, chronic obstructive or restrictive pulmonary disease, cor pulmonale, structural heart disease, rhythm rather than sinus, pulmonary oedema, evidence of jugular vein thrombosis, intra-abdominal hypertension, history of either irradiation or surgery of the neck region, pregnancy, chronic renal failure, presence of active bleeding or poor echocardiographic window. Initial resuscitation was administered as 30 ml/kg of intravenous (IV) crystalloid over 3 h and norepinephrine infusion 0.05–0.2 μg/kg/min titrated according to patient response.[7] Cardiac arrest or inability to maintain the same vasopressors' dose/ventilator settings during the study period were considered as withdrawal criteria.

All patients were deeply sedated (Ramsay sedation scale was ≥4)[8] by IV infusion (midazolam 0.015–0.07 mg/kg/h and fentanyl 1–1.8 μg/kg/h), paralysed and mechanically ventilated (volume-controlled mode, which was adjusted to maintain a plateau pressure <30 cmH_2O, tidal volume of 8–10 ml/kg, respiratory rate [RR] to achieve normocarbia [$PaCO_2$ 30–40 mmHg], positive end-expiratory pressure [PEEP] of 5 cmH_2O and inspired oxygen fraction [FiO_2] of 0.4–0.6 [ICU- ventilator Dräger Savina 300, serial number ASJL-0177, Lübeck, Schleswig-Holstein Germany]).

Before FC testing, all patients were echocardiographically examined via a phased array transthoracic probe (cardiovascular ultrasound SIEMENS ACUSON X-300, Munich, Germany) to assess if the patients can safely tolerate FC (non-displaced interventricular septum and absence of right or left ventricular failure). After that, the left ventricular outflow tract-velocity time integral (LVOT-VTI) was measured as a surrogate of stroke volume SV using pulsed wave Doppler sampling in the centre of LVOT through the apical five-chamber view before FC.[9] The recorded LVOT-VTI value was the average of three consecutive LVOT-VTI measurements at each measuring point to reduce the impact of respiratory VTI variations.[2,5,10] Echocardiographic studies were conducted by the same senior cardiologist.

FC was administered as IV 500 ml normal saline 0.9% over 15 min.[2,11] LVOT-VTI was reassessed immediately after finishing FC. Patients were defined as fluid responders (Rs) or non-responders (NRs) according to the difference between pre- and post-(FC) LVOT-VTI values. If LVOT-VTI, after FC, had increased by ≥15% compared to the pre-FC value, the patient was considered a fluid R. Otherwise, he was considered an NR. No further fluid was administered on disappearance of any sign of hypoperfusion, the onset of signs of volume overload or being fluid non-responsive. Infusion rates of vasopressors and ventilator settings were not changed during the observation interval.

Immediately before and after FC, both IJVDI% and ETCO2 tension (mmHg) were recorded, but their results did not interfere with patient management. The variation of anteroposterior (AP) diameter of internal jugular vein (IJV (in the side without central venous catheter), during a respiratory cycle, was measured using M-mode with a 12-MHz linear probe positioned perpendicular to the IJV short axis (Ultrasound Toshiba Xaria 100, California, USA) by the attending intensivist (who was blinded to echocardiographic data), with the patient in supine position with head elevated to 30°. The IJVDI (%) = (maximal IJV AP diameter during inspiration − minimum IJV expiratory diameter)/ minimum IJV expiratory diameter.[3] ETCO2 tension was measured using a mainstream infrared gas analyser connected to the tip of endotracheal tube (Monitor Spacelabs Medical Ultraview SL, serial number 1387-104122, Washington, USA). FC-induced ΔETCO2 (mmHg) = ETCO2 after FC– ETCO2 before FC.

Other simultaneously collected data, before and after FC, were HR (beats/min), SAP (mmHg) and central venous pressure (CVP) (cmH_2O) as well as arterial and central venous blood gases. Other collected data were

patients' age, gender, weight, indication of intensive care unit (ICU) admission and Sequential Organ Failure Assessment (SOFA) score.[12]

All eligible patients, who had been admitted to SICU during the 112 study period, were included in the study. The minimum calculated sample size, by OpenEpi, version 3, was 35 patients according to the power of statistical test 80%, confidence interval (CI) 95%, positive predictive value (PPV) of IJVDI (84%)[13] and PPV of ΔETCO2 (95%).[4]

Data analysis was performed using the software Statistical Package for the Social Sciences (SPSS) version 24. Quantitative parametric variables were described as means and standard deviations. Quantitative nonparametric variables were described using median and range. Categorical variables were described using their absolute frequencies. To compare the means of two groups, an independent sample *t*-test was used. Non-parametric test (Mann–Whitney) was used to compare the medians of non-parametric data. For intragroup comparison, paired *t*-test (for normally distributed data) or Wilcoxon signed rank test (for non-normally distributed data) was used. Using MedCalc version 15.8, receiver operating characteristic (ROC) curves were drawn for FC-induced ΔETCO2, IJVDI before FC and their combination in a prediction model (after binary logistic regression). The percentage of FC-induced ΔLVOT-VTI (%) was considered as the gold standard reference. The level of statistical significance was set at 5%.

RESULTS

Out of 161 eligible septic patients admitted to SICU during the study period, nine patients were excluded due to the presence of obstructive, restrictive pulmonary diseases or poor echocardiographic window. In this study, 152 patients were included. Further, 12 patients were withdrawn due to inability to maintain the same vasopressor dose. So, 140 patients completed the study and were considered for statistical analysis. Of them, 51 (36.4%) patients were classified as fluid Rs and 89 (63.6%) as fluid NRs [Figure 1].

The patients' median age was 58 (interquartile range [IQR] 53.25–61.75) years. Seventy-seven out of 140 patients were males and 63 patients were females. Patients' average body weight was 85.3 ± 12.4 kg. Patients were admitted either postoperatively after emergency surgery (56 patients), after elective surgery (25 patients), posttraumatic (44 patients) or due to medical emergencies (15 patients). The median SOFA score of all patients was 12 (ranging from 7 to 18, IOR 10–15). There was no significant difference between fluid Rs and NRs with regard to patients' age, body weight, SOFA score or indications of ICU admission ($P > 0.05$). Male/female ratio was significantly higher in fluid Rs compared to NRs (P 0.036) [Table 1].

No statistically significant difference was recorded between Rs and NRs with regard to baseline ETCO2, acid–base, arterial blood gas parameters and central venous oxygen saturation ($ScvO_2$) ($P > 0.05$). Central venous CO_2 tension ($PcvCO_2$) of NRs was higher than that of Rs when measured either before or after FC ($P < 0.05$). After FC administration, no significant difference was recorded between both groups of patients with regard to acid–base and arterial blood gas parameters ($P > 0.05$). Meanwhile, $ScvO_2$, ETCO2 and FC-induced ΔETCO2 of Rs were higher than those of NRs ($P < 0.05$). No significant change was found in arterial blood gases of NRs ($P > 0.05$), but the bicarbonate (HCO_3) level changed significantly after

Table 1: Comparison between fluid Rs and fluid NRs as patients' characteristics and indication of ICU admission

Parameter			Fluid Rs (*n*=51)	Fluid NRs (*n*=89)	*P*
Age (years)		Median (Range)	56 (25–69)	58 (21–74)	0.077[a]
		IQR	(52–60)	(54–66)	
Gender	Male	Number	34	43	0.036[b]
	Female		17	46	
Body weight (kg)		Mean±SD	83.2±12.3	86.6±12.4	0.122[‡c]
SOFA score		Median (Range)	11 (7–18)	12 (8–17)	0.350[a]
		IQR	(9–15)	(10–15)	
Indication of ICU admission	After emergent surgery	Number	17	39	0.223[b]
	After elective surgery	Number	7	18	0.334[b]
	Posttraumatic	Number	21	23	0.060[b]
	Medical emergency	Number	6	9	0.761[b]

[a]Mann–Whitney test, [b]Chi-square test, [c]Independent *t*-test, ICU – Intensive care unit; IQR – Interquartile range; NR – Non-responders; R – Responders; SOFA – Sequential organ failure assessment; SD – Standard deviation

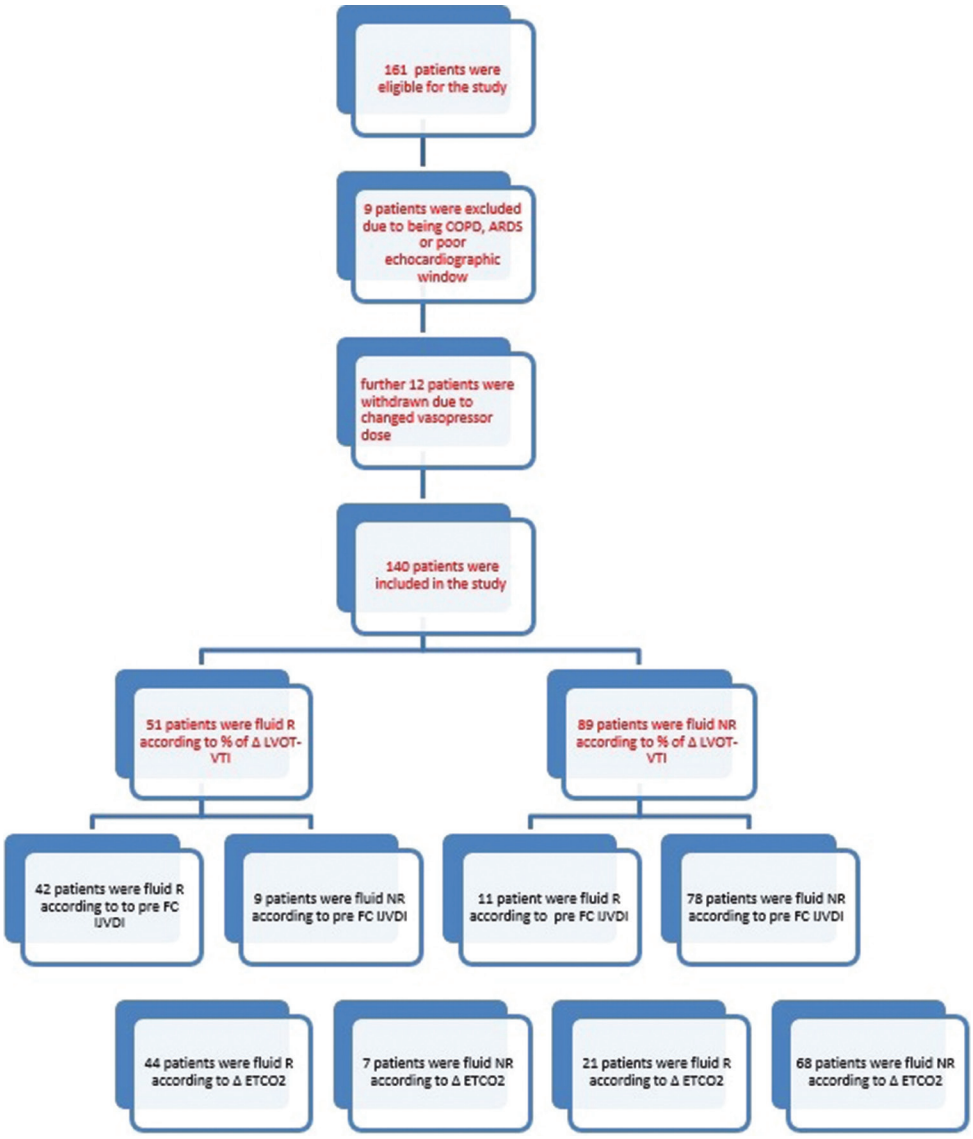

Figure 1: Study flowchart. ΔETCO2 = post- minus pre-(FC) ETCO2, ΔLVOT-VTI: post- minus pre-(FC) left ventricular outflow tract-velocity time interval, CA = cardiac arrest, ETCO2 = end-tidal carbon dioxide, FC = fluid challenge, IJVDI = internal jugular distensibility index, NR = nonresponders, R = responders

FC when compared to baseline values in the same group ($P < 0.05$). In the Rs group, arterial blood gases showed no significant difference between post-FC and baseline values ($P > 0.05$). $PcvCO_2$ of Rs significantly decreased, while pH, HCO_3 level, $ScvO_2$ and ETCO2 values significantly increased after FC compared to baseline values ($P < 0.05$) [Table 2].

There was no significant difference between Rs and NRs in HR (before and after FC), baseline SAP and LVOT-VTI values ($P > 0.05$), but baseline IJVDI was significantly higher in Rs compared to NRs. After FC, SAP and FC-induced change in percentage of LVOT-VTI (ΔLVOT-VTI%) were significantly higher in Rs group than in NRs group ($P < 0.05$). Among Rs, SAP, CVP and LVOT-VTI values significantly increased, while HR and IJVDI values significantly decreased after FC compared to baseline values ($P < 0.05$). After FC, all haemodynamic parameters of NRs (except LVOT-VTI which increased) were comparable to baseline values ($P > 0.05$) [Table 3].

The diagnostic accuracy of FC-induced Δ ETCO2 >2 mmHg was comparable to that of IJVDI > 18% before FC in predicting fluid responsiveness of the studied patients ($P = 0.384$, 95% CI -0.0364-0.0946). A prediction model combining FC-induced ΔETCO2 ≥3 mmHg with pre-(FC) IJVDI% ≥16% achieved significantly higher predictivity of fluid responsiveness when compared to that of either ΔETCO2 ≥2 ($P = 0.003$, 95% CI 0.0255-0.121) or IJVDI >18% ($P = 0.008$, 95% CI 0.0116-0.0772) [Table 4 and Figure 2].

Table 2: Comparison between fluid Rs and NRs with regard to blood gases and ventilatory profile

Parameter			Fluid Rs (*n*=51)	Fluid NRs (*n*=89)	*P*
Arterial pH	Before FC	Median (R) (IQR)	7.33 (7.16–7.5) (7.24–7.39)	7.33 (7.13–7.46) (7.29–7.35)	0.346[a]
	After FC		7.34 (7.2–7.48) (7.26–7.42)	7.32 (7.15–7.45) (7.28–7.34)	0.067[a]
P			<0.0001[b]	0.384[b]	
$PaCO_2$ (mmHg)	Before FC	Median (R) (IQR)	37.4 (27–45) (33.8–38.2)	35.9 (29.6–44) (34–39.6)	0.634[a]
	After FC		37 (28–43.3) (33.9–38.5)	36 (28–43) (33.8–38.9)	0.782[a]
P			0.332[b]	0.110[b]	
$PcvCO_2$ (mmHg)	Before FC	Median (R) (IQR)	42.8 (34–51) (39–44.3)	44 (34–53) (41.7–48)	0.018[a]
	After FC		40 (32–48.4) (37–42.7)	43.4 (34–53.9) (41.1–47.6)	<0.0001[a]
P			<0.0001[b]	0.103[b]	
HCO_3 (mEq/l)	Before FC	Median (R) (IQR)	18 (11.9–30) (16–23)	18.3 (11–28) (16.7–22.7)	0.878[a]
	After FC		18.8 (12–31) (17.3–24.8)	18.6 (11.30–27.8) (17–22.3)	0.294[a]
P			<0.0001[b]	0.044[b]	
PaO_2 (mmHg)	Before FC	Median (R) (IQR)	116 (90–321) (95–144)	135 (80–261) (101–159.5)	0.081[a]
	After FC		118 (93–315) (100–143)	132 (87–260) (102.5–159)	0.133[a]
P			0.157[b]	0.387[b]	
$ScvO_2$ (%)	Before FC	Median (R) (IQR)	67.3 (57.9–83.4) (63–71)	67 (48–86) (59.5–73)	0.278[a]
	After FC		68 (55.6–84.3) (65–75)	66 (50–85) (60–73)	0.025[a]
P			0.035[b]	0.192[b]	
ETCO2 (mmHg)	Before FC	Median (R) (IQR)	30 (25–38) (28–32)	29 (24–38) (27–31)	0.066[a]
	After FC		33 (25–43) (30–35)	29 (25–39) (28–31)	<0.0001[a]
P			<0.0001[b]	0.665[b]	
ΔETCO2 (mmHg)		Median (R) (IQR)	3 (−2 to 6) (2–4)	0 (−4 to 4) (−1 to 1)	<0.0001[a]

[a]Mann–Whitney test, [b]Wilcoxon signed ranks test, ΔETCO2 – Post- minus pre-(FC) ETCO2; FC – Fluid challenge; IQR – Interquartile rang; NR – Non-responders; $PcvCO_2$ – Central venous CO_2 tension; R – Responders; $ScvO_2$ – Central venous oxygen saturation

DISCUSSION

The current study shows that the diagnostic accuracy of FC-induced ΔETCO2 >2 mmHg is comparable to that of pre-(FC) IJVDI >18% for prediction of fluid responsiveness in hypoperfused septic mechanically ventilated patients when FC-induced ΔLVOT-VT ≥15% is used to define SV responsiveness to FC. A model combining ΔETCO2 ≥3 mmHg with IJVDI ≥16% achieved higher predictivity than each independent one.

The accuracy of IJVDI (cut-off values 13%–18%) for fluid responsiveness prediction is comparable to that of pulse pressure variation and inferior vena cava distensibility index (IVCDI) and it is considered easier to measure.[3,13,14] Many trials have assessed either IJVDI or, to a lesser extent, ΔETCO2 as predictors for fluid responsiveness after passive leg raising (PLR) or FC.[2,3,6,13] To our knowledge, the current study was the first to compare their predictivities and add to the importance of FC-induced ΔETCO2 as a simple, easily applicable predictor of fluid responsiveness.

In agreement with the current study, previous studies have revealed that ΔETCO2 ≥5% or ΔETCO2 >2 mmHg can predict fluid responsiveness to PLR in haemodynamically unstable patients.[2,5,15] The current study proved higher predictivity of FC-induced ΔETCO2 ≥2 mmHg (area under the ROC curve [AUC] 0.908) than that of Baloch *et al*.'s[16] study including cardiogenic shock patients (AUC 0.705) and

Table 3: Comparison of haemodynamic parameters before and after fluid challenge in fluid NRs and Rs groups of patients

Parameter			Fluid Rs (*n*=51)	Fluid NRs (*n*=89)	*P*
HR (beats/min)	Before FC	Median (range) (IQR)	93 (60–130) (75–100)	89 (72–130) (86–98)	0.764[a]
	After FC		87 (60–116) (79–98)	89 (75–125) (85–97)	0.242[a]
P			<0.0001[b]	0.880[b]	
SAP (mmHg)	Before FC	Median (range) (IQR)	70 (58–95) (58.5–75)	70 (56–94) (65–76)	0.129[a]
	After FC		81 (60–105) 73.5–86.7)	70 (54–95) (65–77)	<0.0001[a]
P			<0.0001[b]	0.091[b]	
CVP (cmH_2O)	Before FC	Median (range) (IQR)	9 (4–12) (7–10)	12 (6–16) (11–13)	<0.0001[a]
	After FC		11 (4–13) (9–13)	12 (7–16) (11–13)	<0.0001[a]
P			<0.0001[b]	0.055[b]	
IJVDI (%)	Before FC	Median (range) (IQR)	28 (14–39) (22–36)	14 (11–19) (13–17)	<0.0001[a]
	After FC		22 (10.5–37) (17–26)	15 (10–27) (13–18)	<0.0001[a]
P			<0.0001[b]	0.088[b]	
LVOT-VTI (cm)	Before FC	Median (range) (IQR)	16.5 (11.2–22.2) (14.9–18.7)	17 (12.4-23.2) (15.4-19)	0.211[a]
	After FC		20.2 (14.1–25.8) (19.2–22.4)	18 (13.5–23.5) (16–19.5)	<0.0001[a]
P			<0.0001[b]	0.003[b]	
ΔLVOT-VTI%		Median (range) (IQR)	18.7 (15.6–46.4) (16.7–21.2)	3.9 (−12.8 to 14.6) (−3.2 to 8.9)	<0.0001[a]

[a]Mann–Whitney test, [b]Wilcoxon signed ranks test ΔLVOT-VTI – Post- minus pre-(FC) left ventricular outflow tract-velocity time interval; FC – Fluid challenge; IJVDI – Internal jugular distensibility index; NRs – Nonresponders; R – Responders; SAP – Systolic arterial pressure; HR - Heart rate; CVp - Central venous Pressure

Table 4: Performance of ΔETCO2, pre-(FC) IJVDI and their combination as predictors of fluid responsiveness using ΔLVOT-VTI% as gold standard

Parameter	Cutoff value	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)	*P*
ΔETCO2 (mmHg)	>2	0.908 (0.848–0.951)	74.5	94.4	88.4	86.6	80	<0.001
IJVDI before FC (%)	>18	0.938 (0.884–0.971)	82.4	98.9	97.7	90.8	85.7	<0.001
Combined	ΔETCO2 ≥3 + IJVDI before FC ≥16%	0.982* (0.944–0.997)	88.2	95.5	91.8	93.4	91.4*	<0.001

*Significantly higher compared to each independent predictor. ΔETCO2 – Post- minus pre-(FC) ETCO2; ΔLVOT-VTI – Post- minus pre-(FC) left ventricular outflow tract-velocity time interval; AUC – Area under the receiver operating characteristic curve; FC – Fluid challenge; IJVDI – Internal jugular distensibility index; NPV – Negative predictive value; PPV – Positive predictive value, 95% CI - 95% Confidence interval

Jacquet-Lagrèze *et al.*'s[17] study carried out for high-risk surgical patients (AUC 0.800). Heterogenicities between different studies assessing the predictivity of FC-induced ΔETCO2 for fluid responsiveness may be due to different standard references or fluid-loading techniques.[18]

The use of multiple dynamic predictors for fluid responsiveness can improve the diagnostic accuracy of each independent predictor because of assessment of left and right ventricular response to fluid administration.[3] This can be applied to current results as, in combination, ΔETCO2 >3 mmHg increased the predictivity of IJVDI >16% with a significant improvement of overall diagnostic accuracy.

Fluid responsiveness of the right side of the heart (volume/pressure changes) can be transferrable to intrathoracic superior vena cava [SVC], and hence extrathoracic veins (IJVDI).[3] ETCO2 tension increases in response to FC due to the increase in pulmonary blood flow (with increasing CO) that carries more CO_2 for removal by alveolar ventilation.[4,6]

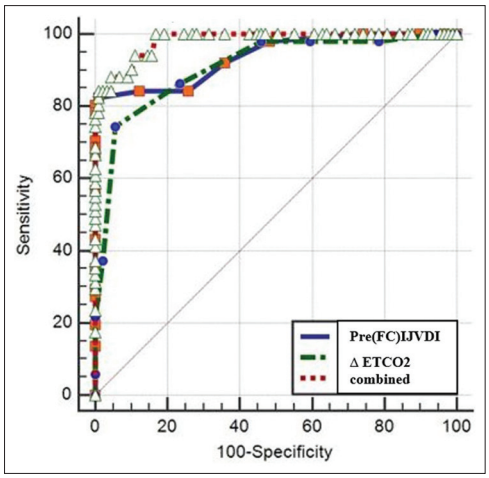

Figure 2: Comparison between the ROC curves of ΔETCO2, IJVDI and their combination as predictors of fluid responsiveness. ETCO2 = post- minus pre-(FC) ETCO2, ETCO2 = end-tidal carbon dioxide, FC = fluid challenge, pre-IJVDI = internal jugular distensibility index before FC, ROC = receiver operating characteristic

The current study is limited as the predictivity of ETCO2 variation for fluid responsiveness cannot be applied to either spontaneously breathing patients or in the presence of metabolic or ventilatory changes.[4,16] IJVDI is *a priori* predictor of fluid responsiveness, while ΔETCO2 is *a posteriori* predictor, and FC, which was used to induce CO_2 change, is not just a test, but it is a treatment option that, if repeated, can lead to volume overload. So, it is recommended to use FC-induced ΔETCO2 if fluid administration is strongly indicated (e.g. persistent circulatory shock signs) and not contraindicated (high risk of volume overload).[5] The overall patient's clinical context and fluid balance should be considered when making interventions based on prediction of fluid responsiveness.

CONCLUSION

The current study concludes that FC-induced ΔETCO2 >2 mmHg can predict fluid responsiveness with a comparable diagnostic accuracy to that of pre-(FC) IJVDI >18% under stable ventilatory and metabolic conditions. A predictive model combining FC-induced ΔETCO2 ≥3 mmHg and IJVDI ≥16% can predict fluid responsiveness with higher accuracy than each independent predictor.

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Conflicts of interest
There are no conflicts of interest.

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