

Correlation Between Changes in End-Tidal Carbon Dioxide and Stroke Volume Variation Detected by Electrical Cardiometry as a Predictor of Fluid Volume Responsiveness in Hemodynamically Unstable Patients in the Intensive Care

Abstract

Background: The requirement for cardiac output (CO) measurements typically restricts the widely used passive leg raising (PLR) test for a set of patients because they need costly or intrusive hemodynamic surveillance equipment. This trial aimed to evaluate the role of end-tidal CO₂ pressure (EtCO₂) monitoring in the prediction of the fluid responsiveness in connection to stroke volume variation (SVV) observed in unstable hemodynamic patients in electrical cardiometry (EC).

Methods: This prospective observational study was carried out on 60 cases aged 18 years or above with hypotension and mechanically ventilated patients in critical care. Patients were classified into two groups according to the SVV: a) Responder group (SVV $\geq$ 10%) and b) non-responder group. All patients were mechanically ventilated and received sedation and muscle relaxation with no spontaneous respiratory effort.

Results: EtCO₂ was significantly increased in responder group than non-responder group at the end (P value = 0.002). SVV was significantly higher in responder group than non-responder group at the baseline (P <0.001). There was a significant negative correlation between SVV and EtCO₂ (r = -0.456, P <0.001) and a significant positive correlation between cardiac index and EtCO₂ (r = -0.456, P = 0.005). Δ EtCO₂ can predict fluid responsiveness significantly (P <0.001) at cut-off > 3 mmHg with 81.4% sensitivity, 88.24% specificity.

Conclusion: EtCO₂ existed as a simple, inexpensive, and non-invasive alternative for the CO in the evaluation of various shock conditions. Δ EtCO₂ can also predict fluid responsiveness significantly (P <0.001) at cut-off > 3 mmHg with 81.4% sensitivity, 88.24% specificity.

Keywords: End-tidal Carbon Dioxide, Stroke Volume Variation, Electrical Cardiometry, Fluid Volume Responsiveness, Hemodynamically Unstable

1. Introduction:

Hemodynamic abnormalities are frequent clinical presentations in intensive care unit (ICU) patients, particularly in severe septic patients. In hemodynamic monitoring and treatment, the assessment of fluid responsiveness has essential clinical importance ⁽¹⁾.

The traditional technique for assessing fluid responsiveness is the fluid challenge. The technique nevertheless causes an additional load of fluid for patients, and several adverse effects such as tissue edema, organ failure, and increased mortality may occur ^(2, 3). It is thus essential to investigate a simple, efficient, and non-invasive technique for assessing fluid responsiveness and volume status ⁽⁴⁾.

The passive leg raising (PLR) technique elicits a transient and reversible increase in cardiac preload through a dynamic preload reliance test. Sudden blood transfer from a semi-recumbent to a supine position with higher legs increases cardiac preload via the venous reservoirs of the legs and splanchnic bed ⁽⁵⁾.

As the hemodynamic effects of PLR are typically rapid and transitory, a rapid-response, ongoing cardiac output (CO) detector is required to detect these changes and accurately distinguish individuals with fluid responsiveness ⁽⁶⁾.

For this aim, many monitoring methods have been proposed: echocardiography, arterial pulse contour analysis ⁽⁷⁾, Esophageal Doppler, and electrical cardiometry (EC), a new non-invasive CO metric ⁽⁸⁾.

This is accomplished by administering a high-frequency transthoracic current and monitoring the voltage changes associated with each heartbeat ⁽¹⁾.

The requirement for CO measurements typically restricts the widely used PLR test to a restricted set of patients because they need costly, onerous, or intrusive hemodynamic surveillance equipment.

For decades, the relationship between partial end-tidal CO₂ pressure (EtCO₂) and CO has been known. Thus, monitoring EtCO₂ in cases with cardiac arrest was suggested to demonstrate a back to spontaneous circulation ^(9, 10). serves as a hemodynamic indication for precordial compression during cardiopulmonary resuscitation ⁽¹¹⁾.

Furthermore, since EtCO₂ was mainly influenced by generating CO₂, alveolar ventilation, and CO tissues, acute fluctuations in EtCO₂ were shown to closely match

changes in CO if stable metabolic conditions and minute ventilation were maintained⁽¹²⁾.

EtCO₂ was thus proposed as a simple, low-cost, and non-invasive alternative to continuous CO monitoring in various stress scenarios⁽¹³⁾.

This research aimed to evaluate the function of EtCO₂ monitoring in predicting the fluid responsiveness in connection to stroke volume variation (SVV) observed in patients with hemodynamic instability in EC.

2. Materials and Methods:

This prospective observational study was carried out on 60 cases aged 18 years or above, both sex with hypotension and mechanically ventilated patients in critical care. **Patients with organ/s failure** at presentation, deep venous thrombosis, limb and pelvic fracture, and embryonic patients were excluded from this study.

Cases were classified into 2 groups according to the SVV: a) Responder group (SVV $\geq$ 10%), b) non-responder group (SVV<10%).

All patients were mechanically ventilated and received sedation and muscle relaxation with no spontaneous respiratory effort.

Monitoring

All patients in ICU were monitored by (pulse oximeter, 5 lead ECG, non-invasive blood pressure, capnogram, temperature probe). A superior vena cava catheter was used to monitor the CVP.

When the patient developed hypotension, mean arterial blood pressure (MAP <65 mmHg) invasive blood pressure for accurate and continuous blood pressure monitoring, and EC was used to detect SVV for CO monitoring.

Hemodynamic monitoring by EC: The circulation of all enrolled patients was measured using EC for stroke volume fluctuation (ICON Cardiotonic, Inc., La Jolla, CA 92307; Osyka Medical GmbH, Berlin, Germany, model C3, serial number 1725303).

We utilized four EC sensors: one about 5 cm above the neck base, second at the neck base, 3rd at the xiphoid level in the lower thorax, and 4th at the lower thorax around 5 cm below the 3rd electrode at the level of the anterior axillary line. EC monitor was connected to the sensor cable, and the patient's data was supplied.

Variations in the volume of strokes (SVV) were monitored constantly in fewer than 30 seconds; after the sensors were placed, the weight, height, gender, and blood pressure were entered, and the ECG and HR were checked in the monitor and EC.

Tidal volume

Tidal volume is essentially every breath a person takes. It is one of the main determinants of minute ventilation and alveolar ventilation. Minute ventilation, also known as total ventilation, is a measurement of the amount of air that enters the lungs per minute. It is the product of respiratory rate and tidal volume. Alveolar ventilation, on the other hand, takes physiological dead space into account. It represents the volume of air that reaches the respiratory zone per minute.

Minute ventilation = respiratory rate x tidal volume

Alveolar ventilation = respiratory rate x (tidal volume - dead space)

Tidal volume is a static lung volume that, along with other static and dynamic lung volumes, is important for diagnosing patients with obstructive and restrictive lung diseases. Spirometry records tidal volume while the patient breathes quietly. In healthy adults, it measures approximately 7 mL/kg of ideal body weight. In an average healthy adult, 500 mL enters the lung with each tidal breath, of which only 350 mL reaches the respiratory zone since dead space measures approximately 150 mL⁽¹⁴⁾.

End-tidal carbon dioxide monitoring

For monitoring of End-tidal carbon dioxide (EtCO₂), it has been collected from the endotracheal tube by means of the side stream CO₂ sensor (from Engstrom Carestation – GE Ventilator, US). The CO₂ sensor may then turn the CO₂ airflow concentration into electrical signals and transmit them to the monitor where they are evaluated and CO₂ concentration characteristics presented.

The study protocol was performed in stages:

In the case of semi-recumbent patients, the first set of measures comprising MAP, heart rate (HR), central venous pressure, SVV, EtCO₂, and cardiac were collected.

The patient's trunk was then reduced from the half-recumbent posture to the supine position using an automated bed elevation method, while the lower limbs were elevated to a 45 angle⁽¹⁵⁾. The patient was maintained for 5 minutes throughout the hemodynamic indicators and EtCO₂ monitoring and recording process.

Patients were classified into fluid responders and non-responders according to SVV.

If SVV ($\geq 10\%$), patients allocated in the fluid responders group and given fluid in the form of normal saline (4ml/kg) over 15 minutes.

After 5 minutes of fluid administration, a new set of measurements was taken, and re-evaluation was done.

When MAP was still <65 mmHg, another PLR test was done, and when SVV ($\geq 10\%$) patients were still fluid responders and were given fluid in the form of normal saline (4ml/kg) over 15 minutes, this was repeated until reaching primary endpoint (MAP ≥ 65 mmHg) or reaching maximum fluid amount (30 ml/kg) over 3 hours.

When PLR is negative SVV ($< 10\%$), the patient is a non-fluid responder and in need of another line to achieve primary endpoint (MAP) ≥ 65 mmHg in the form of vasopressors or inotropes, and EtCO₂ was recorded.

2.1. Measurements

All the patients were subjected to (demographic data (age, weight, sex, BMI), End-tidal carbon dioxide (EtCO₂), mean arterial blood pressure, heart rate, stroke volume variability by cardiometry and cardiac index at baseline and the end, parameters of oxygenation (PaO₂/ FiO₂), Organ/s failure (SOFA score).

The primary endpoint (MAP ≥ 65 mmHg) or reaching maximum fluid amount (30 ml/kg) over 3 hours.

Sample size

The sample size was calculated using MedCalc version 18.2.1. We recruited 60 patients in our study based on the following criteria: 95% confidence limit, 95% power of the study, and area under the curve (AUC) of EtCO₂ to predict fluid responsiveness were 0.93 according to a previous study⁽¹⁶⁾. The null hypothesis was an AUC of 0.75. To overcome dropout, we added 8 cases.

2.3. Statistical analysis

SPSS v26 was used to perform statistical analysis (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and used to compare the two groups using the unpaired Student's t-test. The Chi-square test was used to analyze qualitative variables that were expressed as frequencies and percentages (percent). The Pearson correlation coefficient was used to determine the

degree of correlation between two quantitative variables. ROC curve analysis was used to analyze the overall diagnostic performance of each test. Statistical significance was defined as a P-value ≤ 0.05 using two-tailed tests.

3. Results:

Demographic data were insignificantly different between both groups. SOFA mortality was insignificantly different in both groups. **(Table 1)**

MAP and HR were insignificantly different in both groups at the baseline and the end. EtCO₂ was significantly increased in the responder group than the non-responder group at the end (P = 0.002) and was insignificantly different in both groups at the baseline. SVV was a significant increase in responder group than non-responder group at the baseline (P <0.001). Cardiac index (CI) was significantly decreased in responder group than non-responder group at the baseline (P = 0.003) and was a significant increase in responder group than non-responder group at the end (P = 0.001). PaO₂/FiO₂ was insignificantly different in both groups at the baseline and the end. **(Table 2)**

Duration of mechanical ventilation (MV) and ICU stay were significantly lower in responder group than non-responder group (P = 0.034 and 0.008 respectively), and 28th day mortality was insignificantly different in both groups. **(Table 3)**

There was an insignificant positive mild correlation between MAP and EtCO₂ (r = 0.020, P = 0.879), a significant negative moderate correlation between SVV and EtCO₂ (r = -0.456, P <0.001) and a significant positive mild correlation between CI and EtCO₂ (r = -0.456, P = 0.005). **(Figure 1)**

Δ EtCO₂ can predict fluid responsiveness significantly (P <0.001) at cut-off > 3 mmHg with 81.4% sensitivity, 88.24% specificity, 94.6% PPV, 62.5% NPV, 0.894 AUC (strong predictor) and 0.696 Youden index. **(Figure 2)**

4. Discussion

The passive leg lifting (PLR) technique provides a dynamic preload reliance evaluation, leading to a transient and reversible rise in heart preload. The abrupt blood transfer in the venous tank in the legs and splanchnic compartment moves the patient from a semi-reclining to a supine position with high legs, increasing heart load as a

'self-volume challenge' and improving heart output when both ventricles operate in the steep part of the Frank-Starling curve (CO) ⁽¹⁾.

A quick reaction ongoing CO monitoring is necessary to identify these changes and adequately define individuals who respond with fluids. Numerous strategies for monitoring have been developed for this aim: echocardiography ⁽¹⁷⁾, analysis of arterial pulse contour ⁽⁸⁾, esophageal Doppler ⁽¹⁸⁾, and EC, a new non-invasive CO measurement technique. EtCO₂ has been presented as a low-cost, non-invasive method for continuous CO monitoring in various countries ⁽¹⁹⁾.

In agreement with our results this animal study, Sasaki et al. ⁽²⁰⁾ Students who studied seven sevoflurane-anesthetized, Canine patients on artificial ventilation undergoing open-chest cardiothoracic surgery for isolated ventricular failure, non-invasive electric velocimetry (EV) measurement of CO and SVV compared with a conventional pulmonary artery catheter (PAC) thermodilution technique.

They showed that EV gave more reliable CO readings in dogs during cardiovascular intervention than CI by PAC. Still, not CVP also predicted fluid reactivity in dogs during mechanical breathing ⁽²⁰⁾.

Zhao et al. ⁽²¹⁾ evaluated the accuracy and effectiveness of EC in the perioperative period for plateau-elderly gastrointestinal cancer patients. They were allocated into two equal groups: routine fluid infusion group (control group) and EC system were employed to obtain blood flow dynamic indices including SVV in EC group, and fluid management depends on SVV values. The hospitalization days after surgery in the EC group were much shorter than those in the control group. The crystalloid quantity infused in the EC group was markedly less than that in the control group. They concluded that EC used in the perioperative period could improve the prognosis of old patients undergoing radical correction of gastrointestinal cancers and reduce the incidence of postoperative complications in addition to cost savings

However, in disagreement with our results, Raue et al. ⁽²²⁾ 30 patients treated with severe systemic inflammatory reaction syndrome or hemodynamic instability sepsis in the surgical critical care unit. In a surgical ICU for 10 months, simultaneous thermodilution CO and EV measurements were acquired. They discovered that the results of CO estimates using transthoracic thermodilution and electrical velocimetry were not in accordance. In this experiment, electrical velocimetry cannot substitute intrusive surveillance.

Also, Cox et al. ⁽²³⁾ where 50 cases with ASA 3-4. simultaneously measuring CI through continuous pulmonary thermodilution, thoracic bioimpedance, and standard hemodynamics were evaluated using Aesculon® electronic cardiometry bio impedances (Aesc) for accuracy, precision, and trends in CI measurements compared to continuous pulmonary artery thermoses. They found that the CI acquired by EC's continuous PAC and CI in cardiac surgery patients is uninterchangeable. This distinction may be due to the skin incision made after cardiac surgery.

In the present study, EtCO₂ significantly increased in the respondent group at the end (P = 0.002). It was significantly different in both baseline groups. SVV increased in the respondent group significantly than in the non-responder at the baseline group (P <0.001), and in each group at the end was insignificantly different. CI dropped considerably at the baseline in the response group and the non-responder group (P = 0.003) and rose towards the end of the respondent group much as the non-responder group (P = 0.001).

In agreement with our results, Jin X et al. performed an animal study that caused a hemorrhagic shock to bleed in five pigs followed by bloodshed reinfusion. The injection of live Escherichia coli caused septic shock in five pigs. The cardiogenic shock followed a period of global myocardial ischemia after ventricular fibrillation was induced and reversed in six pigs. EtCO₂ has been monitored constantly. Intermittently, the cardiac index was assessed using standard thermodilution methods. The EtCO₂ cardiac index was linked.

Regarding to Δ EtCO₂ can predict fluid responsiveness significantly (P <0.001) at cut-off > 3 mmHg with 81.4% sensitivity, 88.24% specificity, 94.6% PPV, 62.5% NPV, 0.894 AUC (strong predictor) and 0.696 Youden index .There were insignificant correlations between Δ EtCO₂ and all of Δ MAP, Δ SVV and Δ CI in responder group (r = -0.210, -0.001 and -0.057 respectively, P = 0.176, 0.993 and 0.717 respectively).

In agreement with our findings, García et al. ⁽²⁴⁾ who reported that the PLR-induced increase regions of CO and EtCO₂ (0.97 ± 0.03 SE; CI 95%: 0.85 to 0.99 and 0.94 ± 0.04 SE; CI 95%: 0.82 to 0.99 and 0.94 ± 0.04 SE were not statistically different. Increased by 5% in EtCO₂ or ~ 12% in PLR fluid responsiveness predicted a sensitivity of 90.5% (95% CI: 69.9% to 98.8%) and 95.2% (95% CI: 76.2% to 99.9%) respectively, with a specificity of 93,7%. (95 percent CI: 69.8 to 99.8 percent).

Also, Monnet et al. ⁽¹⁶⁾ reported that there were correlations between fluid-induced variations in EtCO₂ and CI ($r(2) = 0.45$, $p = 0.0001$). Because of the 40 patients with PLR, volume expansion improved CI by 15% in 21 "volume responders." A PLR-induced rise in EtCO₂ by 5% predicted the fluid CI increment by 15%, with a sensitivity of 71% (95% confidence interval: 48%-89%) and a specificity of 100% (82%-100%). The ability to anticipate the changes in CI caused by PLR was no different. The area under the receiver function curve (ROC) for variations in pulse pressure caused by PLR was not statistically different from 0.5.

Moreover, Xiao-ting et al. ⁽²⁵⁾ stated the area underneath the curve was 0.849 (95% confidence interval, 0.739-0.930). During the mini-FC, fluid reactance with a 93,4% specificities and 33,3% sensitivity in a receiver operational curve was presented to exceed or equal to 3%, and AUC was 0,781. (95 percent confidence interval, 0.646-0.915).

Our study has some limitations, such as the Sample size being relatively small and may need further studies with increasing sample size. More randomized trials need to be conducted to verify the findings of our study.

5. Conclusions:

EtCO₂ existed as a simple, inexpensive, and non-invasive alternative for CO in evaluating various shock conditions. Δ EtCO₂ can also predict fluid responsiveness significantly ($P < 0.001$) at cut-off > 3 mmHg with 81.4% sensitivity, 88.24% specificity

Ethical Approval and Consent :

Approval from the institutional ethical committee (Approval code: 32880/01/19) and registration on clinicaltrials.gov (ID: NCT03932617) was done before recruiting patients. A written informed consent was obtained from the patients.

6. References

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Table 1: Demographic data and SOFA mortality in both groups

		Responder Group (n = 43)	Non-responder Group (n = 17)	P value
Age (years)		41.88 ± 10.14	38.35 ± 11.77	0.251
Sex	Male	24 (55.8%)	11 (64.7%)	0.529
	Female	19 (44.2%)	6 (35.3%)	
Weight (kg)		80.65 ± 10.88	75.94 ± 10.15	0.129
Height (m)		1.63 ± 0.07	1.61 ± 0.08	0.328
BMI (kg/m ²)		30.41 ± 4.66	29.49 ± 4.77	0.495
SOFA		1.53 ± 0.98	1.88 ± 1.22	0.255

Data presented as mean ±SD or frequency (%), BMI: body mass index, SOFA: sequential organ failure assessment score, * significant as P value <0.05

Table 2: MAP (mmHg) , HR (beats/min) and EtCO₂ (mmHg), SVV (%), CI (L/min/m²) and PaO₂/FiO₂ in both groups

	Responder Group (n = 43)	Non-responder Group (n = 17)	P value
MAP			
Baseline	53.47 ± 6.53	55.53 ± 5.83	0.261
End	73.44 ± 5.17	71.06 ± 3.38	0.085
HR			
Baseline	112.23 ± 9.85	113.47 ± 10.90	0.672
End	87.35 ± 7.46	89.71 ± 13.32	0.388
EtCO₂			
Baseline	27.91 ± 2.87	27.35 ± 2.87	0.503
End	32.58 ± 3.21	29.47 ± 3.47	0.002*
SVV			
Baseline	14.91 ± 2.87	6.59 ± 1.54	<0.001*
End	7.81 ± 2.68	6.53 ± 1.12	0.062
CI			
Baseline	2.63 ± 0.52	3.12 ± 0.62	0.003*
End	3.73 ± 0.40	3.27 ± 0.58	0.001*
PaO₂/FiO₂			
Baseline	254.60 ± 60.81	227.18 ± 72.33	0.141
End	291.79 ± 59.74	285.71 ± 69.76	0.736

Data presented as mean ±SD MAP: mean arterial blood pressure, HR: heart rate, EtCO₂: end-tidal CO₂ pressure, SVV: stroke volume variation, *: significant as P value <0.05

Table 3: Duration of MV, ICU stay and 28th day mortality in both groups

		Responder Group (n = 43)	Non-responder Group (n = 17)	P value
Duration of MV (days)		3.70 ± 1.15	4.47 ± 1.46	0.034*
ICU stay (days)		6.79 ± 1.60	8.18 ± 2.10	0.008*
28 th day mortality (N)	Died	10 (23.3%)	8 (47.1%)	0.070
	Alive	33 (76.7%)	9 (52.9%)	

Data presented as mean ±SD or frequency (%), * Significant as P value <0.05, ICU: intensive care unit, MV:

Mechanical ventilation

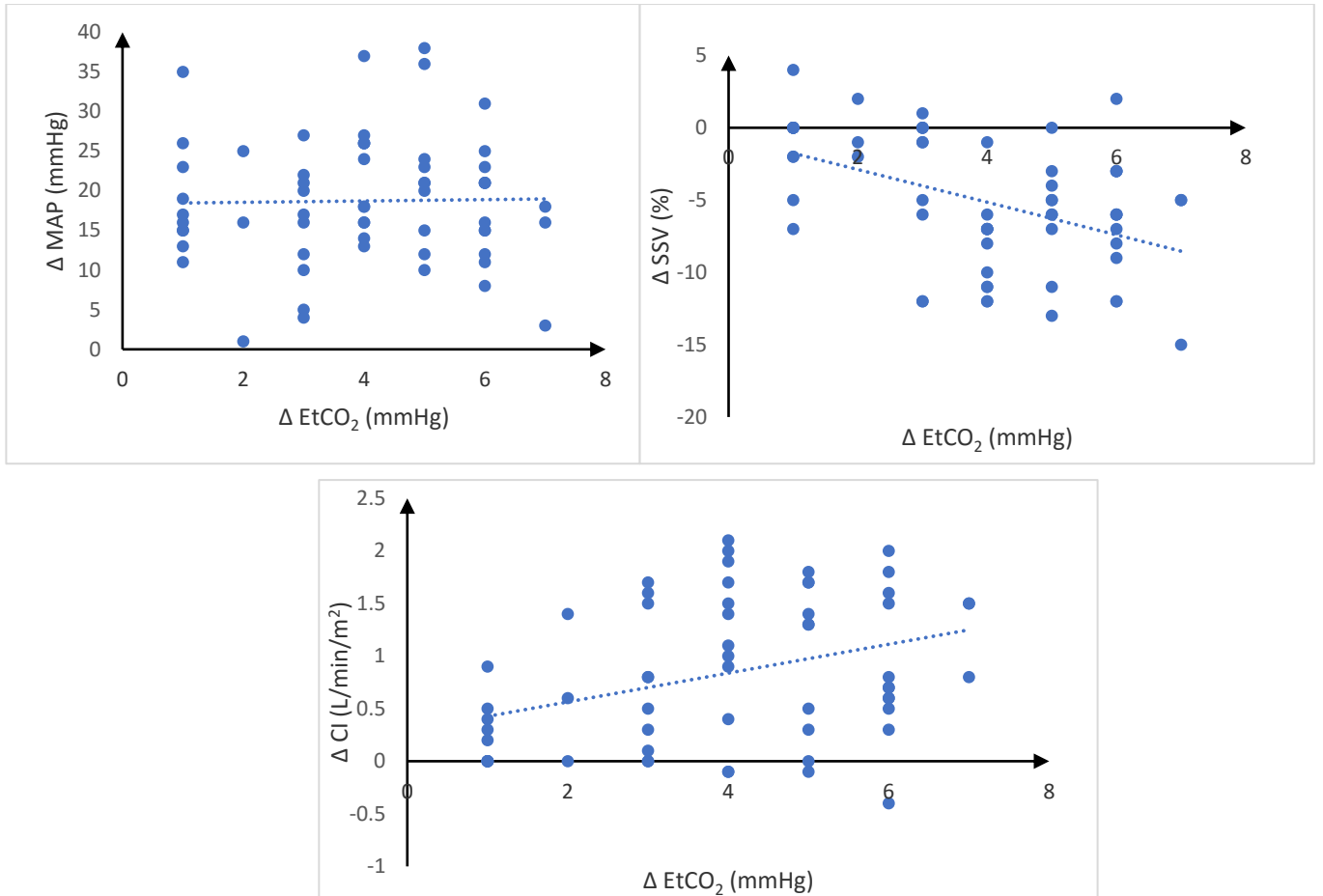


Figure 1: Correlation between ΔEtCO_2 and (ΔMAP , ΔSVV and ΔCI)

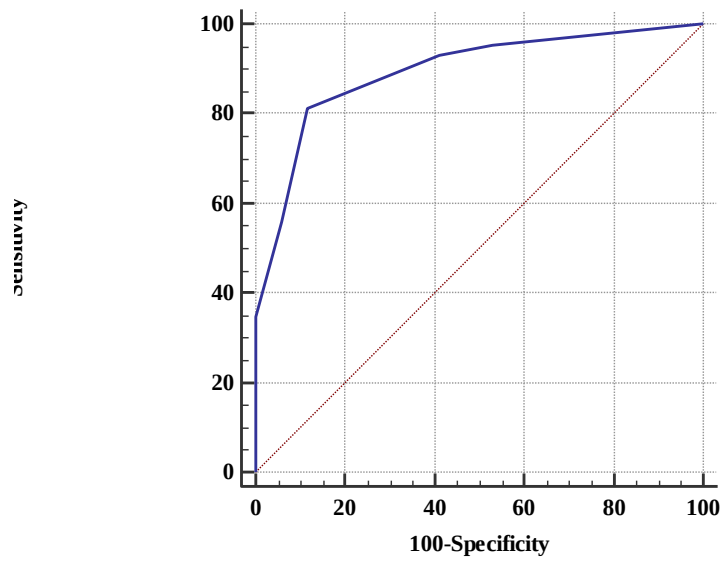


Figure 2: ROC curve of Δ EtCO₂ in prediction of fluid responsiveness

Figure captions:

Figure 1: Correlation between ΔEtCO_2 and (ΔMAP , ΔSVV and ΔCI)

Figure 2: ROC curve of ΔEtCO_2 in prediction of fluid responsiveness