Title: Central venous–arterial PCO_2 gap and LVOT-VTI as predictors of fluid responsiveness in patients with severe shock.

Abstract

Background& aim: Shock is characterized by inadequate tissue oxygenation due to impaired oxygen delivery, increased demand, or inefficient utilization. Assessing fluid responsiveness is crucial to avoid under- or over-resuscitation. The central venous-to-arterial CO_2 difference (Pcv-aCO_2 gap) and left ventricular outflow tract velocity-time integral (LVOT-VTI) are proposed dynamic and biochemical markers for guiding fluid therapy. The study was done to evaluate the predictive value of Pcv-aCO_2 gap and LVOT-VTI for fluid responsiveness in critically ill patients with shock following a mini-fluid challenge.

Methods: This prospective cohort study enrolled 140 adult ICU patients (APACHE II ≥25) requiring vasopressors and serum lactate 2 mmol/L.this study was done in Assiut University Hospital between January 2023–January 2024. Exclusions included poor echocardiographic windows, severe COPD, or advanced liver disease. Patients received a 250 mL crystalloid mini-fluid challenge (normal saline0.9%), and fluid responsiveness was defined as a ≥12% increase in LVOT-VTI. Pcv-aCO_2 gap was measured before and after fluid administration.

Results: Out of 140 patients, 100 (71.4%) were responders and 40 (28.6%) non-responders. Non-responders were older, more often female, and had higher rates of diabetes. Meanwhile, mean arterial pressure was better in responder group. Pcv-aCO_2 gap was significantly higher in non-responders before (7.98 ± 2.90 vs. 5.09 ± 1.20 mmHg; $p<0.001$) and after fluid challenge (6.18 ± 1.78 vs. 2.44 ± 1.67 mmHg; $p<0.001$). LVOT-VTI increased significantly only in responders. Pcv-aCO_2 gap 6 mmHg predicted non-responsiveness with 89% sensitivity, 82% specificity, and 85% accuracy. Non-responders had longer ICU stay, greater need for mechanical ventilation, and higher mortality.

Conclusion: Combining LVOT-VTI and Pcv-aCO_2 gap provides a practical, non-invasive approach to assess fluid responsiveness. A Pcv-aCO_2 gap 6 mmHg with minimal LVOT-VTI change reliably identifies non-responders, highlighting the limitations of conventional perfusion markers and supporting individualized fluid management in critically ill patients.

Keywords:

Hemodynamic monitoring; Mini-fluid challenge; Tissue perfusion; Critical care; Vasopressor therapy.

Introduction

Shock is a condition characterized by inadequate tissue and cellular oxygenation, resulting from decreased oxygen delivery, increased oxygen demand, impaired oxygen utilization, or a combination of these factors. Managing fluid balance in patients with acute hemodynamic instability is challenging, as intravenous fluids can enhance stroke volume and tissue perfusion within the limits described by the Frank-Starling law **[1]**.

The venous-to-arterial carbon dioxide tension difference serves as an indirect indicator of cardiac output by reflecting the balance between CO2 production and its delivery to the lungs. In patients with septic shock, studies have observed inverse changes over time between the central venous-to-arterial CO2 tension difference (Pcv-aCO2 gap) and cardiac output, highlighting its potential utility in monitoring hemodynamic status **[2]**.

Traditional dynamic indices such as pulse pressure variation (PPV), stroke volume variation (SVV), and passive leg raising have been widely used to predict preload responsiveness. However, these methods have important limitations, including dependence on controlled mechanical ventilation, regular cardiac rhythm, and adequate tidal volume, which restrict their applicability in many ICU patients. In contrast, integrating the left ventricular outflow tract velocity–time integral (LVOT-VTI), a real-time echocardiographic measure of stroke volume change, with the central venous–arterial carbon dioxide difference (Pcv-aCO_2 gap), a biochemical marker of tissue perfusion adequacy, provides a comprehensive evaluation

of both macro- and microcirculatory responses to fluid therapy. This combined approach may therefore overcome the physiological and technical limitations of conventional surrogates and enable a more individualized assessment of fluid responsiveness at the bedside [3]

Clinical studies have shown that the ratio of $P_{cv\text{-}a}CO_2$ over the arterial-to venous oxygen content was a good indicator of oxygen supply dependency (tissue hypoxia) in critically ill patients. This indicator could perhaps be used to identify such patients and guide the usage of $P_{cv\text{-}a}CO_2$ [2,4] . In this context, our prospective, hospital-based study evaluated the use of left ventricular outflow tract-velocity time integral (LVOT-VTI) and the central venous-to-arterial carbon dioxide difference (Pcv-aCO2 gap) as dynamic and biochemical predictors of fluid responsiveness following a mini-fluid challenge in shocked patients

Patients and Methods:

Study setting& design

This was a single-center, prospective observational study that was conducted at Critical Care Unit (CCU), Internal Medicine Department at Assiut University Hospital. It was done in the period between January 2023 and January 2024.

This study was an observational, non-interventional cohort study; fluid administration and clinical management followed standard ICU protocols.

Inclusion and exclusion criteria

The study included critically ill adult patients (≥18 years) admitted with shock requiring vasopressor support. **Vasopressor requirement** was defined as the need for continuous norepinephrine infusion at ≥0.1

µg/kg/min **for at least 30 minutes to maintain a mean arterial pressure (MAP) ≥65 mmHg**.

Shock type was defined according to established diagnostic criteria:
• **Septic shock** — suspected or confirmed infection with a serum lactate 2 mmol/L despite adequate fluid resuscitation and ongoing vasopressor therapy to maintain MAP ≥65 mmHg (Sepsis-3 definition) [5]
• Hypovolemic shock — evidence of reduced intravascular volume from blood loss or fluid depletion
• Mixed shock — coexistence of distributive and hypovolemic components and coexistence of distributive and cardiogenic shock without elevated left atrial pressure.
Any patient with one or more was excluded; suboptimal imaging quality precluding accurate LVOT-VTI measurement, patients with cardiogenic shock, or severe heart failure, patients with severe chronic obstructive pulmonary diseases and/or advanced hepatic disease

Methodology:

Each patient was subjected to, full history and clinical examination. Patients' demographic data, comorbidities, acute physiology and chronic health evaluation (APACHE) II score were reported. Routine investigations were done (blood glucose, kidney function tests, CBC). Blood gases (ABG, and VBG) were withdrawn. Relevant microbiological data, sepsis management bundles according to surviving sepsis campaign 2021 guidelines were subjected to patients within 1 hour of diagnosis

Blood gases analysis and calculation of Pcv–aCO_2 gap.

Arterial and central venous blood gases were measured. The central venous blood was collected from a central venous catheter with the tip confirmed to be in the superior vena cava, near or at the right atrium, by radiograph. Pcv–aCO_2 gap was calculated as the difference between the central venous carbon dioxide tension and the arterial carbon dioxide tension. High gap was defined with $P_{cv\text{-}a}CO_2$ 6 mmHg) and normal gap was defined with $P_{cv\text{-}a}CO_2 \leq 6$ mmHg [6]

Echocardiography

The left ventricular (LV) outflow time-velocity integral (TVILVOT) in centimeters will be obtained by placing a pulsed wave sample volume in the LV outflow tract when imaged from the apical 5-chamber view.

Fluid challenge test (FCT)

We gave the patient 250 ml crystalloid (normal saline 0.9%) as a mini fluid challenge. LVOT VTI was measured by pulsed wave Doppler before and after the fluid challenge (100 x SV max-SV min/ (SV max + SV min) x 0.5). echocardiography and blood gases were repeated at 5 minutes after infusion of FCT, All LVOT-VTI measurements were performed by the same experienced operator, who was blinded to Pcv-aCO_2 gap results, to minimize inter-observer and measurement bias.

according to the results of the fluid challenge test, we subdivided our patients to responders and non-responders, with an increase of 12% defining fluid responsiveness.[7]

Enrolled patients were divided based on their initial ΔPCO2, Mini-fluid challenge test to :

High gap was defined with $P_{cv-a}CO_2$ 6 mmHg) and normal gap was defined with $P_{cv-a}CO_2 \leq 6$ mmHg

Responder and non-responder to mini FCT

Statistical analysis and Sample size calculation:

G*Power 3.1.9.2 software program was used to calculate the sample size. Based on the 28-day mortality percentage of ICU patients 29.6 % [^]. With a confidence limits 5% and a confidence level of 80% the minimum patients required for this study is 137 participants. To avoid any drop out were enrolled a total of 140 critical ill-patients

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). The Shapiro test was used to determine compliance of the data to normal distribution. Quantitative data were expressed as mean ± standard deviation (SD).

Quantitative data with normal distribution were compared by Student t test (between two means) while quantitative data with abnormal distribution were compared by Mann-Whitney U test (between two means). Chi^2 test was used for comparison the nominal data.

Predictors of fluid non-responsiveness were identified using multivariable logistic regression analysis. Also, accuracy of $P_{cv-a}CO_2$ in prediction the fluid responsiveness in critically ill-patients was determined by receiver operator characteristics curve (ROC). Level of confidence was kept at 95% and hence, *p* value was considered significant if < 0.05.

The primary endpoint was to determine the predictive value of Pcv-aCO_2 gap for fluid responsiveness defined by ≥12% increase in LVOT-VTI

after mini-fluid challenge. Secondary endpoints included ICU stay, need for mechanical ventilation, and mortality.

:**Ethical approval and consent of participants**

The study was conducted according to the principles of the Declaration of e withHelsinki and was approved by the Hospital's Ethics Committe approval number IRPThe purpose of the study was .٢٠٠٠٧٢-٢٠٢٣-٠٤ .and written informed consent was obtained ،explained to all participants .٠٥٦٧٩٧٧٨gov with NCT.The study was registered on clinicaltrials

Results

Based on LVOT-VTI after FCT; a total of 40 (28.6%) patients were considered to be fluid non-responsive (non-responder group) and 100 (71.4%) patients were considered fluid responsive (responder group).

Baseline data of patients based on respond to FCT (table 1):

Responder group had significantly lower mean age (59.67 ± 12.98 vs. 65.01 ± 10.65 (years); $p< 0.001$). Also, majority of responder group (80%) was males while majority of non-responders was females (62.5%).

Table 1: Baseline data of patients based on respond to FCT

	Response to challenge test		***P* value**
	Responder (n= 100)	**Non-responder (n= 40)**	
Age (years)	59.67 ± 12.98	65.01 ± 10.65	< 0.001
Sex			0.01
Male	80 (80%)	15 (37.5%)	
Female	20 (20%)	25 (62.5%)	
Body mass index (kg/m^2)	23.45 ± 2.09	24.11 ± 1.87	0.81
Smoker	12 (12%)	4 (10%)	0.23
Diabetes mellitus	19 (19%)	15 (37.5%)	0.04
Hypertension	22 (22%)	10 (25%)	0.44
CKD	7 (7%)	2 (5%)	0.19

Hepatic disease	6 (6%)	3 (7.5%)	0.08

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. CKD: chronic kidney disease; FCT: fluid challenge test

Type of shock and hemodynamics based on respond to challenge test (table 2):

Both groups had insignificant differences as regard hemodynamics changes before or after challenge test with exception of improvement in MAP was noticed in responder group after the test.

Table 2: Type of shock and hemodynamics based on respond to fluid challenge test

	All patients (n= 140)	**Response to challenge test**		***P*1 value**
		Responder (n= 100)	**Non-responder (n= 40)**	
Type of shock				0.71
Septic	81 (57.9%)	60 (60%)	21 (52.5%)	
Hypovolemic	14 (10%)	10 (10%)	4 (10%)	
Combined shock	45 (32.1%)	30 (30%)	15 (37.5%)	
Heat rate (b/m)				
Before the test	99.90 ± 4.56	100.45 ± 8.70	99.67 ± 3.45	0.23
After the test	98.80 ± 4.10	98.01 ± 2.56	99.01 ± 4.31	0.67
P 2 value	0.09	0.11	0.45	
SBP (mmHg)				
Before the test	98.33 ± 6.11	99.56 ± 5.09	97.45 ± 2.6	0.10
After the test	106.89 ± 8.10	109 ± 7.98	104.03 ± 8.19	0.88
P 2 value	0.09	0.16	0.19	
DBP (mmHg)				
Before the test	56.17 ± 6.90	56.78 ± 7.80	55.32 ± 6.09	0.11
After the test	58.55 ± 7.10	59.11 ± 8.11	59 ± 7	0.20
P 2 value	0.45	0.18	0.10	
MAP (mmHg)				
Before the test	70.55 ± 6.80	71 ± 5.55	70.17 ± 6.22	0.54
After the test	75.60 ± 5.91	76 ± 6.78	72 ± 5.60	**0.02**
P 2 value	**0.02**	**0.01**	0.19	
Pulse pressure (mmHg)				
Before the test	43.90 ± 12.19	44.05 ± 13.45	43.19 ± 11.09	0.34
After the test	56.11 ± 16.59	56.09 ± 15.98	56.17 ± 17.08	0.61
P 2 value	0.43	0.09	0.18	

Data expressed as mean (SD). P value was significant if <0.05.

P1 compares between both groups, p2 compares data of the same group before and after the test

Venous and arterial blood gases (supplementary tables 1-2):

Both groups had insignificant differences as regard venous and arterial blood gases before and after FCT.

responders had significantly lower Pcv–aCO_2 gap before (6.27 ± 1.20 vs. 7.98 ± 2.90; *p*< 0.001) and after (2.44 ± 1.67 vs. 6.18 ± 1.78 (mmHg); p< 0.001) the challenge test. Pcv–aCO_2 gap was significantly decreased in responder group after the test compared to data before the test. Meanwhile, Pcv–aCO_2 gap was insignificantly decreased in non-responder group after the test compared to data before the test

Table 3: Pcv–aCO_2 gap in the studied groups before and after challenge test

	All patients (n= 140)	**Response to challenge test**		***P*1 value**
		Responder (n= 100)	**Non-responder (n= 40)**	
Before the test	6.89 ± 2.11	6.27 ± 1.20	7.98 ± 2.90	**< 0.001**
After the test	3.90 ± 1.90	2.44 ± 1.67	6.18 ± 1.78	**< 0.001**
***P*2 value**	**0.01**	**< 0.001**	0.99	

Data expressed as mean (SD). *P* value was significant if < 0.05.
P 1 compares between both groups, *p*2 compares data of the same group before and after the test

Echocardiographic findings and LVOT-VTI based on response (table 4):

Responders had significantly higher LVOT-VTI (18.45 ± 1.45 vs. 15.90 ± 1.24 (cm); *p*= 0.02) after challenge test.

Table 4: Echocardiographic findings and LVOT-VTI based on response

	Response to challenge test		***P* value**
	Responder (n= 100)	**Non-responder (n= 40)**	
Ejection fraction (%)	47.66 ± 5.22	46.45 ± 6.21	0.34
LVEDD (cm)	5.11 ± 0.14	5.22 ± 0.22	0.54
LVESD (cm)	3.67 ± 0.79	3.70 ± 0.11	0.68
Stroke volume (ml)	48.91 ± 5.68	47.11 ± 2.18	0.90
E-wave/A-wave	1.5 ± 0.20	1.53 ± 0.16	0.26

Mitral deceleration time (s)	0.18 ± 0.05	0.17 ± 0.01	0.60
Cardiac output (l/minute)	3.4 ± 0.44	3.0 ± 0.89	0.88
LVOT-VTI (cm)			
Before the test	16.56 ± 2.24	16.08 ± 3.11	0.20
After the test	18.45 ± 1.45	15.90 ± 1.24	**0.02**

Data expressed as mean (SD). *P* value was significant if < 0.05.

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVOT-VTI; left ventricular outflow tract – velocity time integral.

Outcome in studied patients based on response to challenge test (table 5):

Length of stay was significantly longer among non-responder group (15.02 ± 3.46 vs. 7.89 ± 2.22 (days); $p< 0.001$). Also, non-responder group had significantly higher frequency of need to MV (50% vs. 13%; $p< 0.001$) and mortality (37.5% vs. 10%; $p< 0.001$).

Table 5: Outcome in studied patients based on response to challenge test

	Response to challenge test		***P* value**
	Responder (n= 100)	**Non-responder (n= 40)**	
APACHE-II	31.34 ± 2.19	33.19 ± 3.21	0.34
Length of stay (days)	7.89 ± 2.22	15.02 ± 3.46	**< 0.001**
Need to MV	13 (13%)	20 (50%)	**< 0.001**
Mortality	10 (10%)	15 (37.5%)	**< 0.001**

Data expressed as mean (SD), frequency (percentage). *P* value was significant if < 0.05.
MV: mechanical ventilation

Correlation between Pcv–aCO_2 gap and LVOT-VTI before and after FCT (figures 1-2):

There was significant negative correlation between LVOT-VTI and Pcv–aCO_2 gap before (r= -0.69) and after (r= -0.65) FCT.

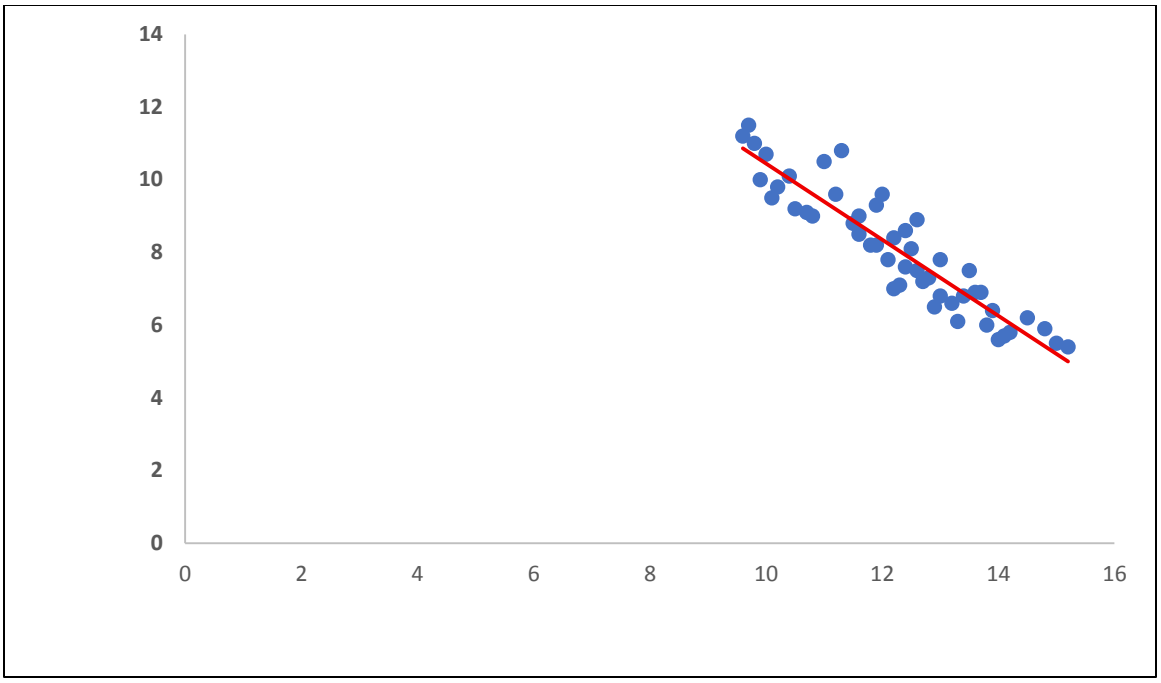

Figure 1: Correlation between Pcv–aCO_2 gap gap and LVOT-VTI before FCT

A significant inverse correlation was observed between baseline LVOT-VTI and Pcv–aCO_2 gap (r = −0.69), indicating an association between reduced stroke volume and impaired CO_2 clearance before fluid challenge.

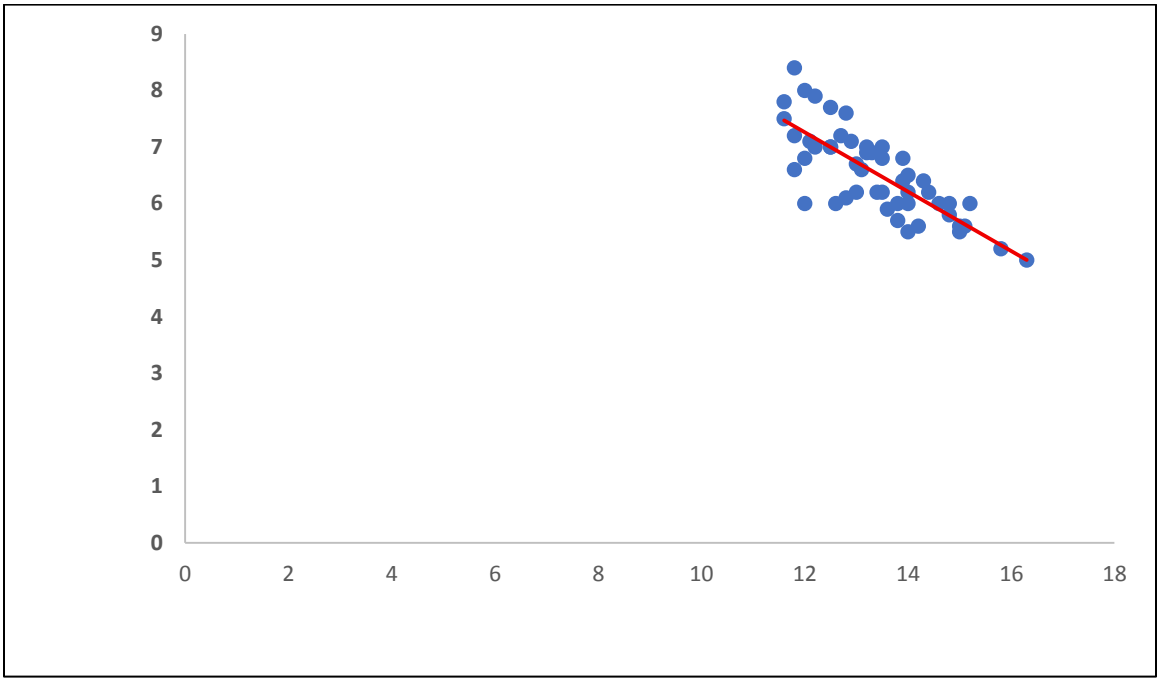

Figure 2: Correlation between Pcv–aCO_2 gap and LVOT-VTI after FCT

The inverse correlation persisted after fluid challenge (r = −0.65), suggesting that failure to augment stroke volume is associated with sustained perfusion abnormalities in fluid non-responders.

Predictors of fluid non-responsiveness after FCT (table 6, figure 3):

The predictors for fluid non-responsive in critical patients after challenge test were old age (odd's ratio= 2.09) and Pcv–aCO_2 gap (odd's ratio= 4.33). Pcv–aCO_2 gap at cutoff 6 mmHg had 89% sensitivity, 95% specificity with overall accuracy was in predicting fluid non-responsive in critical patients after challenge test

Table 6: Predictors of fluid non-responsiveness in critical patients after challenge test

Variables	Odd's ratio	95CI	*P* value
Old age	2.09	1.89- 4.89	**< 0.001**
Female sex	0.87	0.34- 1.67	0.11
Diabetes mellitus	1.09	0.40- 2.22	0.29
Smoking	1.23	0.89- 2.46	0.51
Urea (mmol/l)	0.98	0.55- 1.98	0.31
Creatinine (mmol/l)	1.17	0.34- 2.34	0.89
Ph	1.80	0.78- 3.01	0.34
$P_{cv-a}CO_2$ gap	4.33	2.67- 9.6	**< 0.001**
Ejection fraction	1.74	0.98- 2.90	0.87

Data expressed as mean (SD), frequency (percentage). *P* value was significant if < 0.05.
MV: mechanical ventilation

Table 7: Predictive value of $P_{cv-a}CO_2$ gap test in fluid non-responsiveness

Variables	Value
Sensitivity	89%
Specificity	82%
Positive predictive value	80%
Negative predictive value	90%
Accuracy	85%
Cutoff point	6
Area under curve	0.854
P value	< 0.001

P value was significant if < 0.05.

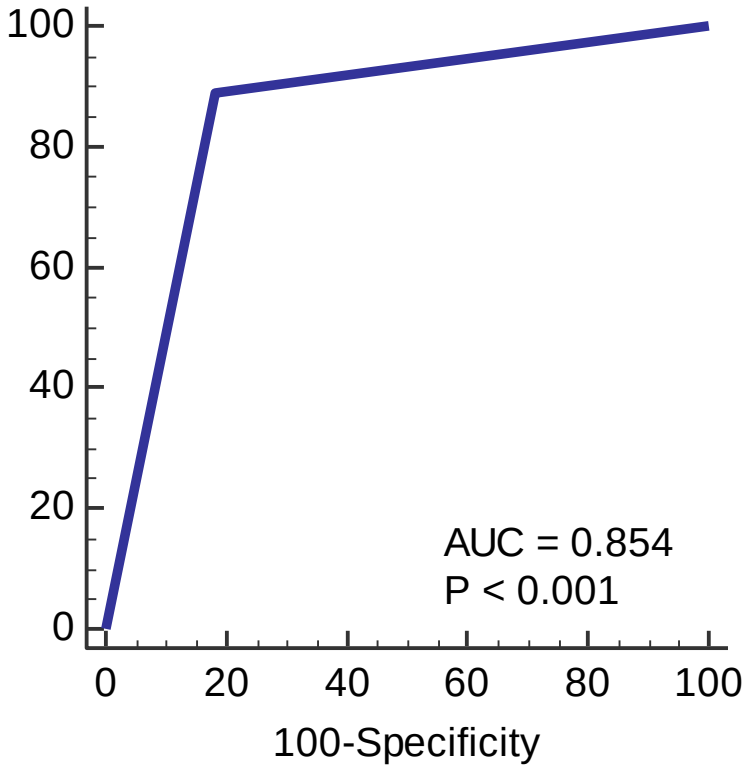

Figure 3: Predictive value of $P_{cv\text{-}a}CO_2$ gap test in fluid non-responsiveness in critical patients after challenge test

Discussion

The optimal cardiac output is achieved when it matches metabolic needs with adequate organs perfusion. This can be indirectly assessed by measuring Pcv–aCO_2 gap. The Pcv–aCO_2 gap is a surrogate for cardiac output. It was suggested that Pcv–aCO_2 gap 6 mmHg suggests a persistent shock state that may be amenable to fluid resuscitation with or without inotropes support (Malate 2018) [3]

The principal finding of this study was that fluid responders exhibited a significantly lower Pcv–aCO_2 gap both before and after fluid challenge, whereas non-responders maintained a persistently elevated gap. Moreover, the Pcv–aCO_2 gap emerged as the strongest independent predictor of fluid non-responsiveness (OR 4.33), indicating a clinically meaningful effect size. A cutoff value 6 mmHg demonstrated excellent discriminatory performance (AUC 0.854), supporting its robustness as a bedside marker.

From a physiological perspective, the central venous–arterial CO_2 difference reflects the adequacy of blood flow required to remove metabolically produced CO_2 from peripheral tissues. Vallet 2018 demonstrated that an increased veno-arterial CO_2 gradient during shock reflects inadequate tissue perfusion due to insufficient blood flow rather than impaired oxygen delivery alone[11].

Accordingly, a persistently elevated Pcv–aCO_2 gap following fluid administration suggests ongoing flow inadequacy despite apparent macrocirculatory optimization.

This phenomenon likely reflects microcirculatory stagnation or heterogeneous perfusion, a well-recognized feature of septic and mixed shock states. In such conditions, normalization of systemic variables such as mean arterial pressure or cardiac output does not necessarily translate into effective tissue perfusion, highlighting the dissociation between macro- and microcirculation [12].

This interpretation is further supported by the significant negative correlation observed between LVOT-VTI and the Pcv–aCO_2 gap, both before and after fluid challenge. As stroke volume increased, the Pcv–aCO_2 gap decreased, consistent with enhanced convective washout of

CO_2 . Conversely, failure of the CO_2 gap to normalize despite fluid loading suggests persistent perfusion heterogeneity, reinforcing its role as a functional marker of ineffective resuscitation [3,14].

The strong predictive performance of the Pcv–aCO_2 gap observed in this study aligns with findings reported by Nassar et al 2021., who demonstrated its utility in identifying fluid non-responders in septic shock patients [10]. Differences in cutoff performance and predictive accuracy between studies may be explained by greater illness severity in our cohort, inclusion of mixed shock phenotypes, and use of a mini-fluid challenge rather than larger volume expansion. Similar associations between CO_2 gap dynamics and cardiac output response have been described by Faris et al 2024. and Mallat et al 2024. [13,15].

LVOT-VTI played a central role in defining fluid responsiveness by directly quantifying stroke volume changes. Nevertheless, LVOT-VTI is inherently preload-sensitive and operator-dependent, and its interpretation may be influenced by loading conditions and technical factors. Accordingly, LVOT-VTI should be considered a complementary rather than confirmatory tool. When integrated with the Pcv–aCO_2 gap, it allows simultaneous assessment of macrocirculatory response and tissue-level perfusion adequacy, providing a more comprehensive hemodynamic evaluation.

Clinically, these findings suggest that a persistently elevated Pcv–aCO_2 gap following a preload challenge may serve as an early signal to halt further fluid administration. Unlike serum lactate, which may remain elevated due to delayed clearance or non-hypoxic mechanisms, the CO_2 gap responds rapidly to changes in blood flow, making it particularly useful for real-time resuscitation guidance [2,4]. In such patients,

escalation toward vasopressor optimization, inotropic support, or strategies targeting microcirculatory dysfunction may be more appropriate than continued fluid loading.

Fluid non-responders experienced significantly longer ICU stays, higher rates of mechanical ventilation, and increased mortality. These associations likely reflect persistent tissue hypoperfusion and illness severity rather than a direct causal effect of fluid restriction or administration. Given the observational nature of this study, causality cannot be inferred; however, the consistent relationship between elevated Pcv–aCO_2 gap, fluid non-responsiveness, and adverse outcomes underscores the prognostic relevance of this marker [13].

The observed inverse relationship between LVOT-VTI and the Pcv-aCO_2 gap, which was consistent both before and after fluid challenge, provides physiological coherence to the combined use of these parameters. While LVOT-VTI reflects macrocirculatory stroke volume response, the Pcv-aCO_2 gap captures the adequacy of flow-dependent CO_2 clearance at the tissue level, as previously described [3]. The persistence of this relationship after fluid loading supports the concept that failure to augment stroke volume is accompanied by sustained perfusion abnormalities. Together with the high diagnostic accuracy of the Pcv-aCO_2 gap demonstrated by ROC analysis, these findings reinforce the complementary role of echocardiographic and biochemical indices in evaluating fluid responsiveness and identifying patients unlikely to benefit from further fluid administration [3,11]

This study has some limitations. Its single-center design and exclusion of cardiogenic shock limit generalizability.

LVOT-VTI was used as both the reference standard and a dynamic marker, this presents a potential for circular reasoning, that future studies could address by incorporating an independent reference standard.

vasopressor titration during the fluid challenge was not standardized. Finally, direct assessment of the microcirculation was not performed, precluding definitive mechanistic conclusions.

Conclusion:

This study demonstrates that a persistently elevated central venous–arterial PCO_2 gap (6 mmHg) following a standardized mini-fluid challenge is a strong and independent marker of fluid non-responsiveness in patients with severe shock. When interpreted alongside LVOT-VTI, the Pcv-aCO_2 gap provides complementary insight into the dissociation between macrocirculatory response and tissue perfusion, allowing more accurate identification of patients unlikely to benefit from further fluid administration. Importantly, this physiological phenotype was associated with worse clinical outcomes, highlighting the potential role of integrated biochemical and echocardiographic assessment in individualized fluid resuscitation strategies. These findings should be interpreted in light of the observational design and warrant confirmation in prospective interventional studies.

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