

Efficacy of Left Ventricular Outflow Tract and Carotid Artery Velocity Time Integral as Predictors of Fluid Responsiveness in Patients with Sepsis and Septic Shock

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ABSTRACT

Background: Transthoracic echocardiography is a reliable method to measure a dynamic change in left ventricular outflow tract velocity time integral (LVOTVTI) and stroke volume (SV) in response to passive leg raising (PLR) and can predict fluid responsiveness in critically ill patients. Measuring carotid artery velocity time integral (CAVTI) is easier, does not depend on adequate cardiac window, and requires less skill and expertise than LVOTVTI. The aim of this study is to identify the efficacy of Δ CAVTI and Δ LVOTVTI pre- and post-PLR in predicting fluid responsiveness in critically ill patients with sepsis and septic shock.

Methods: After the institutional ethics committee's clearance and informed written consent, 60 critically ill mechanically ventilated patients aged 18 to 65 years were recruited in this prospective parallel-group study with 20 patients in each group: sepsis (group S), septic shock (group SS), and control (group C). Demographic parameters and baseline acute physiology, age and chronic health evaluation-II and sequential organ failure assessment scores were noted. LVOTVTI, SV, and CAVTI were measured before and after PLR along with other hemodynamic variables. Patients having a change in SV more than 15% following PLR were defined as "responders."

Results: Twenty-three patients (38.33%) were responders. Area under receiver-operating characteristic curve for Δ CAVTI could predict responders in control and sepsis patients only. The correlation coefficients between pre- and post-PLR Δ CAVTI and Δ LVOTVTI were 0.530 ($p = 0.016$), 0.440 ($p = 0.052$), and 0.044 ($p = 0.853$) in control, sepsis, and septic shock patients, respectively.

Conclusion: Following PLR, Δ CAVTI does not predict fluid responsiveness in septic shock patients and the correlation between Δ CAVTI and Δ LVOTVTI is weak in septic shock patients and only modest in sepsis patients.

Keywords: Fluid responsiveness, Passive leg raising, Sepsis, Transthoracic echocardiography, Velocity time integral.

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HIGHLIGHTS

Why is this topic important?

Identifying appropriate patients with fluid responsiveness is the key to fluid resuscitation in sepsis and septic shock. Carotid artery Doppler parameters may be easy surrogates to echocardiography-derived, more sophisticated parameters in the emergency department.

What does this study attempt to show?

Whether carotid artery velocity time integral (CAVTI) and derived stroke volume (SV) correlate well with the echocardiography-derived left ventricular velocity time integral and SV in response to passive leg raising in mechanically ventilated patients with sepsis and septic shock.

What are the key findings?

CAVTI does not have a good correlation with the left ventricular outflow tract velocity time integral (LVOTVTI) in patients with sepsis and septic shock.

How is patient care impacted?

CAVTI should not be used to assess fluid responsiveness in place of echocardiography-derived parameters, like LVOTVTI and SV.

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Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.¹ Mortality from sepsis and septic shock is high with a crude mortality rate of around

24%.² Adequate fluid resuscitation is the first line of therapy in the management of septic shock.³ Recent evidences suggest that both inadequate and overzealous fluid resuscitation are associated with poor outcomes.⁴

The use of static measures of fluid status, such as central venous pressure (CVP), alone to predict response to fluid challenge may not be effective.¹ Use of dynamic preload indices may select fluid-responsive patients and avoid unnecessary fluid administration.⁵ Dynamic goal-directed fluid therapy in high-risk surgical patients has been found to decrease postoperative morbidity and length of intensive care unit (ICU) stay.⁶

Transthoracic echocardiography is a reliable and noninvasive method of assessment of fluid responsiveness and cardiac output in critically ill patients.⁷ Measurement of left ventricular outflow tract velocity time integral (LVOTVTI), derived stroke volume (SV), and cardiac output reliably predicts fluid responsiveness in critically ill patients.⁸ SV change in response to passive leg raising (PLR) fluid challenge is a dynamic parameter and has been found to be highly predictive of fluid responsiveness.⁹

Recent studies have shown that ultrasound Doppler assessment of carotid artery velocity time integral (CAVTI) and carotid artery (CA) blood flow can be a feasible and reliable method to predict fluid responsiveness.¹⁰ Measuring CAVTI is easier, does not depend on adequate cardiac windows, and requires less skill and expertise than LVOTVTI. Hence, CAVTI has the potential to replace LVOTVTI measurement in regular clinical practice. Therefore, we planned a prospective observational study to determine the efficacy of change in CAVTI to predict fluid responsiveness and correlation of the changes in CAVTI with that of LVOTVTI and SV in response to PLR fluid challenge.

METHODS

Study Setting and Population

After obtaining institute ethics committee's approval (IESC/T-291/23.06.2015) and written informed consent from participants or their legally acceptable representatives, this prospective parallel-group observational study was performed on 60 critically ill adult patients aged between 18 and 65 years and on mechanical ventilation. The study was registered in the National Clinical Trial Registry of India (www.ctri.nic.in; CTRI/2017/11/010434). All patients were divided into three groups: sepsis (group S, $n = 20$), septic shock (group SS, $n = 20$), and control (group C, $n = 20$). Sepsis and septic shock were defined as per sepsis three definitions.¹ Control patients were hemodynamically stable and not in sepsis. All patients were on mechanical ventilation. Patients with a body mass index >30 kg/m² and any contraindication to PLR (raised intracranial pressure, intracranial space-occupying lesions, and pelvic/lower limb fractures), valvular heart disease, cardiac arrhythmia, cardiomyopathy, and CA stenosis were excluded.

Study Protocol

The following variables were recorded at inclusion: demographic data, diagnosis, comorbid illnesses, hemodynamic parameters, and sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation (APACHE)-II scores. Ultrasonography-derived variables were noted pre- and post-PLR as per protocol.

A focused ultrasonography (IMAGIC Agile, Kontron Medical, WA, USA) was done with a phased array echocardiography probe. On echocardiography, SV was determined from left ventricular

velocity time integral (determined by pulsed wave (PW) Doppler in LVOT in apical five-chamber view) and LVOT cross-sectional area (derived from LVOT diameter in parasternal long-axis view). Common carotid artery (CCA) was scanned in the short-axis view at the level of the cricoid cartilage, and the diameter was recorded. Then, the transducer was rotated 90° to obtain a long-axis image of the CCA at the same position. This position was marked and used in subsequent imaging. The CCA diameter was measured from intimal to intimal edge perpendicular to the vessel wall in long-axis view. PW Doppler was applied in this long-axis view over CCA and CAVTI was determined automatically through digitalized Doppler spectral envelopes, tracing total (both systolic and diastolic) waveforms. Doppler sample gate was obtained in the middle of the artery with an angle parallel to the CCA wall and this was maintained the same before and after PLR.¹⁰ Each measurement was repeated thrice and then the average of the measurements was taken in the final analysis to reduce intraobserver variability.

All ultrasonography images were obtained with the patients in 45° semi-upright position and then supine position with the legs passively raised at 45° for 1 minute by a foam wedge. LVOTVTI, CAVTI, and SV were noted in both positions along with hemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and CVP). Patients having a change in SV of more than 15% after PLR were defined as "responders" and the rest as "nonresponders." A single investigator, unaware of group allocation, performed all the echocardiographic examinations. He was not part of the clinical team and an opaque curtain was placed in front of the monitor screen and infusion pumps to make him unaware of group allocation. He was trained in focused critical care echocardiography and performed such measurements in one hundred patients before the start of study. A second physician who was not part of this study recorded demographic and hemodynamic data before and after PLR.

Sample Size Calculation and Statistical Analysis

We could not find any previous study on the correlation of CAVTI in patients with sepsis and septic shock. Since the current study is a preliminary observational study, we chose to include twenty patients in each group (viz. control, sepsis, and septic shock) with a total sample size of 60.

The data were entered in Microsoft Excel spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD and median. The normality of data was tested using Kolmogorov-Smirnov test. If the normality was rejected, then nonparametric test was used. All quantitative variables were compared using an unpaired t-test/Mann-Whitney test (when the data sets were not normally distributed) between two groups and analysis of variance/Kruskal-Wallis test between three groups. Paired t-test was used for comparison between pre and post. Qualitative variables were correlated using Chi square test. The agreement between LVOTVTI and CAVTI was evaluated by Bland-Altman plot. Receiver-operating characteristic (ROC) curve was made to find out the cutoff point of Δ CAVTI and Δ LVOTVTI in percentage, which can predict responders with best sensitivity and specificity. A p -value of <0.05 was considered statistically significant.

RESULTS

A total of 60 patients were studied with 20 patients in each of the three groups. Demographic parameters were comparable between the three groups. However, baseline SOFA and APACHE-II scores were significantly different for obvious reasons that the study population was different between the groups (Table 1). Changes in hemodynamic parameters pre- and post-PLR in all three groups are provided in Table 2.

Correlation between Δ CAVTI and Δ LVOTVTI was performed. Pearson correlation coefficient was 0.530 ($p = 0.016$), 0.440 ($p = 0.052$), and 0.044 ($p = 0.853$), respectively in group C, group S, and group SS (Fig. 1). Similarly, Δ CAVTI showed a good correlation with Δ SV in group C ($r = 0.518$; $p = 0.019$) and in group S ($r = 0.646$; $p = 0.002$) but only a weak correlation in group SS ($r = 0.343$; $p = 0.139$) (Fig. 2). The agreement between CAVTI and LVOTVTI has been reported in Table 3.

Twenty-three patients (38.33%) were responders and thirty-seven (61.67%) were nonresponders. Among the study groups, responders were 35% in control group, 45% in sepsis group, and 35% in septic shock group. ROC curve was drawn (Fig. 3) and cutoff values of Δ CAVTI and Δ LVOTVTI were computed in each group, which can predict fluid responsiveness. Areas under receiver-operating characteristic curve (AUROCs) of Δ CAVTI and Δ LVOTVTI were 0.74 and 0.91, respectively with a cutoff value of Δ CAVTI $>10.64\%$ (sensitivity 71.43%, specificity 84.62%; $p < 0.004$) and Δ LVOTVTI $>1.92\%$ (sensitivity 100%, specificity 76.92%; $p < 0.0001$) in group C. AUROCs of Δ CAVTI and Δ LVOTVTI in group S were 0.90 and 0.89, respectively with a cutoff value of Δ CAVTI $>6.4\%$ (sensitivity 88.89%, specificity 81.82%; $p < 0.0001$) and Δ LVOTVTI $>7.07\%$ (sensitivity 77.78%, specificity 90.91%; $p < 0.0001$). In group SS, AUROCs of Δ CAVTI and Δ LVOTVTI were 0.69 and 0.84 with the best cutoff value $>14.76\%$ (sensitivity 71.43%, specificity 69.23%; $p = 0.12$) and $>13.5\%$ (sensitivity 85.71%, specificity 92.31%; $p < 0.001$).

Table 1: Demographic and baseline data [data expressed as median (IQR)]

Parameters	Group C (n = 20)	Group S (n = 20)	Group SS (n = 20)	Significance (p-value)
Age	42.5 (21.5–56)	39 (27.5–52)	45.5 (29–54.5)	0.806
Sex (M/F)	13/7	12/8	13/7	0.931
BMI	23.96 (21.5–26.9)	23.3 (21–25.7)	25.98 (21.4–28.2)	0.728
SOFA	4 (3–4)	6 (5.5–7)	15 (13.5–16)	<0.001
APACHE II	7 (7–9.5)	17.5 (14.5–21)	24.5 (21.5–27.5)	<0.001
Diagnosis				NS
Postoperative (abdominal/orthopedic surgery)	20 (16/4)	0	0	
Pneumonia		12	8	
Peritonitis		3	2	
Puerperal sepsis		1	3	
Urosepsis		3	4	
Meningitis		1	1	
Acute on chronic liver failure		0	2	

Table 2: Hemodynamic parameters pre- and post-PLR [data expressed in median (IQR)]

	Group C (n = 20)	Group S (n = 20)	Group SS (n = 20)
HR—Pre-PLR	101.5 (90.5–112)	112.5 (94.5–130)	112.5 (98.5–126)
HR—Post-PLR	105 (88.5–114)	113 (100.5–134)	117 (103.5–126)
MAP—Pre-PLR	88 (80–96.7)	83 (72–98)	74.5 (69–86)
MAP—Post-PLR	93 (83.3–98.3)	84.5 (75.8–95.1)	80 (73.5–88.5)
CVP—Pre-PLR	11 (7.5–12.5)	10 (7–13)	7.5 (6.5–11)
CVP—Post-PLR	11 (9–14)	12 (8–14)	8.5 (7–13)
LVOTD—Pre-PLR	1.7 (1.2–1.8)	1.51 (1.2–1.7)	1.74 (1.6–1.8)
LVOTD—Post-PLR	1.73 (1.3–1.8)	1.56 (1.3–1.7)	1.78 (1.7–1.8)
LVOTVTI—Pre-PLR	30.6 (20.5–41.1)	37.4 (22.8–48.4)	14.9 (12.7–17.7)
LVOTVTI—Post-PLR	32 (23.2–41.1)	40.4 (20.7–45.4)	15.5 (15–21.7)
CAD—Pre-PLR	0.76 (0.7–0.8)	0.72 (0.6–0.7)	0.70 (0.6–0.7)
CAD—Post-PLR	0.75 (0.7–0.8)	0.72 (0.6–0.7)	0.70 (0.6–0.7)
CAVTI—Pre-PLR	20.8 (14.3–28.9)	23.2 (13.3–27)	7.7 (4–9.5)
CAVTI—Post-PLR	20.6 (15.6–27.6)	25 (15–30.7)	8.5 (5.1–10.8)
SV—Pre-PLR	58.74 (44.5–78.5)	56.5 (38.7–77)	34.72 (30.2–44.5)
SV—Post-PLR	60.84 (48.2–77)	61.1 (49.9–86.2)	38.49 (34.1–53.1)
CO—Pre-PLR	5.5 (3.4–7.8)	6.4 (4.1–8.3)	4 (3.4–4.6)
CO—Post-PLR	6 (4.9–8.9)	6.7 (5.1–10.4)	4.4 (3.9–6.0)

HR: heart rate; MAP: mean arterial pressure; CO: cardiac output; CAD: carotid artery diameter

DISCUSSION

The main finding of our study was that change in CAVTI and LVOTVTI post-PLR maneuver showed a modest correlation in control and sepsis patients, but a weak correlation in patients with septic shock. We used the change in SV in response to a PLR maneuver as the gold standard in our study to predict fluid responsiveness in the context of previous literature defining its role as a reliable estimate and a predictor of fluid responsiveness.¹¹

CA diameter and velocity assessments using Doppler echocardiography are reliable, reproducible, and easy to perform at the bedside. In the absence of advanced invasive hemodynamic monitors and expertise in advanced echocardiography, using CAVTI as a proxy measure of cardiac output can help us titrate the fluid management in the emergency department or during initial resuscitation in the ICU. However, the literature on CAVTI as a measure of fluid responsiveness has shown variable and often contradictory results.^{12,13}

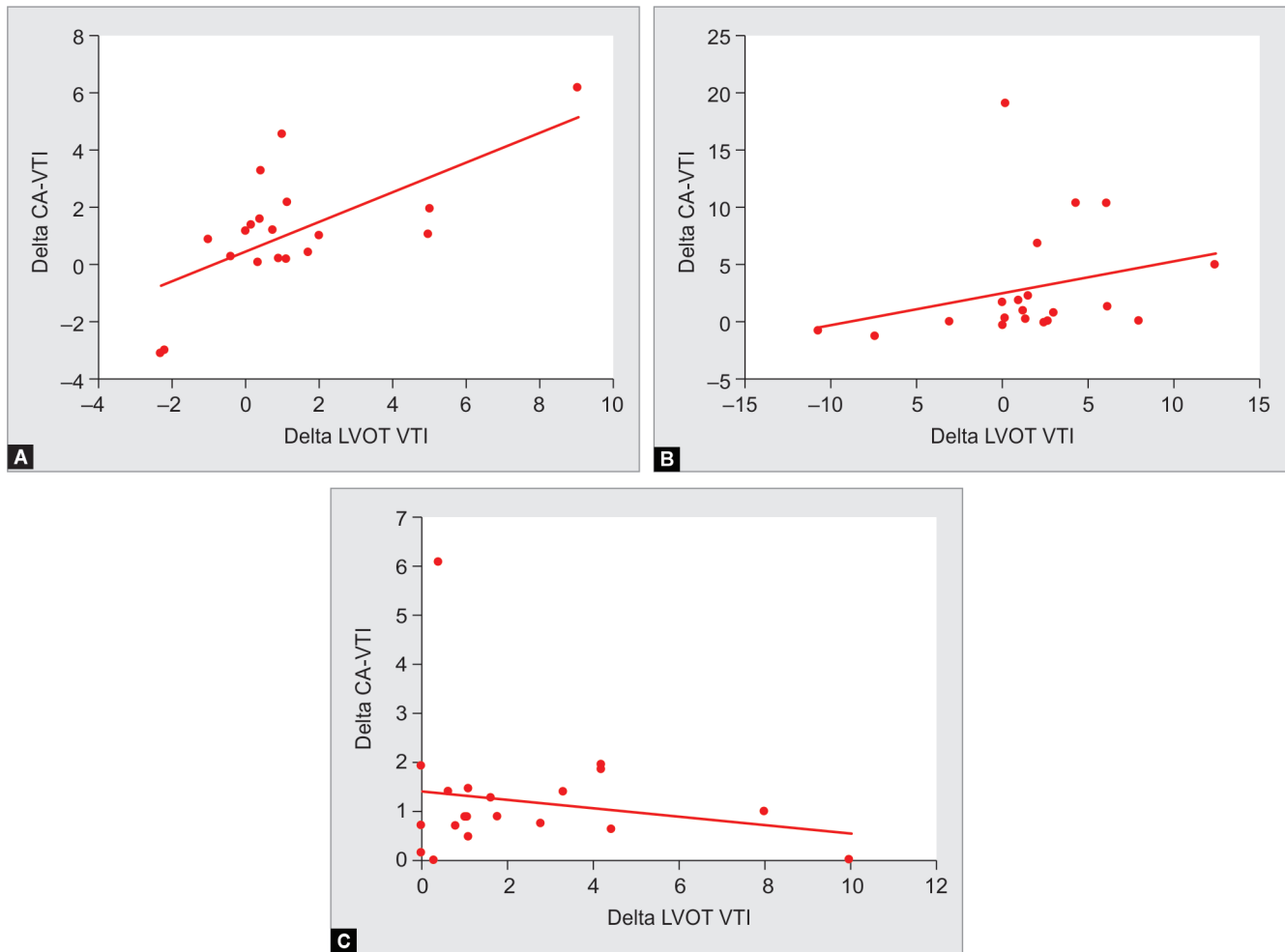


Fig. 1: Correlation between Δ CAVTI and Δ LVOTVTI in all three groups (A Control group, B Sepsis group and C Septic Shock group)

Marik et al.¹⁴ studied the use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following PLR in hemodynamically unstable patients. Carotid blood flow was increased among the responders (53%) and showed an excellent correlation with PLR change to SV ($p = 0.003$). However, thoracic bioreactance was used as the gold standard reference method for measuring SV index, against which carotid blood flow was compared. The accuracy of bioreactance as a reliable measure of cardiac output has been questioned in further studies.¹⁵ The investigators did not report the absolute values of carotid blood flow in their study but reported only the relative changes in velocities. This raises questions about whether the values obtained were within the physiological range. We, therefore, chose to use echocardiography-based SV derived from LVOTVTI as the gold standard in our study, which is perhaps the best noninvasive measure of SV and cardiac output.¹⁶

The CA peak velocity variation with respiration has been used to guide volume resuscitation.^{10,17} While the effect of respiratory variation in inducing a change in blood flow velocity is based on the principle of heart–lung interaction, it requires patients to be mechanically ventilated with low tidal volumes. We chose to study CAVTI as we felt that this could potentially find more widespread applications as patients need not be on mechanical ventilation for

the measurements to be reliable. Change in CAVTI may not truly reflect a change in carotid blood flow due to the flow-mediated dilation of the vessels. Marik et al. found that fluid responders had an increase in CA diameter to fluid challenge compared to nonresponders, which the authors suggested could be a marker of endothelial integrity.¹⁴ However, we observed a nonsignificant change in CA diameter pre- and post-PLR. Therefore, it is unlikely that analysis with carotid blood flow instead of CAVTI would have significantly altered the results. Moreover, in real-life scenarios, CAVTI is easy to measure and less time consuming than carotid blood flow, which requires measurement of both diameter and velocity time integral and subsequent calculations.

However, the findings of our study showed a poor correlation of CAVTI in the subset of patients with septic shock and only a modest correlation in patients with sepsis. It is an important finding as these are the subsets of patients who might benefit from a goal-directed fluid therapy to reverse tissue hypoperfusion and organ dysfunction. A previous study by Giroto et al. has shown similar results when using PLR to study the change in CA peak velocity and blood flow.¹⁸ Further, studies in healthy volunteers and cardiac surgical patients have shown a poor correlation between cardiac index and blood flow velocity in the peripheral sites viz. carotid and femoral arteries.^{12,13}

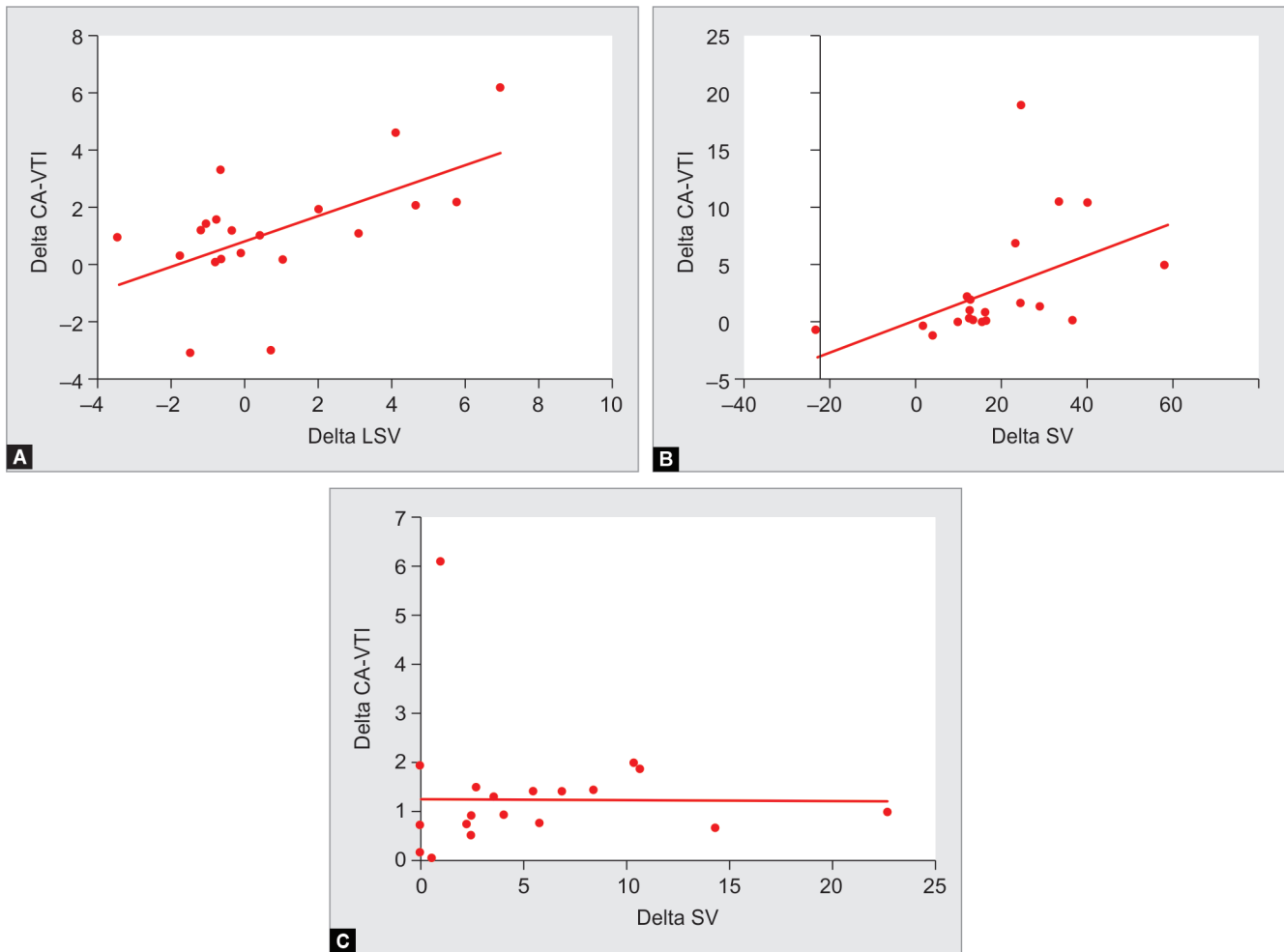


Fig. 2: Correlation between Δ CAVTI and Δ SV in all three groups (A Control group, B Sepsis group and C Septic shock group)

Table 3: Agreement between LVOTVTI and CAVTI

	Limits of agreement	Mean difference (95% CI)	Range
Before PLR	-22.9, 1.2	-10.9 (-12.4, -9.3)	7.5, 43.3
After PLR	-23.2, 1.5	-10.8 (-12.4, -9.2)	8.7, 45.3

While intuitively one may feel that any change in SV to be instantaneously reflected in peripheral vessel blood flow velocities, the findings of this study and the ones previously described challenge this notion seriously. There could be a few possible explanations for these findings. Firstly, the brain is able to tightly regulate cerebral blood flow. Autoregulation of the brain prevents any increase in cerebral blood flow and volume consequent to an increase in cardiac output by PLR. While we did find some degree of correlation in control and septic patients ($r = 0.51$ and 0.64), such a relationship was lost in patients with septic shock ($r = 0.3$). The extent of disruption of dynamic cerebral autoregulation and neurovascular coupling in a septic state is not entirely clear. Animal studies have shown that loss of neurovascular coupling occurs in septic shock, cerebral hypoperfusion being the putative mechanism for sepsis-associated encephalopathy.¹⁹

Furthermore, in critically ill patients with sepsis and septic shock, the relationship between cardiac output and CAVTI is influenced by

the effect of interventions and multiple confounding factors, such as the use of inotropes and vasopressors, partial pressure of carbon dioxide, temperature, history of hypertension, age, or the presence of organ dysfunction.²⁰⁻²³ Therefore, it is not surprising that our study failed to find a reliable relationship between LVOTVTI-derived SV and CAVTI in critically ill, septic patients in response to PLR. Secondly, the Doppler signals of the carotid vessels are sensitive to artifacts, especially at higher blood flows. Accurate volumetric assessment of carotid blood flows requires the underlying flows to be strictly laminar, conditions which may not be met in patients with underlying atherosclerosis or vessel narrowing.²⁴ Thirdly, the delay in measuring CAVTI or LVOTVTI may affect the accuracy of these measurements.

The absence of a predictable relationship between SV measured by LVOTVTI and CAVTI in critically ill patients raises serious doubts on the reliability and accuracy of CAVTI as a bedside measure to titrate fluids in critically ill patients. We separately studied patients with sepsis and septic shock given the fact that more intense vasoplegia may occur as the patients progress in the spectrum of illness from sepsis to a shock state.

Limitations

There are a few limitations of our study. Due to the small sample size of responders in each group, the sensitivity and specificity



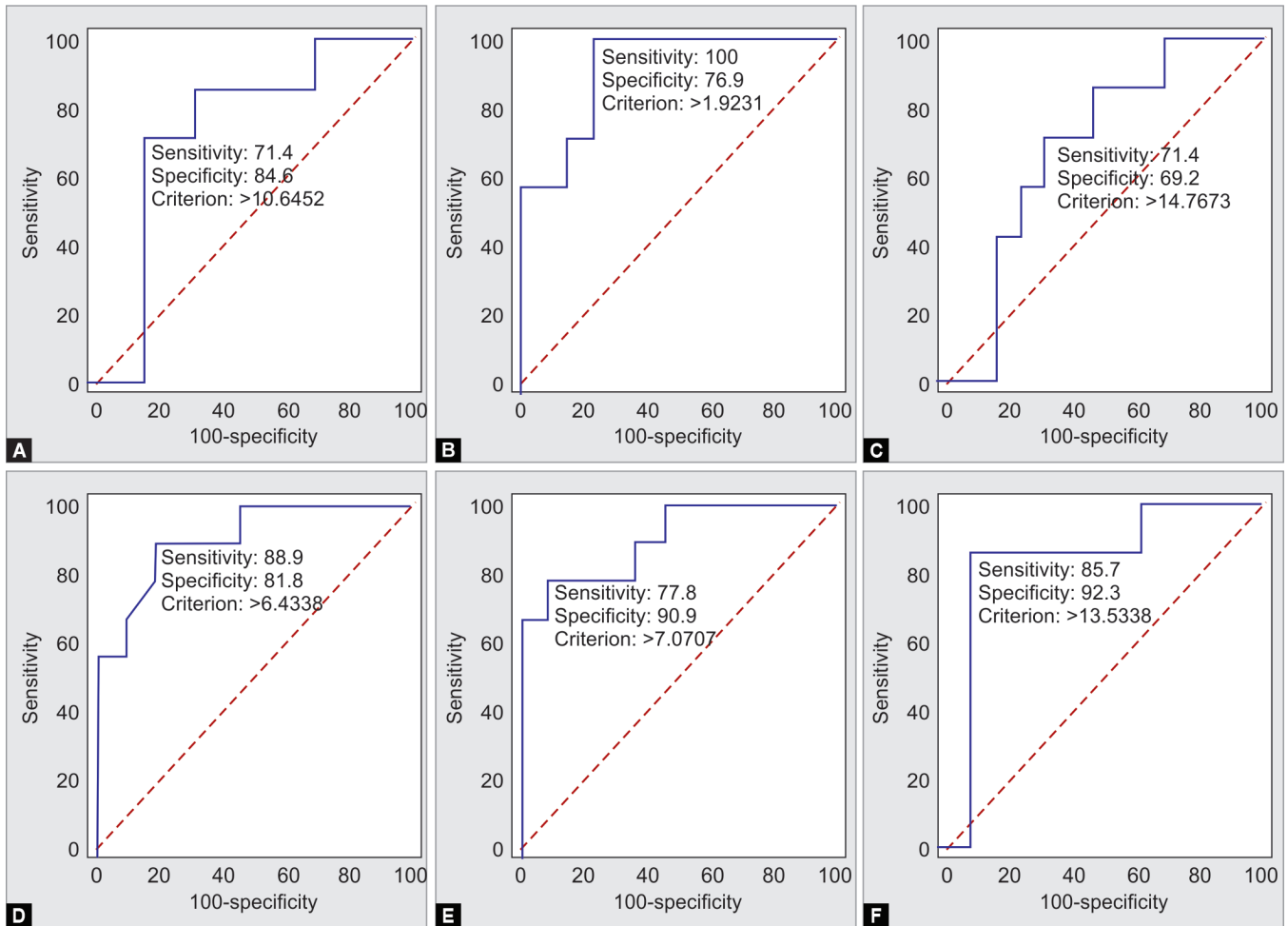


Fig. 3: AUROCs of Δ CAVTI and Δ LVOTVTI in groups C, S and SS (3A - Δ CAVTI in group C; 3B - Δ LVOTVTI in group C; 3C - Δ CAVTI in group SS; 3D - Δ CAVTI in group S; 3E - Δ LVOTVTI in group S; 3F - Δ LVOTVTI in group SS)

of CAVTI reported in the current study might not be replicated or generalizable to a larger population. However, given the only modest relationship between CAVTI- and LVOTVTI-derived SVs observed in our study, we feel that it is unlikely that a larger sample size would have markedly altered the results. Secondly, we correlated the change in CAVTI and not the change in CA blood flow with that of SV. Thirdly, there is always an element of interobserver variation with ultrasonographic measurements. In a study by Proue et al., studying peak femoral blood flow velocity, the interobserver variability was reported as high as $8.4 \pm 9.2\%$.²⁵ To nullify the effect, in our study the same investigator with robust experience in bedside ultrasonography performed all the measurements. However, this might be difficult to replicate in the real world.

CONCLUSION

To conclude, change in CAVTI in response to PLR maneuver does not correlate with the change in LVOTVTI-derived SV and therefore may not be considered reliable as a dynamic bedside measure of fluid responsiveness in patients with septic shock. While it did show a modest correlation in patients with sepsis, due to its wide range of cutoffs and variable results in the literature, it may not be used as a reliable guide to administering fluids in sepsis patients.

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