



# The Validity of Carotid Doppler Peak Velocity and Inferior Vena Cava Collapsibility Index in Identifying the Fluid Responders in Mechanically Ventilated Septic Shock Patients

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## Abstract

**BACKGROUND:** Measures of carotid artery flow or inferior vena cava (IVC) diameter (IVC-d) were recently shown to predict fluid responsiveness.

**AIM:** The objective of the study is assessment of fluid responsiveness by measuring carotid Doppler peak velocity in a single respiratory cycle ( $\Delta$ CDPV) and respiratory variation in IVC-d ( $\Delta$ IVC-d) against the increase in the cardiac index by echocardiographic calculations in mechanically ventilated septic shock patients.

**METHODS:** Thirty mechanically ventilated septic shock patients were included in a prospective observational study, we excluded patients <18 years or non-septic causes of shock. A fluid bolus 7 ml/kg crystalloid solution given within 30 min, we measured central venous pressure (CVP), mean arterial pressure (MAP), pulse pressure,  $\Delta$ IVC-d, and  $\Delta$ CDPV before and after. Patients were categorized either fluid responders (R) or non-responders (NR) according to more than 15% increase in cardiac output.

**RESULTS:** R versus NR group showed a significant difference in cardiac output, MAP and  $\Delta$ CDPV measures pre- and post-fluid boluses as ( $5.26 \pm 4.42$  L/min vs.  $10.62 \pm 5.73$  L/min,  $69.48 \pm 9.70$  mmHg vs.  $84.90 \pm 10.36$  mmHg and  $24.43 \pm 11.87\%$  vs.  $33.22 \pm 11.00\%$ ) with  $p = (0.007, 0.05$  and  $0.01)$ , respectively. While,  $\Delta$ IVC-d and  $\Delta$ CVP pre- and post-fluid boluses did not show any statistical difference as ( $11.91 \pm 9.41\%$  vs.  $13.51 \pm 9.56\%$ ,  $5.86 \pm 5.22$  cmH<sub>2</sub>O vs.  $7.22 \pm 4.82$  cmH<sub>2</sub>O) with  $p = (0.87$  and  $0.68)$  respectively,  $\Delta$  CDPV increase in R group showed sensitivity 81% and specificity 66.7%.

**CONCLUSION:**  $\Delta$ CDPV was more precise and even easier assessment tool with better sensitivity and specificity for evaluation of fluid responsiveness than the  $\Delta$ IVC-d and CVP in septic shock patients on mechanical ventilation.

Edited by: Mirko Spiroski

Citation: Soliman M, Magdi A, Fatthy M, El-Sherif R. The Validity of Carotid Doppler Peak Velocity and Inferior Vena Cava Collapsibility Index in Identifying the Fluid Responders in Mechanically Ventilated Septic Shock Patients. Open Access Maced J Med Sci. 2022 Feb 15; 10(B):383-388.

<https://doi.org/10.3889/oamjms.2022.8375>

**Keywords:** Septic shock; Fluid responsiveness; Mechanical ventilation; Carotid Doppler peak velocity; Respiratory variation in inferior vena cava diameter; Central venous pressure

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Received: 22-Dec-2021

Revised: 16-Jan-2022

Accepted: 05-Feb-2022

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Funding: No organizational funding supported, Funded by authors.

Competing Interests: The authors have declared that no competing interests exist

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## Introduction

Sepsis is defined as life-threatening organ dysfunction due to a deregulated host response to infection which can result in grave complications such as septic shock which is a subset of infection with circularity and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. One of the lines for the treatment is to administer intravenous fluids as the first step to improve blood pressure [2]. A fluid challenge will cause an increase in stroke volume only when patients' cardiac preload is in the low volume status [3], [4]. Determining the optimal amount of fluid to be administered remains a critical issue through continued inquiry. Analysis of large databases suggests that there may be a U-shaped response curve, where limited amounts as well as large amounts of fluid administration are associated with worse outcomes. The best response was observed when fluid resuscitation was administered in volumes between 15 and 45 mL/kg [5]. However, studies have shown that not every patient advantages from aggressive intravenous hydration [6]. Only 40% of hypotensive patients with sepsis respond to it with

improvement in blood pressure [2], [7]. Those who do not respond are liable to develop high intravascular pressure, pulmonary edema, or acute heart failure with high associated mortality [8], [9], [10].

Therefore, precise fluid resuscitation and careful assessment of fluid responsiveness should be fastidiously evaluated and always weigh between the benefits and the risks of intravenous fluids [11]. Static indicators of fluid responsiveness such as central venous pressure (CVP) and pulmonary capillary wedge pressure are poor predictors of fluid responsiveness [12], [13]. In contrast, indices relying on the cardiopulmonary interactions in mechanically ventilated patients have been shown to be good predictors of fluid responsiveness [13]. Respiratory variation in aortic blood peak velocity had high sensitivity and specificity to predict fluid responsiveness [14], [15]. However, measurements of aortic blood flow velocity need a transesophageal ultrasound which is an invasive procedure. Several studies had been done to evaluate the noninvasively respiratory variation of brachial artery peak velocity flow to predict fluid responsiveness in mechanically ventilated patients and concluded that it is a feasible tool for predicting fluid responsiveness, with

efficiency similar to other well-known dynamic parameters of preload [16], [17]. Measures of carotid artery flow or inferior vena cava (IVC) diameter (IVC-d) were recently shown to predict fluid responsiveness [16], [17], [18].

### Aim of the study

Our aim is to assess the fluid responsiveness by measuring carotid Doppler peak velocity and respiratory variation in IVC-d against the increase in the cardiac index by echocardiographic calculations as a reference in mechanically ventilated patients in septic shock.

### Methods

This is a multicenter, prospective, and cohort study on 30 critically ill mechanically ventilated patients in septic shock. We included in our study only patients who were mechanically ventilated and in septic shock for which the treating intensivist was considering fluid challenge and titration of vasopressor doses based on patients' response to therapy. The study was performed in Cairo University Intensive Care Unit, Assalam International Hospital, and Al Safa Hospital for 1 year. We excluded patients <18 years, shock other than septic shocks, known cardiac disease, end-stage renal disease who required hemodialysis, intra-abdominal hypertension, and carotid artery stenosis >55%. All the patients were subjected to IV fluid bolus by 7 ml/kg crystalloid solution over 30 min. Static and dynamic indices were obtained before fluid bolus (T0) and after fluid bolus (T1) by a well-trained echocardiography operator. Patients who achieved an increase of 15% or more in the cardiac output – calculated by echocardiography – after the fluid challenge were classified as “responders” (R), and those with an increase of <15% in CO or those with no increase were classified as “non-responders” (NR). CVP, mean arterial pressure, pulse pressure, difference between diameters of IVC during inspiration and expiration ( $\Delta$ IVC-d) in single respiratory cycle, and difference between velocities of carotid Doppler peak velocity in single respiratory cycle ( $\Delta$ CDPV) were all measured by the same well-trained echocardiography operator then data were calculated and followed (Figure 1).

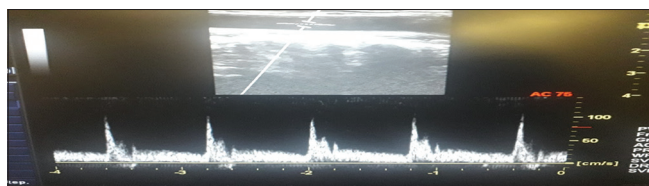


Figure 1: Measurement of variation in carotid peak systolic velocity. At 50 % in this patient

Carotid peak systolic velocity was measured using a 5–10-mHz linear array transducer. Devices used were: GE LOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia.

At 50% in this patient and Toshiba Xario™ 200- Japan: Maximum and minimum peak systolic velocities were measured in a single respiratory cycle, and the respiratory variation in carotid Doppler peak velocity “ $\Delta$ CDPV” was calculated with the following formula:

$$\frac{(\text{MaxCDPV} - \text{MinCDPV})}{2} \times 100,$$

expressed as a percentage [18]. IVC-d measurement was performed with a two views IVC using 2–6 MHz curved transducer with longitudinal two views at a subxyphoidal long axis just caudal to the hepatic vein inlet. Devices used were: GE LOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia, and Toshiba Xario™ 200- Japan. Maximum and minimum diameters over a single respiratory cycle were recorded and respiratory variation in IVC-d was calculated with the formula:

$$\frac{(\text{Max IVC} - d - \text{Min IVC} - d)}{2} \times 100,$$

expressed as a percentage [19].

Cardiac output was measured using a 1.5–7-mHz phased array transducer. Devices used were: GELOGIQ™ P9- South Korea, FUJIFILM SonoSite M-Turbo®- Malaysia, and Toshiba Xario™ 200- Japan. Two views were obtained: Long parasternal view and apical five chambers view. Measurement of LVOT diameter was obtained in the parasternal long axis view during systole while assess LVOT Velocity Time Integral: Using pulsed wave Doppler in the apical five chamber view. Stroke volume was calculated with the formula: Stroke volume = left ventricle outflow tract “LVOT” area  $\times$  LVOT velocity time interval “VTI” =  $\text{Pi} \times 3.14 \times (\text{LVOT diameter}/2)^2 \times \text{LVOT VTI}$  [20]. Then, cardiac output was calculated by formula: Cardiac output = stroke volume  $\times$  heart rate. The parameters on the ventilator were kept constant during data recording. Inotropes or vasopressors rate was not changed and stimulation of the patients was avoided.

Data were summarized by descriptive statistics using mean, standard deviation, median, minimum and maximum in quantitative data, and using frequency (count) and relative frequency (percentage) for categorical data. Mean values and standard deviation were compared using simple t-test (for two variables) or ANOVA test (for more than two variables). Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [21]. For comparing categorical data, Chi-square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is <5 [22]. Correlations between quantitative variables were done using Spearman correlation coefficient [23]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of

significant parameters for detection of responders. Data were coded and entered using the statistical package Statistical Package for the Social Sciences version 25.  $P \leq 0.05$  was considered statistically significant.

## Results

In our study, we included 30 patients in septic shock on controlled mechanical ventilation according to the inclusion criteria, positive culture results, and need of vasoactive drug infusion. Stroke volume, CVP, IVC-d, and CDPV were measured in all patients before and after fluid boluses. Baseline characteristics of the patients are shown in Table 1.

**Table 1: Characteristics and baseline parameters before all fluid challenges between responders and non-responders**

Variable	Responsive (n: 21)	Non-responsive (n: 9)	p-value
Age	64.95 ± 12.59	68.22 ± 21.18	0.193
Gender			
Male	10 (48%)	6 (67%)	0.440
Female	11 (52%)	3 (33%)	
APACHE II	16.05 ± 3.23	18.44 ± 3.81	0.164
SOFA score 0	11.48 ± 2.82	12.11 ± 2.80	0.625
SOFA score 5	12.95 ± 3.68	12.56 ± 3.97	0.790
TLC (×10 <sup>3</sup> /μl)	17.19 ± 8.38	18.60 ± 10.18	0.859
Lactate (mmol/l)	6.36 ± 3.64	8.04 ± 4.67	0.397
Mortality rate	17 (81%)	7 (77.8%)	1
Comorbidities			
Hypertension	3 (62%)	5 (56%)	1
Diabetes mellitus	8 (38%)	5 (56%)	0.443
Ischemic heart disease	9 (43%)	5 (56%)	0.694
Immunocompromised	8 (38%)	5 (56%)	0.443
Malignancy	6 (29%)	4 (44%)	0.431
Chronic kidney disease	3 (14%)	3 (33%)	0.329
COPD	4 (19%)	1 (11%)	1

All data are expressed as mean (standard deviation), TLC: Total leukocytes count, APACHE II: Acute Physiology and Chronic Health Evaluation II, range from 0 to 71, SOFA: Sequential Organ Failure Assessment score, range from 0 to 24, with higher scores indicating a greater risk of mortality.

Pneumonia was the most common cause of sepsis in our study (42.4%) followed by soft-tissue infection and urosepsis in six patients each (18.2% for each). Acute Physiology and Chronic Health Evaluation II score was calculated for all patients within 24 h of diagnosis of septic shock (16.8 ± 3.5). Sequential Organ Failure Assessment (SOFA) score was calculated for all patients within 24 h of diagnosis of septic shock (SOFA day [1]) and on day 5 (SOFA day [5]); SOFA (1) calculation was (11.7 ± 2.8), and SOFA (5) calculation was (12.8 ± 3.7). There was no a single comorbidity that has a significant impact on fluid responding or even can predict how will be the patients react to the fluid boluses. Out of 30 patients who were enrolled in the study, 24 patients (80%) died and only 6 patients (20%) survived. Patients included in the study were segregated according to the fluid responsiveness – increase in stroke volume through echocardiography by ≥15% of basal cardiac output was considered responding – into 21 fluid responsive “R” (70%) and 9 (30%) non-responsive “NR” [24]. The overall mortality rate was 80% “24 patients” with no difference between responders and non-responders patients responsive

“R” (70%) and 9 (30%) non-responsive “NR.” The overall mortality rate was 80% “24 patients” with no difference between responders and non-responders patients.

Monitoring hemodynamic parameters such as CVP did not have a significant change before and after fluid boluses. The two significant points about CVP were the higher values in NR and the narrow range in non-responders which reveal the nature of rigid venous reservoir in those patients (Table 2). Echocardiography was used to assess fluid assessment precisely by measuring aortic peak velocity + VTI variation and considered as the gold standard way to assess fluid status with sensitivity 76.2%, specificity 88.9%, and  $p = 0.013$ . IVC parameters change during inspiration and expiration were unpredictable of volume responsiveness as they had insignificant change with the fluid bolus in responsive patients ( $p: 0.87$ ). CDPV was significantly increased in response to increased intravascular volume in responsive group especially in comparison with IVC parameters with sensitivity 81%, specificity 66.7%, and  $p = 0.046$ . There were no correlation between IVC parameters and carotid artery parameters. ROC curve was calculated for the use of  $\Delta$ CDPV as a diagnostic tool of fluid responsiveness in septic shock. The optimal cutoff point was ≥26% with a good sensitivity (Table 3).

**Table 2: Responders versus non-responders main parameters before and after fluid boluses**

Variable	Responsive (n: 21)	Non-responsive (n: 9)	p-value
$\Delta$ CVP	5.86 ± 5.22	7.22 ± 4.82	0.689
CO			
Before IV fluids	5.26 ± 4.42	6.95 ± 6.55	0.722
After IV fluids	10.62 ± 5.73	5.82 ± 5.26	0.011*
SV			
Before IV fluids	104.81 ± 50.89	115.56 ± 82.56	0.929
After IV fluids	141.33 ± 84.39	95.22 ± 61.67	0.022*
$\Delta$ D-IVC			
Before IV fluids	11.91 ± 9.41	12.18 ± 5.83	0.449
After IV fluids	13.51 ± 9.56	9.28 ± 7.22	0.104
$\Delta$ CDPV			
Before IV fluids	24.43 ± 11.87	24.78 ± 10.49	1
After IV fluids	33.22 ± 11.00	23.67 ± 10.27	0.045*

Data were written as mean (standard deviation),  $\Delta$ CDPV: Respiratory variation in carotid Doppler peak velocity, SV: Stroke volume,  $\Delta$ D-IVC: Respiratory variation in inferior vena cavadiameter, CO: Cardiac output, CVP: Central venous pressure.

## Discussion

Our study showed that  $\Delta$ CDPV was more precise and easier in interpretation than other older methods (CVP and respiratory variation in IVC-d) for evaluating fluid responsiveness in septic shock and mechanically ventilated patients. Furthermore, the  $\Delta$ CDPV has a high correlation with stroke volume index (SVI) increase after fluid boluses. Cardiac output and stroke volume measured by echocardiography had the highest significant values among the whole parameters that were measured either static or dynamic ( $p = 0.007$  and  $0.01$ ), respectively, with sensitivity and



**Table 3: Cutoffs and diagnostic performances of significant predictors**

	AUROC	p value	95% Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
			Lower Bound	Upper Bound			
SV	0.765	0.024	0.563	0.966	98.5	76.2	88.9
CO	0.791	0.013	0.600	0.982	8.85	66.7	88.9
CDPV max	0.733	0.046	0.550	0.916	145	52.4	88.9
$\Delta$ CDPV	0.733	0.046	0.531	0.934	26	81	66.7

AUROC: Areas under the receiver operating characteristic curves,  $\Delta$ CDPV: Respiratory variation in carotid Doppler peak velocity, SV: Stroke volume, CDPV: Max carotid Doppler peak velocity maximum velocity in single respiratory cycle, CO: Cardiac output.

specificity (86% and 89%), respectively, and this proves that it should be the reference tool for any new tests evaluating fluid responsiveness. Similarly, Philippe Vignon *et al.* found that an increase of aortic blood flow of 10% or more during passive leg rising has a good sensitivity and specificity (97% and 94%, respectively) in identifying fluid responders [24]. Moreover, another study concluded that respiratory variations in VTI can predict fluid responsiveness in ventilated patients, at a threshold of 20%. Even though they proved that the respiratory variations in peak aortic flow predict fluid responsiveness in patients with septic shock under mechanical ventilation have a high sensitivity with a calculated threshold of 12% [25]. Furthermore, Feissel *et al.* reported high accuracy, sensitivity, and specificity (100% and 89%, respectively) of respiratory variation in aortic blood velocity (cutoff value >12 %) for prediction of fluid responsiveness in mechanically ventilated septic shock patients [26]. In the same time, CDPV shows the second higher specificity for fluid responsiveness after cardiac output measured by echocardiography. ( $p = 0.012$ , AUROC of 0.73, 95% CI: 0.531–0.934 with sensitivity and specificity of 0.81 and 0.66) according to the statistical calculations: (Figure 2).

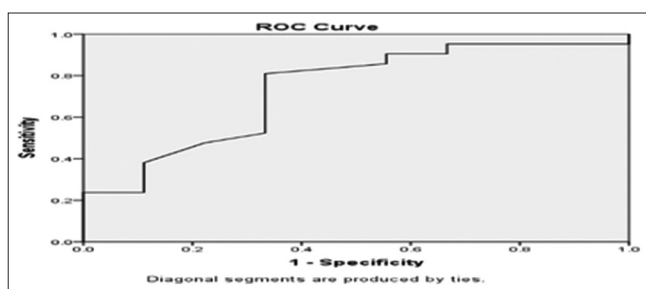


Figure 2: ROC curve for  $\Delta$ CDPV

Our results were nearly similar as Song *et al.* who conducted an analytical study on 40 patients post-operative elective coronary artery bypass surgery and divided patients as responders if SVI increased  $\geq 15\%$  after volume administration by IV bolus 6 ml/kg. The CDPV was calculated as the difference between the highest and lowest values of peak velocity over a single respiratory cycle as our study and shows that the AUC of CDPV was 0.85 ( $p < 0.001$ , 95% CI: 0.72–0.97) with sensitivity and specificity of 0.83 and 0.82 [27]. It has a higher sensitivity and specificity compared to our study as the population of the study was more homogeneous than our patients (Post-CABG vs. Septic shock). On the

same stream, Miguel *et al.* concluded that the  $\Delta$ CDPV had an AUROC of 0.88 (95 % CI 0.77–0.95) and has a superior predicting power for fluid responsiveness compared to stroke volume variation [14]. Besides the previous studies, an observational study was done on 49 patients of which 27 patients were classified as responders for the fluid challenge (responder group) and 22 as non-responders. There were no statistically significant differences in demographic and clinical variables while  $\Delta$ CDPV was found to be the best predictor of fluid responsiveness value for fluid responders (in comparison with stroke volume variation, ultrasound assessments of respiratory variations in IVC-d [ $\Delta$ IVC], and brachial artery peak velocity). It was associated with 78% sensitivity and 90% specificity and AUC of 0.910 [28].

On the other hand, respiratory variation of IVC-d showed no significant change before and after fluid challenge ( $11.91 \pm 9.41\%$  vs.  $13.51 \pm 9.56\%$ , respectively, with  $p = 0.87$ ). Our results were similar to the study done by Peter Bentzeret who carried out a large meta-analysis ( $n = 173$  patients) which showed that 95% CI for likelihood ratios—the probability of the test to be positive in patients with the disease to probability to be positive in patients without disease – are wide values – the percentage of variation across studies – are high which indicate a high degree of heterogeneity [29]. Furthermore, Muller *et al.* found that in 40 spontaneously breathing shocked patients, the respiratory variations of IVC performed are not better than static indices of preload, such as measuring the pulmonary artery occlusion pressure. In this trial, respiratory variability in IVC-d (>40%) was mostly fluid responsive, but lower values were not. Therefore, it does not have a significant threshold value [30]. However, on contrary to those studies, some studies such as Barbier *et al.* who studied the validity of respiratory variations in IVC to predict fluid responsiveness in mechanically ventilated patients and found that these measurements were initially validated in patients on mechanical ventilation, with 12 and 18% cutoff values separating fluid non-responders from responders [31]. This discrepancy can be explained as IVC-d can be affected by multiple factors, for example, operators variance, the IVC can moving in and out of the plane of US beam with respiration, mimicking a false changes in measures. Moreover, work of breathing with any spontaneous ventilation has a significant impact on IVC size over the respiratory cycle [32].

## Conclusions

Our study showed that  $\Delta$ CDPV was a more precise and even easier assessment tool with better sensitivity and specificity for evaluation of fluid responsiveness than the IVC-d in patients with septic shock on mechanical ventilation. Furthermore,  $\Delta$ CDPV has a high correlation with SVI increasing parameters assessed by echocardiography after fluid boluses. On the other hand and in comparison, CVP showed low accuracy in predicting fluid responsiveness. Echocardiography was still our gold standard method for fluid assessment as it showed very high specificity and sensitivity for fluid response.

### Limitations

Other than the need for a well-trained operator for assessment of the IVC, carotid Doppler, and echography within a short time after admission of included patients for proper assessment of fluid response; there were no other limitations.

### Further studies

We need further studies and meta-analysis to focus on carotid Doppler measurement against IVC-d or against echocardiography assessment to clarify the best method for evaluation of fluid responsiveness.

## References

- Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Intens Care Med.* 2018;44(6):925-8. <https://doi.org/10.1007/s00134-018-5085-0> PMID:29675566
- Leisman DE, Doerfler ME, Ward MF, Masick KD, Wie BJ, Gribben JL. Survival benefit and cost savings from compliance with a simplified 3-hour sepsis bundle in a series of prospective, multisite, observational cohorts. *Crit Care Med.* 2017;45(3):395-406. <https://doi.org/10.1097/CCM.0000000000002184> PMID:27941371
- Wiesenack C, Fiegl C, Keyser A, Prasser C, Keyl C. Assessment of fluid responsiveness in mechanically ventilated cardiac surgical patients. *Eur J Anaesthesiol.* 2005;22(9):658-65. <https://doi.org/10.1017/s0265021505001092> PMID:16163911
- Slama M, Masson H, Teboul JL, Arnould ML, Nait-Kaoudjt R, Colas B, et al. Monitoring of respiratory variations of aortic blood flow velocity using esophageal Doppler. *Intens Care Med.* 2004;30(6):1182-7. <https://doi.org/10.1007/s00134-004-2190-z> PMID:15004667
- Liu V, Morehouse JW, Soule J, Whippy A, Escobar GJ. Fluid volume, lactate values, and mortality in sepsis patients with intermediate lactate values. *Ann Am Thorac Soc.* 2013;10:466-73. <https://doi.org/10.1513/AnnalsATS.201304-099OC> PMID:24004068
- Vandervelden S, Malbrain ML. Initial resuscitation from severe sepsis: One size does not fit all. *Anaesthesiol Intens Ther.* 2015;47:44-55. <https://doi.org/10.5603/AIT.a2015.0075> PMID:26578400
- Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med.* 2017;376(23):2235-44. <https://doi.org/10.1056/NEJMoa1703058>
- Smith JS. Current recommendations for diagnosis and management of sepsis and septic shock. *J Am Acad PAs.* 2013;26(10):42-5. <https://doi.org/10.1097/01.JAA.0000435007.55340.07> PMID:24201922
- Mallat J, Meddour M, Durville E, Lemyze M, Pepy F, Temime J, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth.* 2015;115(3):449-56. <https://doi.org/10.1093/bja/aev222> PMID:26152341
- Lammi MR, Aiello B, Burg GT, Rehman T, Douglas IS, Wheeler AP, et al. Response to fluid boluses in the fluid and catheter treatment trial. *Chest.* 2015;148(4):919-26. <https://doi.org/10.1378/chest.15-0445> PMID:26020673
- Chen C, Kollef MH. Conservative fluid therapy in septic shock: An example of targeted therapeutic minimization. *Crit Care.* 2014;18(4):481. <https://doi.org/10.1186/s13054-014-0481-5> PMID:25185073
- Pinsky MR, Teboul JL. Assessment of indices of preload and volume responsiveness. *Curr Opin Crit Care.* 2005;11(3):235-9. <https://doi.org/10.1097/01.ccx.0000158848.56107.b1> PMID:15928472
- Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology.* 2005;103(2):419-28. <https://doi.org/10.1097/00000542-200508000-00026> PMID:16052125
- Ibarra-Estrada MA, López-Pulgarín JA, Mijangos-Méndez JC, Díaz-Gómez JL, Aguirre-Avalos G. Respiratory variation in carotid peak systolic velocity predicts volume responsiveness in mechanically ventilated patients with septic shock: A prospective cohort study. *Crit Ultrasound J.* 2015;7(1):12. <https://doi.org/10.1186/s13089-015-0029-1> PMID:26123610
- Dinh VA, Ko HS, Rao R, Bansal RC, Smith DD, Kim TE, et al. Measuring cardiac index with a focused cardiac ultrasound examination in the ED. *Am J Emerg Med.* 2012;30(9):1845-51. <https://doi.org/10.1016/j.ajem.2012.03.025> PMID:22795411
- Zhu W, Wan L, Wan X, Wang G, Su M, Liao G, et al. Measurement of brachial artery velocity variation and inferior vena cava variability to estimate fluid responsiveness. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2016;28(8):713-7. <https://doi.org/10.3760/cma.j.issn.2095-4352.2016.08.009> PMID:27434562
- García MI, Cano AG, Monrové JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. *Crit Care.* 2009;13(5):R142. <https://doi.org/10.1186/cc8027> PMID:19728876
- Caillard A, Gayat E, Tantot A, Dubreuil G, M'Bakulu E, Madadaki C. Comparison of cardiac output measured by

- oesophageal Doppler ultrasonography or pulse pressure contour wave analysis. *Br J Anaesth*. 2015;114(6):893-900. <https://doi.org/10.1093/bja/aev001>  
PMid:25735709
19. Varas JL, Díaz CM, Blancas R, Gonzalez OM, Ruiz BL, Montero RM, *et al*. Inferior vena cava distensibility index predicting fluid responsiveness in ventilated patients. *Intens Care Med Exp*. 2015;3(Suppl 1):A600. <https://doi.org/10.1186/2197-425X-3-S1-A600>
20. Otto CM, Pearlman AS, Gardner CL, Enomoto DM, Togo T, Tsuboi H, *et al*. Experimental validation of Doppler echocardiographic measurement of volume flow through the stenotic aortic valve. *Circulation*. 1988;78:435-41. <https://doi.org/10.1161/01.cir.78.2.435>
21. Chan Y. Biostatistics 102: Quantitative data-parametric and non-parametric tests. *Blood Pressure*. 2003;140:79.  
PMid:14700417
22. Chan Y. Biostatistics 103: Qualitative data-tests of independence. *Singapore Med J*. 2003;44(10):498-503.  
PMid:15024452
23. Chan Y. Biostatistics 104: Correlational analysis. *Singapore Med J*. 2003;44(12):614-9.  
PMid:14770254
24. Vignon P, Repessé X, Bégot E, Léger J, Jacob C, Bouferrache K, *et al*. Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated patients. *Am J Respir Crit Care Med*. 2017;195(8):1022-32. <https://doi.org/10.1164/rccm.201604-0844OC>
25. De Backer D, Fagnoul D. Intensive care ultrasound: VI. Fluid responsiveness and shock assessment. *Ann Am Thorac Soc*. 2014;11(1):129-36. <https://doi.org/10.1513/AnnalsATS.201309-320OT>  
PMid:24460447
26. Feissel M, Michard F, Mangin I, Ruyer O, Faller J, Teboul J. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest*. 2001;119(3):867-73. <https://doi.org/10.1378/chest.119.3.867>  
PMid:11243970
27. Song Y, Kwak Y, Song J, Kim Y, Shim J. Respiriophasic carotid artery peak velocity variation as a predictor of fluid responsiveness in mechanically ventilated patients with coronary artery disease. *Br J Anaesth*. 2014;113(1):61-6. <https://doi.org/10.1093/bja/aeu057>  
PMid:24722322
28. Lu N, Xi X, Jiang L, Yang D, Yin K. Exploring the best predictors of fluid responsiveness in patients with septic shock. *Am J Emerg Med*. 2017;35(9):1258-61. <https://doi.org/10.1016/j.ajem.2017.03.052>  
PMid:28363617
29. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-309. <https://doi.org/10.1001/jama.2016.12310>  
PMid:27673307
30. Muller L, Bobbia X, Toumi M, Louart G, Molinari N, Ragonnet B, *et al*. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: Need for a cautious use. *Crit Care*. 2012;16(5):R188. <https://doi.org/10.1186/cc11672>
31. Barbier C, Loubières Y, Schmit C, Hayon J, Ricôme JL, Jardin F, *et al*. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intens Care Med*. 2004;30(9):1740-6. <https://doi.org/10.1007/s00134-004-2259-8>  
PMid:15034650
32. Charbonneau H, Riu B, Faron M, Mari A, Kurrek MM, Ruiz J, *et al*. Predicting preload responsiveness using simultaneous recordings of inferior and superior vena cavae diameters. *Crit Care*. 2014;18(5):473. <https://doi.org/10.1186/s13054-014-0473-5>  
PMid:25189403