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Assessment of dynamic left ventricular outflow track obstruction as fluid responsiveness marker in mechanically ventilated septic patients

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Abstract:

Background: Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Similar to poly trauma, acute myocardial infarction, or stroke, early identification and appropriate management in the initial hours after sepsis develops improves outcomes. In a patient with septic shock, a fluid challenge will cause an increase in stroke volume; according to the Frank-Starling curve [1].Relative hypovolemia has been described in the setting of septic shock. However, only 50 % of patients with hemodynamic instability are fluid responsive [2]. **Purpose**: Assessment of Fluid responsiveness in ventilated septic shock patients according to presence of LVOT obstruction and to judge the power of prediction of other hemodynamic parameters. **Methods:** A prospective observational study was carried out on 50 adult mechanically ventilated patients with septic shock. Two sets of measurements were performed before and immediately after volume expansion. Cardiac output (CO), stroke volume (SV), IVC distensibility index (dIVC), LVOT velocity) m/s ،Mean and peak pressure gradient (mmHg) were measured by transthoracic echocardiography. Fluid challenge responders were defined as patients whose cardiac output was increased ≥15 %. The area under the receiver operating characteristic curve (AUC) was compared for each predictive parameter. **Results:** During the study period, LVOT obstruction was found in 18 patients (36 %). Mortality rate at 60 days was found to be higher in patients with LVOT than in patients without LVOT obstruction (75% versus 25%, $p < 0.01$). Around 90 % of patients with LVOT obstruction were fluid responders versus 60 % from patient without LVOT obstruction (P-value=0.04). IVC distensibility index predicts fluid responsiveness at a cutoff point 17% with a sensitivity 88% and specificity 83 %(p-value < 0.001 and AUC= 0.934) **Conclusions:** LVOT obstruction in the early phase of septic shock is not rare (more than one third of septic shock patients) and is associated with a high mortality rate. Patients who have LVOT, are more fluid responsive than whom have no LVOT. IVC distensibility index carries important baseline parameters that could predict fluid responsiveness in mechanically ventilated patients with septic shock

Keywords: Sepsis; dynamic LVOT obstruction; fluid responsiveness; IVC distensibility

1. Introduction:

Hypovolemia is a very frequent clinical situation in the intensive care unit (ICU) and is primarily treated with volume expansion. Unfortunately, only 40–70 % of critically ill patients with acute circulatory failure display a significant increase in their cardiac output (CO) in response to volume expansion In septic shock, fluid infusion is usually recommended [1] but may be harmful particularly in patients with acute respiratory distress syndrome (ARDS) [2, 3]. It is therefore essential to have reliable tools for predicting the efficacy of volume expansion and thus distinguishing patients who might benefit from volume expansion from those in whom the treatment is likely to be inefficacious or harmful

Currently, both static and dynamic parameters are utilized for prediction of fluid responsiveness. Static parameters (e.g., central venous pressure and pulmonary artery occlusion pressure) are much less reliable than dynamic parameters, which are based on respirophasic variation in stroke volume (e.g., pulse pressure variation and changes in aortic blood flow) [4]. Most common dynamic parameters are invasive (arterial and/or central venous cannulation is required) and expensive. Echocardiography is a well-established method for evaluating fluid responsiveness [3, 4]. On the other hand, the early phase of septic shock is associated with hypovolemia, hyperkinesia and low left ventricular (LV) afterload (making catecholamine infusion necessary), which are hemodynamically situations which may induce IVO [5].

2. Aim of the study

To detect the prevalence of Hypovolemia in ventilated septic shock patients according to presence of LVOT obstruction and its clinical implications & to judge the power of prediction of different hemodynamic modalities for assessment of Fluid responsiveness in ventilated septic shock patients

3. Patients and methods

This is a prospective observational study that was carried out on 50 patients with septic shock and on controlled mechanical ventilation who were admitted to the Critical Care Department, Beni-Suef University Hospital from August 2018 to September 2019

Inclusion criteria: Our study included controlled mechanically ventilated adult patients who were diagnosed as severe sepsis and septic shock as defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Feb. 2016)[6]

Excluded from the study:

Age under 18 years, non-septic causes of shock e.g. heart failure, valvular disease or arrhythmias, acute coronary syndrome or major cardiac dysrhythmia, Hypertrophic obstructive cardiomyopathy (HOCM) , Presence of massive pericardial effusion, intra-abdominal hypertension, contradictions for

fluid challenge as volume overload and Contraindication to central venous catheterization.

Methods:

All patients included in this study were subjected to the following: full clinical examination, APACHE II score was calculated for all patients on admission .SOFA score was calculated for all patients on daily basis

Before taking measurements and during the study period The patients were sedated using Propofol bolus dose with 1-2.5mg/kg IV loading dose and Atracurium 0.4-0.5 mg/kg IV over 60 seconds, then 0.08-0.1 mg/kg 20-45 minutes after initial dose to maintain neuromuscular block and to overcome patient dys-synchrony.

All patients were mechanically ventilated using volume-controlled mode (tidal volume 6 to 8 ml/kg, respiratory frequency 12-15 breaths per minute, positive end-expiratory pressure (PEEP) 0-5cmH2O, plateau pressure was kept below 30 cmH2O. Ventilator settings and dosage of inotropic and vasopressors drugs were kept constant during the whole study period to be sure that the hemodynamic changes were related to volume infusion.

Mean arterial pressure was maintained above 65mmHg by adjusting the doses of vasopressors and inotropic drugs before starting the study

A fluid bolus of 500ml isotonic saline 0.9% was administered over 10 minutes. Within the 1st 6hrs from admission to ICU, we assessed patients for the following hemodynamic parameters-Two sets of measurements were performed before and immediately after volume expansion-Cardiac output (CO), stroke volume (SV), IVC distensibility index (dIVC) and LVOT velocity (m/s), Mean and peak pressure gradient (mmHg) were measured by transthoracic echocardiography

• We defined LVOT obstruction: If peak velocity across LVOT is $\geq$ 0.9 m/s [7, 8]

Echocardiography data:

Echocardiography was performed by trained echocardiographer who was blind about studied data before and after fluid bolus. Transthoracic echocardiography examination was performed using Vivid-S5 with Cardiac Sector Probe 5S-RS (2 - 5 MHz) (General Electric, GE) Fairfield Connecticut, USA

a) Left ventricular outflow tract (LVOT) obstruction

The location of intraventricular obstruction was analyzed at the level of the LVOT. The visualization of left ventricular systolic obliteration ("*kissing papillary muscles sign*") may be indicative of hypovolemia. Continuous and Pulsed Doppler were applied on Left Ventricular Outflow Tract (LVOT) to asses max velocity and flow pattern. LVOT obstruction was suggested when peak velocity across the LVOT $\geq$ 0.9 m/s. [7] All these parameters were recorded during the end-expiratory phase.

b) Cardiac output:

Cardiac output was calculated from measurements of aortic annulus radius from the parasternal long axis view and aortic VTI measured on aortic blood flow recorded using pulsed Doppler at the level of the aortic annulus from an apical five-chamber view. Applying the following equation

$SV=\pi r^2 \times VTI_{(A)}$

, where r = radius of the aortic annulus in cm.

$\pi = 22/7$

The stroke volume (SV) normal values are 45 ± 13 ml/m.

Cardiac Output = SV x heart rate. Information from each examination performed before & after IV fluids maneuver was compared.

c) Parameters of inferior vena caval dynamics (IVC)

Inferior vena cava diameter was obtained from subcostal view in a longitudinal section. The IVC diameter was measured in M-mode coupled to 2D mode 2 cm before the IVC joined the right atrium. The M-mode tracing was perpendicular to the IVC[14].

IVC distensibility index= (max diameter – min diameter) / (min diameter) x 100

4. Results:

Patients were classified according to the presence of LVOT obstruction (If peak velocity at LVOT is ≥ 0.9 m/s) into two groups as follow:

Group (A): without LVOT obstruction, 32patients (64%).

Group (B): with LVOT obstruction, 18patients (36%).

There were no statistically difference between group A and group B as regard the Demographic data, Causes of sepsis, Co-morbidities and scoring system.

Table (1): patient's baseline characteristics

Characteristics	**Group A N=32(%)**	**Group B N=18(%)**	**P-value**
Sex			0.192
Female	22(68.8)	9(٥٠)	
Male	10(31.3)	9(50)	
Age	55.9±19.4	59.4±14	0.495
Co-morbidities			
Smoking	6.3%	١٦.٧%	٠.٢٣٩
HTN	43.8%	٣٨.٩%	٠.٧٣٨
DM	50%	٣٨.٩%	٠.٤٤٩
CKD	31.3%	٣٨.٩%	٠.٥٤٨
Malignancy	9.4%	5.6%	0.633
Cause of sepsis			
Chest infection	15(46.9)	11(61.1)	٠.333
UTI	5(15.6%)	4(22.2)	٠.560
Surgical	9(28.1)	3(16.7)	٠.362
abdominal	3(9.4)	1(5.6)	0.633
Sepsis sequel:			
AKI	15(46.9)	4(22.2)	0.085
ARDS	8(25)	6(33.3)	0.529
CRP mg/L	133.7±66.4	125.4±69.2	0.678
APACHE II	22.8±5.7	23.4±6.6	0.771
SOFA	11.3±2.6	10.3±2.56	0.238
ICU stay(days):	14.8±6.2	12.9±7.1	0.42

a) Hemodynamic parameters

Before IV fluid bolus:

There was a significant difference between the two groups before fluid bolus as regard the dIVC, LVOT peak pressure gradient, mean pressure gradient, LVOT max. Velocity and aortic VTI with P-value=0.035, 0.001, 0.001, 0.001&0.036respectively

While there was no statistical difference between the two groups as regard the HR with p-value: 0.553 table (2)

Table (2) Comparison between group A & B before IV fluid bolus

Parameters before fluid bolus	**Group A**	**Group B**	**P-value**
HR: (beat/min)	101.1±14	98.2±19.8	0.553
dIVC%:	15.8±5.6	19.6±6.5	0.035
LVOT mean(mmHg):	1.1±0.3	4.9±4	<0.001
LVOT peak(mmHg):	2.3±0.6	9±3.2	<0.001
LVOT V max (m/s):	0.7±0.1	1.3±0.4	<0.001
Aortic VTI(Cm/Sec):	17.8±3.9	20.5±4.7	0.036

After I.V. fluid bolus

There was statistical significance difference between two groups after fluid bolus as regard LVOT peak pressure gradient, mean pressure gradient, LVOT max. Velocity and aortic VTI with P-value=0.001, 0.001, 0.001& 0.014 respectively

While there was no statistical difference between the groups as regard HR and dIVC, with p-value: 0.193 & 0.628 respectively Table (3)

Table (3) after IV fluids

	Group A	**Group B**	**P-value**
Parameters after f bolus			
HR: (beat/min)	98.9±11.8	93.8±15.8	0.193
dIVC%:	8.9±2.9	8.4±3.9	0.628
LVOT mean(mmH	0.9±0.3	2.7±1.2	**0.001**
LVOT peak(mmH	1.9±0.6	5.2±2.3	**0.001**
LVOT V max (m/s	0.7±0.1	1.1±0.2	**0.001**
Aortic VTI(Cm/Se	20.9±4.6	24.8±5.9	**0.014**

b) According to need of IV vasopressors and inotropes

Table (4) showed that there was no statistical significant difference between the two groups regarding their need to inotropes or vasopressors, doses and whatever early or late.

Table (4) Comparison between the two groups regarding inotropes and vasopressors

Inotropes & vasopressors	**Group A**	**Group B**	**P-value**
Need to Noradrenalin			

e No Yes	0% 100%	0% 100%	0.99
Noradrenaline (mic/kg/min): Mean±SD	0.53±0.4	0.58±0.35	0.575
Time of nor-adrenaline (Hr): Mean±SD	5.1±1.6	4.9±1.9	0.771
Need to adrenaline No Yes	43.8% 56.3%	44.4% 55.6%	0.962
Adrenaline (mic/kg/min): Mean±SD	0.4±0.35	0.62±0.3	0.094
Time of adrenaline (Hr): Mean±SD	5.7±1.1	5.8±1.8135	0.812

c) Comparison according to fluid responsiveness

88.9% of patients in group B were fluid responders versus 62.5% from patient in group A (P-value=0.04). Table (5)

Table (5) Comparison between the two groups regarding fluid responsiveness

Responsiveness to fluid bolus	**Group A № (%)**	**Group B № (%)**	**P-value**
Response No Yes	12(37.5%) **20(62.5%)**	2(11.1%) **16(88.9%)**	**0.04**

d) ICU stay and mortality

There was no statistical significant difference between the two groups regarding their ICU length of stay (P-value: 0.336) However, the mortality was significantly higher in group B 72.2% compared to group A 34.4% (P-value=0.010).table (6)

Table (6) Comparison between group A and group B regarding ICU stay and mortality:

Characteristics	**Group A № (%)**	**Group B № (%)**	**P-value**
ICU stay(days): Mean±SD	13.9±6.8	11.9±7.2	0.336
Mortality Non-survivors Survivors	11**(34.4%)** 21(65.6%)	13**(72.2%)** 5(27.8%)	**0.010**

ROC curve for IVC distensibility index

Table (7) cut-off points for IVC distensibility index

Variables	**AUC**	**Cut-off**	**Sensitivity**	**Specificity**	**P-value**
dIVC%	0.934	16.5	86%	86%	<0.001

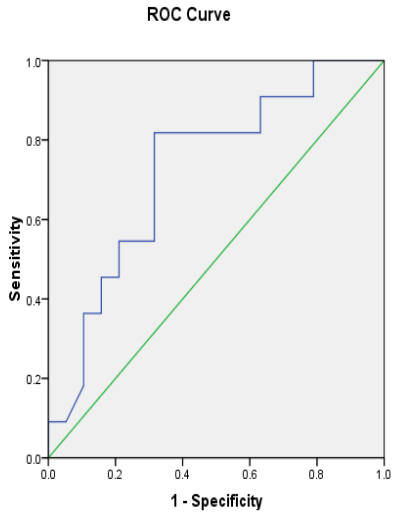

Fig (1): ROC curve

ROC curve was calculated for IVC distensibility index, the area under curve (AUC) was 0.934 with 95% CI from 0.834 to 1. The cutoff point 16.5% carried a sensitivity 86% and specificity 86 %, positive predictive value84.3% and negative predictive value was 80%

5. Discussion:

The clinical determination of the intravascular volume can be extremely difficult in critically ill and injured patients as well as those undergoing major surgery. This is problematic as fluid loading is considered the first step in the resuscitation of hemodynamically unstable patients. Yet, multiple studies have reported that only about 50% of hemodynamically unstable patients in the ICU and operating room respond to a fluid challenge. Cardiac filling pressures including the central venous pressure and pulmonary artery occlusion pressure have traditionally been used to guide fluid management. However, studies performed over the last 30 years have demonstrated that cardiac filling pressures are unable to predict fluid responsiveness [14].

On the other hand, the early phase of septic shock is associated with hypovolemia, hyperkinesia and low left ventricular (LV) afterload (making catecholamine infusion necessary), which are hemodynamically situations which may induce IVO. Nevertheless, there has been no previous study of the incidence of left ventricular obstruction in septic shock, or of the fluid responsiveness of patients presenting with this obstructive flow pattern. Furthermore, clinical consequences of this obstruction have not been analyzed (5)

So, this study aimed to assess the LVOT obstruction for predicting fluid needs in mechanically ventilated septic patients.

Our patients were classified regarding the flow pattern (LVOT) at a peak velocity LVOT ≥0.9 m/s into two groups as follow: group (A): Thirty two patients without Left intra-ventricular flow obstruction (64%) and group (B): Eighteen patients with Left intra-ventricular flow obstruction (36%)

Similar to our study, Samir Elhadidy et al 2019 studied 40 patients with septic shock over a period of 1 year for the presence of Doppler signs of dynamic IVO. There were 13 (32 %) had a documented dynamic Lt Intraventricular obstruction (IVO) flow pattern and 27 patients (68%) didn't have IVO. [12]

Our study had no significant differences in age and gender distribution. Also, there was no statistical significant difference between the two groups regarding co-morbidities and causes of sepsis (P-value<0.05). There was no statistical significant difference between the two groups regarding their ICU length of stay (P-value:0.336) In before fluid bolus, our study found no statistical significant difference between two groups as regarding the APACHE II score and SOFA score (P-value>0.05)

Chauvet et al. (2015) studied a total of 47 patients with septic shock with left ventricular obstruction. Twenty-seven patients (57 %) were male. The mean age was 69 ± 11 years (range 37 to 85. Average length of stay in the ICU was 12 ± 10 days (range 1 to 51). The cause of sepsis was divided between pneumonia (51 %), peritonitis (26 %), cellulitis (9 %), urinary infection (6 %), pericarditis (4 %), endocarditis (2 %) and pancreatitis (2 %), and was not statistically different in the group of septic shock patients without obstruction. [13]

Also Samir Elhadidy et al 2019 studied 40 patients with septic shock over a period of 1 year for the presence of Doppler signs of dynamic IVO. There were no statistically significant differences between both groups regarding the Demographic data, Causes of sepsis, Co-morbidities and ICU stay (12)

Our study results found that there was statistical significance difference between the two groups before fluid bolus as regarding the dIVC, LVOT peak pressure gradient, mean pressure gradient, LVOT max. Velocity and aortic VTI with P-value=0.035, 0.001, 0.001, 0.001&0.036 respectively

While there was no statistical difference between the two groups as regarding the HR with p-value: 0.553

Similarly; Samir Elhadidy et al 2019, there was no statistically significant difference between both groups regarding SBP, DBP, MBP and HR with P-value: 0.568, 0.331, 0.441& 0.711 respectively. However the IVC collapsibility index had p- value:0.05.There was statistically significant difference between both groups regarding LVOT VTI, LVOT mean P.G, LVOT peak P.G, LVOT V max and mid cavitary mean P.G (p value <0.001).(12)

In our study, there was a significantly higher prevalence of fluid responsiveness among patients with left ventricular obstruction 88.9% versus 62.5% in patients without obstruction (P-value=0.04)

In Chavuet et al. (2015) study, thirty five of the 47 patients (79 %) had an increase ≥12 % in cardiac index; 40 patients (87 %) had an increase greater than 12 % in their stroke index (SI). Ninety eight percent of patients presented at least a 10 % rise in SI, and all patients increased their SI after volume infusion. (13)

Samir Elhadidy et al 2019, Twenty-eight patients of all studied patients (40 patients) were fluid responsive (70%) but There was no significant difference between both groups as

regards the incidence of fluid responsiveness (p value: 0.271) (12)

Regarding the mortality, our patients with left ventricular obstruction had a significantly higher mortality rate 72.2% versus 34.4% in patients without obstruction (P-value=0.010).

In agreement to our study, Samir Elhadidy et al 2019, ICU mortality was statistically higher in the group of septic shock patients with LV obstruction when compared with patients without obstruction (10/13 (76.9 %) versus 7/27 (25.9 %), p< 0.002)). (12)

In Chavuet et al. (2015) study, ICU mortality was statistically higher in the group of septic shock patients with LV obstruction when compared with patients without obstruction (25/47 (53 %) versus 41/171 (24 %), p < 0.01)) as the mortality at 28 days was (26/47 (55 %) versus 57/171 (33 %), p < 0.01). [13]

Also Morelli et al. (2013) who studied effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock, found a high mortality rate in patients with hyperkinesias characterized by a heart rate higher than 95 beats/minute. We may expect that among these patients some may have small and hyperkinetic left ventricles and LV obstruction, as in our study group, The high mortality found in our study may therefore be the same as the high mortality found by Morelli et al. This may be, in part, explained by severe hypovolemia and severity of the sepsis with severe vasodilatation, catecholamines and then hyperkinesia of the left ventricle. (14)

In our study, there was no statistical significant difference between the two groups regarding their need to inotropics or vasopressors and their doses and start time (P-value>0.05) LVOT obstruction isn't related to inotropes and vasopressors.

In agreement with our study, Chavuet et al. (2015) reported that septic patients have high circulating catecholamine levels and their intravascular volume is acutely lost to increased permeability, leading to often severe hypovolemia. The treatment instituted in sepsis may also add risk factors as vasopressors used on hypovolemic patients and inotropes both contribute to the hypercontractility, and the frequent use of loop diuretics and sometimes even β-agonists for the treatment of respiratory distress, all are contributing factors to the development of intraventricular obstructive gradients. Moreover, it is an interesting finding of this study that 100 % of the patients were already receiving one or more of these (aggravating) therapies, but there was no significant difference compared to the group without obstruction. (13)

For IVC distensibility index, the area under curve (AUC) was 0.934 with 95% CI from 0.834 to 1. The cutoff point 16.5% carried a sensitivity 86% and specificity 86 %, positive predictive value84.3% and negative predictive value was 80%

Also, Feissel M. et al 2004 studied the respiratory variations in inferior vena cava diameter as a guide to fluid therapy. The study was conducted on 39 mechanically ventilated patients with septic shock to investigate the effect of volume loading with 8mL/kg of 6% hydroxyethylstarch on CO. It concluded that dIVC of [(Dmax – Dmin) / 0.5 (Dmax + Dmin)] or [(Dmax – Dmin)/Dmin] can segregate responders (increase in CO>15%) from non-responders with a sensitivity and specificity of around 90% . ΔDIVC was significantly greater (25±15 vs 6±4%, P<0.001) in responders than in non-responders. ΔDIVC value of 12% allowed discrimination between responders and non-responders with a positive predictive value of 93% and a negative predictive value of 92%. (9)

Also Zhongheng Zhang et al 2013 did a systematic analysis aiming at investigating the diagnostic accuracy of ΔIVC in predicting fluid responsiveness. A total of 8 studies involving 235 patients were eligible for analysis. Cutoff values of ΔIVC varied across studies, ranging from 12% to 40%. The pooled sensitivity and specificity in the overall population were 0.76 (95% confidence interval CI: 0.61–0.86) and 0.86 (95% CI: 0.69–0.95), respectively. The study concluded that ΔIVC measured with point-of-care ultrasonography is of great value in predicting fluid responsiveness, particularly in patients on controlled mechanical ventilation and those resuscitated with colloids. (10)

Similar to our study, Mohammed bakry et al 2013 studied 40 mechanically ventilated septic patients to evaluate respiratory changes in IVC diameter versus pulse pressure variation as fluid responsiveness predictor. They concluded that Baseline PPV value to detect fluid responsiveness tested was 13% with AUC 95.1%, sensitivity 95.8% and specificity 93.8%. Baseline IVC distansability index Cut-off point to detect fluid responsiveness was 18% with AUC 87.8%, sensitivity 91.7% and specificity 87.5%. Baseline CVP value to detect fluid responsiveness was 8cmH2O with AUC 35.4% (unreliable method), sensitivity 66.7% and specificity 62.5%. (11)

6. Conclusion:

- LVOT obstruction in the early phase of septic shock is not rare (over a one third of septic shock patients) and is associated with more fluid responsiveness and high mortality rate.
- IVC distensibility index carries important baseline parameters that could predict fluid responsiveness in mechanically ventilated patients with septic shock

Limitations & Recommendations:

- This study was performed on mechanically ventilated sedated patients so we recommend assessing these variables in spontaneous breathing population.
- The studied population was septic shock patients so we recommend testing fluid

responsiveness variables in other causes of circulatory failure

• At last, we need to increase the clinical applicability by large-scale, multi-center clinical trials in the future .

7. References:

1. Hofer CK, Cannesson M (2011) Monitoring fluid responsiveness. Acta Anaesthesiol Taiwan 49:59–65.
2. Alsous F, Khamiees M., DeGirolamo A, et.al (2000) Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. Chest, 2000. 117: p. 1749-1754**.**
3. Wiedemann HP, Wheeler AP, Bernard GR, Hayden D, et al (2006) National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network,., Comparison of two fluid-management strategies in acute lung injury. N Engl J Med, 2006. 354: p**.**2564-2575.
4. Teboul JL, Monnet X (2008) Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. CurrOpinCrit Care 14:334–9
5. Jhawar MB, B.S., Alpert MA, et al. (2011) Left ventricular outflow tract and mid-cavity obstruction may cause false-positive dobutamine stress echocardiograms. Eur J Echocardiogr, 2011. 12: p. E14.
6. Shankar-Hari M, P.G., Levy ML, et al; (2016) Sepsis Definitions Task Force: Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016. 315: p. 775–787.
7. Panza JA, M.T., Maron BJ. (1992) Development and determinants of dynamic obstruction to left ventricular outflow in young patients with hypertrophic cardiomyopathy. Circulation, 1992. 85: p. 1398-1405.
8. Alvarado Sánchez JI, Amaya Zúñiga WF, Monge García MI. (2017) Predictors to intravenous fluid responsiveness. J Intensive Care Med.
9. Feissel, M., Michard, F., Faller, J. P. & Teboul, J. L., (2004) the respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med., 2004. 30: p. 1834-1837.
10. Zhongheng Zhang, Sheng Y. et al,2014 Ultrasonographic Measurement of the Respiratory Variation in the Inferior Vena Cava Diameter Is Predictive of Fluid Responsiveness in Critically Ill Patients**:** Systematic Review and Meta-analysis Ultrasound in Medicine & Biology, 2014. 40(5): p. 845-853.
11. Mohamed Bakry, Randa Ali, mohammed A. Hammoda et al ،(2013) respiratory changes in IVC diameter versus pulse pressure variation in predicting fluid responsiveness in mechanically ventilated septic patients, Cairo university.

12. Elhadidy S, M. Rafeaa, Elazab A. et al (2019) , Dynamic left intraventricular obstruction in patients with septic shock: pathogenetic role and prognostic implications. Res Opin Anesth Intensive Care, 2019. 6: p**.** 424-428.
13. Chauvet JL, Delastre O, et al. (2015), Early dynamic left intraventricular obstruction is associated with hypovolemia and high mortality in septic shock patients. Crit Care, 2015. 19(١): p. 262.
14. Morelli A, E.C., Westphal M, Rehberg S, Kampmeier T٤ et al.(2013) , Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA, 2013. 310: p. 1683-1691