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A Two Parameters for the Evaluation of Hypovolemia in Patients with Septic Shock: Inferior Vena Cava Collapsibility Index (IVCCI), Delta Cardiac Output

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCEFG **Cem Kivılcım Kaçar**
BCDEFG **Osman Uzundere**
ABCDEFG **Abdulkadir Yektaş**

Department of Anesthesiology and Reanimation, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Corresponding Author: Abdulkadir Yektaş, e-mail: abdulkadir.yektas@saglik.gov.tr
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Background: The aim of this study was to determine the correlation between inferior vena cava collapsibility index and changes in cardiac output measured during passive leg raising test in patients with spontaneous breathing and septic shock.

Material/Methods: Fifty-six patients were included in the study. All of these 56 patients were diagnosed with septic shock and had spontaneous breathing under continuous positive airway pressure. Patients exclusions included: patients with cardiac pathology, not septic shock, pregnant, spontaneous breathing, increased intra-abdominal pressure, inferior vena cava could not be visualized, arrhythmia and pulmonary hypertension. Exclusion criteria for the study were as follows: 1) left ventricular systolic dysfunction, 2) cardiomyopathy, 3) medium severe heart valve disease, 4) patients with arrhythmia; 5) pulmonary hypertension, 6) patients without spontaneous breathing (for inferior vena cava collapsibility index, it is not evaluated), 7) patients with >60 mmHg CO_2 in arterial blood gas; 8) pregnant patients; 9) patients with neurogenic shock, cerebrovascular incident or traumatic brain injury, 10) patients whose inferior vena cava and parasternal long axis cannot be visualized, and 11) patients with increased intra-abdominal pressure.

Patients were placed in neutral supine position, and the inferior vena cava collapsibility index and cardiac output 1 were recorded. In passive leg raising test, after which the cardiac output 2 is recorded in terms of L/min. The percentage increase between the 2 cardiac outputs was calculated and recorded.





Results: A moderately positive correlation was also observed between the inferior vena cava collapsibility index and delta cardiac output ($r=0.459$; $r^2=0.21$), which was statistically significant ($P<0.001$). The cutoff value for the delta cardiac output was 29.5.

Conclusions: In conclusion, we found that the inferior vena cava collapsibility index, which is one of the dynamic parameters used in the diagnosis of hypovolemia in patients with septic shock, is correlated with delta cardiac output after leg raising test. We believe that, based on a clinician's experience, looking at 1 of these 2 parameters is sufficient for the identification of hypovolemia in patients diagnosed with septic shock.

MeSH Keywords: **Cardiac Output • Echocardiography • Hypovolemia • Vena Cava, Inferior**

Abbreviations: **CVP** – central venous pressure; **IVC** – inferior vena cava; **IVCCI** – inferior vena cava collapsibility index; **SV** – stroke volume; **CO** – cardiac output; **PLRT** – passive leg raising test; **Vpeak** – velocity peak; **ICU** – Intensive Care Unit; **CPAP** – continuous positive airway pressure; **PEEP** – positive end-expiratory pressure; **APACHE II score** – Acute Physiology and Chronic Health Evaluation score; **IVC_{min}** – minimum inferior vena cava diameter; **IVC_{max}** – maximum inferior vena cava diameter; **LVOT** – left ventricular outflow tract; **VTI** – velocity time integral; **PW** – PulseWave; **ΔCO** – delta cardiac output; **ROC** – receiver operating characteristic; **AUC** – area under the curve; **LR** – likelihood ratio

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Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. Early and effective fluid resuscitation and vasopressor treatment during sepsis and septic shock is very important for the recovery from septic tissue hypoperfusion.

In patients with sepsis and septic shock, correcting hypotension and improving tissue perfusion requires an increase in cardiac preload (fluid) and vasopressor treatment. In this case, the diagnosis of hypovolemia and completing the intravenous volume of the patient is as important as initiating vasopressor therapy. Static and dynamic tests can be used for cardiac preload estimation. Static tests, such as pulmonary artery occlusion pressure, right and left ventricular end-diastolic volume, central venous pressure, and inferior vena cava diameter, have limited sensitivity. Dynamic tests, such as respiratory changes in aortic blood flow velocity, inferior vena cava collapsibility index (IVCCI), and changes in stroke volume (SV) and cardiac output (CO) via passive leg raising test (PLRT), may be more useful in clinical practice [2]. All of these parameters measured through dynamic tests can be non-invasively evaluated by echocardiography [3–6].

The IVCCI reflects the decrease in the inferior vena cava diameter during inspiration [7]. Although the literature describes cutoff values ranging from 39% to 42% for the IVCCI in terms of response to fluid expansion [7–9], the cutoff value of 40% has been most commonly reported [10–12]. IVCCI describes hypovolemia associated with low RAP [13]. PLRT is a maneuver that directs the blood volume in the lower half of the body toward the heart. It is observed as an increase in CO as a result of increased preload [14].

The IVCCI and PLRT were shown to accurately predict fluid response in mechanically ventilated critical patients [10,14,15]. IVCCI is a dynamic parameter which has been studied in literature. However, it is not always possible to visualize the inferior vena cava. In this case, it is important to measure some parameters from the heart independent of abdominal pathologies in order to diagnose hypovolemia.

The aim of this study was to determine the correlation between inferior IVCCI and Δ CO measured during passive leg raising test in patients with spontaneous breathing and septic shock. For IVCCI, >40% in liters is used as an indicator of hypovolemia. To obtain a cutoff value that can be used as an indicator of hypovolemia for changes in Δ CO based on a value of >40% for IVCCI.

Material and Methods

Patients

This prospective observational study was performed between June 2017 and December 2017 at the tertiary anesthesiology and reanimation Intensive Care Unit (ICU) of our hospital after the ethic committee approval (2017/94). Written and signed informed consent was obtained from the relatives of the patients included in the study.

Sample size calculation was performed using G Power version 3.1.9.4. Based on a 2-tailed alpha error of 0.05, a power of 0.95, and an effect size of 0.5, a total of 42 patients was calculated as the minimum sample size required to achieve statistical power. Fifty-six patients aged 18 to 90 years old who were admitted to the Emergency Department (ED) and diagnosed as septic shock (lactate above 2 mmol/L and systolic artery pressure below 100 mmHg) were included in the study. The patients were intubated in the ED by intravenous administration of 0.1 mg/kg midazolam and 1 μ g/kg remifentanyl. No muscle relaxant was used during or after intubation. Patients were admitted to ICU. The patients were connected to mechanical ventilator in continuous positive airway pressure (CPAP) mode by adjusting 5 cm H₂O positive end-expiratory pressure (PEEP) and adequate pressure support to provide 4–6 mL/kg tidal volume. We performed the measurements after patients' spontaneous breathing returned and the patients were seen in the ED, intubated and immediately taken to the ICU. Measurements were performed within the first 10 minutes and then vasopressor treatment was started with fluid.

Exclusion criteria for the study were as follows: 1) left ventricular systolic dysfunction, 2) cardiomyopathy, 3) medium severe heart valve disease, 4) patients with arrhythmia; 5) pulmonary hypertension, 6) patients without spontaneous breathing (for IVCCI is not evaluated), 7) patients with >60 mmHg CO₂ in arterial blood gas; 8) pregnant patients; 9) patients with neurogenic shock, cerebrovascular incident or traumatic brain injury, 10) patients whose inferior vena cava and parasternal long axis cannot be visualized, and 11) patients with increased intra-abdominal pressure.

The patients' age, gender, weight, height, Acute Physiology and Chronic Health Evaluation (APACHE II) score at ICU admission, and inotropic drug use were recorded. In all patients; electrocardiogram (ECG), SpO₂ assessment, and intraarterial cannulation were performed while they were in the supine position with a Nihon Kohden BSM-9101K monitor (Nihon Kohden Europe GmbH; Raiffeisenstrasse 10, D-61191 Rosbach, Germany), followed by the application of continuous invasive arterial pressure measurement, peripheral body temperature monitoring from the skin, and central venous pressure monitoring with a

central venous catheter. Our study protocol was approved by the institutional ethics committee, and the study was carried out in accordance with the 2008 Helsinki Declaration criteria.

Echocardiographic evaluation

Echocardiographic imaging and measurements were performed using the GE Vivid e device (United Medical Instruments; 832 Jury Court, San Jose, CA, USA) with transthoracic echocardiography probe [2,7]. All measurements were performed together by a cardiologist and an intensive care specialist with echocardiography training.

Patients were placed in neutral supine position [2,7,16]. Parasternal long axis is best displayed but not always available in the neutral position, subcostal 4 chamber view might be effective options; in all of our patients, we were able to obtain images from the parasternal long axis. The inferior vena cava, aorta, and vertebrae were visualized from the subxiphoid window (Figure 1). The inferior vena cava, right atrium entry, and hepatic vein were visualized by turning the probe counterclockwise without changing probe location. The cursor was placed at 1 cm distal to the hepatic vein's inferior vena cava entry point, and the inferior vena cava diameter was monitored for 30 seconds in the M-Mode. The screen was frozen, and the diameter was measured from where the inferior vena cava diameter was the narrowest (IVC_{min}) and the widest (IVC_{max}) (Figure 2). Left ventricular out flow tract (LVOT) diameter was measured from the parasternal long axis window and recorded (Figure 3). The LVOT peak velocity time integral (VTI) were measured from the apical 5-space window by Doppler examination in PW (PulseWave) mode. During the measurement, the 30-second image was frozen and VTI (VTI_1) was measured from the largest wave. After basal measurements were made, PLRT required that the head was raised 45 degrees from the hip joint while the patient was in the supine

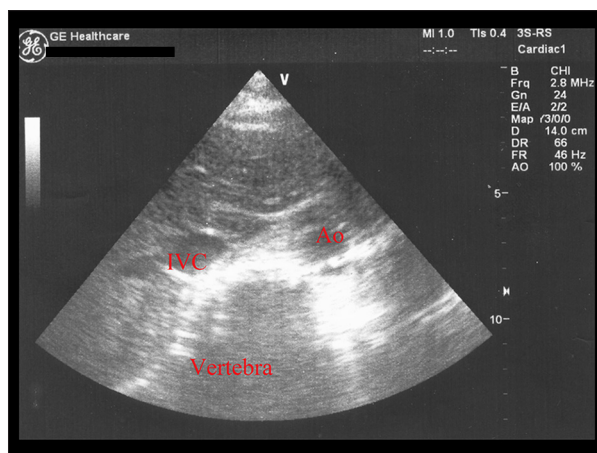


Figure 1. View of inline of vena cava inferior. IVC – inferior vena cava; Ao – aorta.

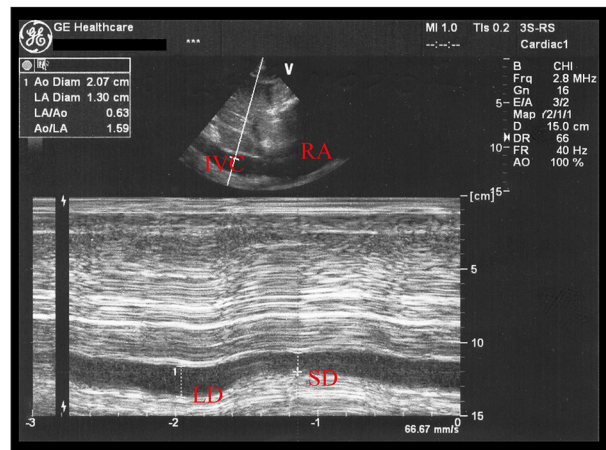


Figure 2. View of outline of vena cava inferior. RA – right atrium; IVC – inferior vena cava; SD – small diameter; LD – large diameter.

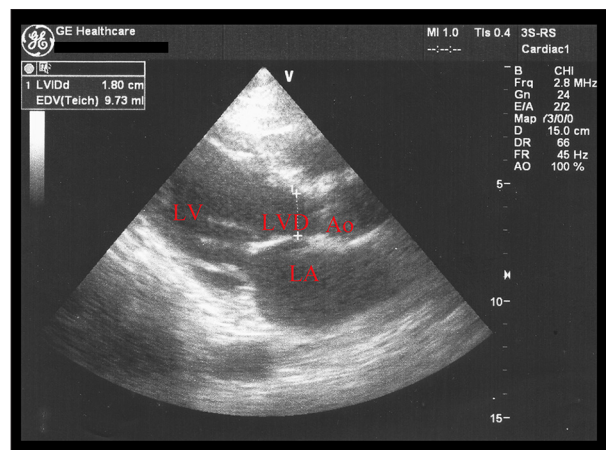


Figure 3. Parasternal long axis window in echocardiogram. Ao – aorta; LA – left atrium; LV – left ventricle; LVD – LVOT diameter.

position and kept in this position for 2 minutes to measure and record VTI_1 . The patient was then placed in supine position again. The legs are then raised 45 degrees from the waist and kept in this position for 1 minute, after which the VTI measurement from the LVOT was repeated (VTI_2) and recorded in terms of cm. There was 1 minutes of time between VTI_1 and VTI_2 measurements [17]. (Figure 4A, 4B). All measurements repeated 3 times and the 3 measurements were averaged. There was 2 minutes of time between each measurement. The first of the 3 measurements was performed by a cardiologist on duty. The second of the 3 measurements was performed by a cardiologist of study. The third of the 3 measurements was performed by an intensive care specialist of study. Results of 3 measurement were collected by an anesthesiologist as intra observer. All the data finally were collected by anesthesiologist as inter observer.

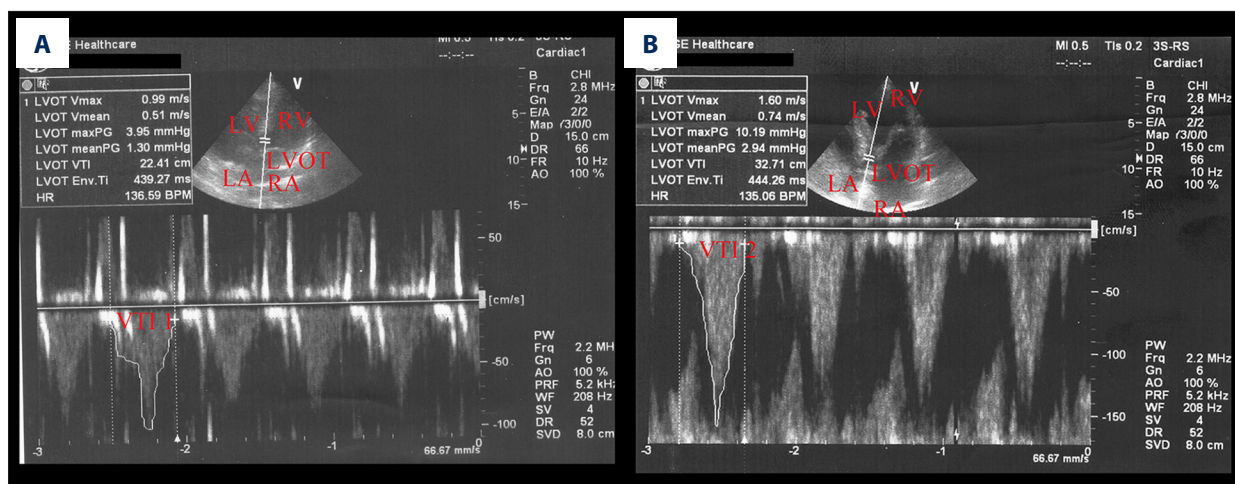


Figure 4. (A) Velocity time integrale 1. (B) Velocity time integrale 2. VTI 1 – velocity time integrale 1; VTI 2 – velocity time integrale 2; RA – right atrium; RV – right ventricle; LA – left atrium; LV – left ventricular; LVOT – left ventricular outflow tract.

The IVCCI was calculated using the following formula: $IVCCI = (IVC_{max} - IVC_{min}) / IVC_{max}$. ΔCO was calculated using the following formula: $CO = \text{heart rate} \times \pi \times (LVOT \text{ diameter} / 2)^2 \times VTI$ [4,7,17]. In our study, we made the second CO measurement by modifying PLRT [17]. The percentage increase (delta CO, ΔCO) between the cardiac output values measured in the supine position and after the leg raise test (CO_1 and CO_2 , respectively) was calculated using the following formula: $\Delta CO = (CO_2 - CO_1 / CO_1) \times 100$.

All measurements were made and recorded. Calculations were made from the recorded data and IVCCI and ΔCO were calculated as a result. For IVCCI, >40% was reported as an indicator of hypovolemia in the literature. ROC analysis was performed based on 40% value of IVCCI. The cutoff value was found parallel to the hypovolemia indicator for IVCCI >40%. Specificity and sensitivity values were also found for CO increase percentage.

Statistical analysis

Statistical analyses were performed with SPSS version 16.0 for Windows. Numerical data were expressed as mean and standard deviation, whereas categorical data were expressed as frequency and percentage. Kolmogorov-Smirnov test was used to evaluate whether the numerical data had normal distribution. Pearson correlation test was used to identify the relationship between the IVCCI and ΔCO values. The degree of correlation between the groups was determined according to Pearson’s correlation coefficient (r) value. As such, $r < 0.2$ was considered as no or very weak correlation, $0.2 \leq r < 0.4$ was considered as weak correlation, $0.4 \leq r < 0.6$ was considered as moderate correlation, $0.6 \leq r < 0.8$ was considered as strong correlation, and $r > 0.8$ was considered as very strong correlation. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff values. $P < 0.05$ was considered statistically significant in all analyses.

Table 1. Baseline characteristics of the study group.

	n*	Mean±SD**
Age (year)	56	49.96±17.18
Height (cm)	56	172.28±8.21
Weight (kg)	56	81.05±10.00
	n	%
Gender		
Male	25	44.60
Female	31	55.40
Inotropic support		
–	32	57.10
+	24	42.90
Source of sepsis		
Lung	23	50.00
Intra-abdominal	14	25.00
Urinary	10	17.85
Skin	5	8.92
Unclear	4	7.14

* Number; ** Standard Deviation.

Results

A total of 56 patients were admitted to the ICU were included in the study. The demographic data and clinical features of the patients are presented in Table 1 (mean±standard deviations and %).

The results of hemodynamic measurements obtained from echocardiographic assessments are presented in Table 2 (mean±standard deviations and %).

Table 2. Hemodynamic variables of the study group.

	n*	Mean±SD**
Vena Cava Inferior Collapsibility Index	56	40.41±19.41
Velocity Time Integral 1 (cm)	56	18.93±7.45
Velocity Time Integral 2 (cm)	56	22.97±7.92
Aortic diameter (mm)	56	2.02±0.43
Cardiac output 1 (ml)	56	6766.03±4049.78
Cardiac output 2 (ml)	56	7582.53±4063.50
Heart rate 1 (bpm)	56	108.87±28.09
Heart rate 2 (bpm)	56	100.08±22.13
ΔCardiac output	56	16.03±19.84

	n	%
Vena Cava Inferior Collapsibility Index ≥%40	28	50
Vena Cava Inferior Collapsibility Index <%40	28	50

* Number; ** Standard Deviation.

Evaluation of the correlation between the IVCCI and ΔCO values obtained from the patients revealed a moderate positive correlation between the IVCCI and ΔCO ($r=0.351$) (Figure 5), which was statistically significant ($P=0.008$). There was a moderate positive correlation between the IVCCI and ΔCO ($r=0.459$) (Figure 5), which was statistically significant ($P<0.001$) (Table 3, Figures 5, 6).

Based on the ROC analysis performed with a cutoff value of 40% and above for IVCCI, the cutoff value for ΔCO, the cutoff value was 29.5 when $AUC=0.794$, $LR=5.53$, $sensitivity=39.3\%$, and $specificity=92.9\%$ ($P<0.001$) (Figure 6).

Discussion

According to the latest sepsis guideline, it is recommended that septic shock diagnosis should be made immediately, and fluid and vasopressor treatment should be initiated within the first hour [1]. In our study, we investigated whether the IVCCI and ΔCO values obtained by echocardiography and used for predicting fluid requirements were correlated with one another. In addition, a review of the literature found the IVCCI cutoff value in patients with septic shock was accepted as 40% in terms of response to fluid expansion [10–12]. We thus considered the IVCCI cutoff value as 40% and aimed to identify a cutoff value for ΔCO; we also examined whether 1 of these 2 parameters was, based on a clinician's general experience, sufficient for the diagnosis of hypovolemia in patients with septic shock.

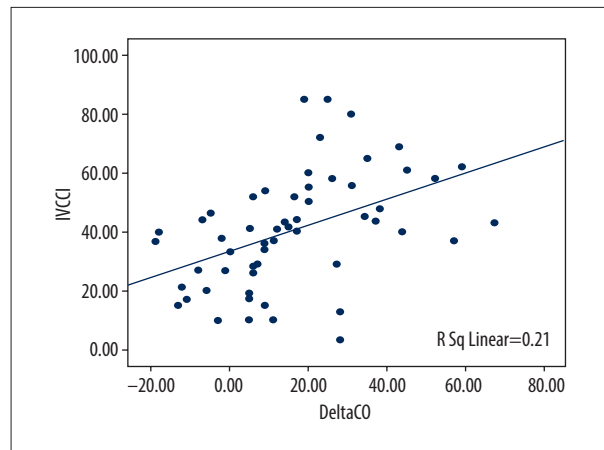


Figure 5. Correlation between VCICI and ΔCO. IVCCI – inferior vena cava collapsibility index; Delta CO=ΔCO, Delta cardiac output; R Sq Linea – R squared linear.

Table 3. Correlation analysis between VCICI* ve ΔCO**.

	VCICI	ΔCO	
VCICI		0.459	r
		0.000#	P
ΔCO	0.459		r
	0.000#		P

* Vena Cava Inferior Collapsibility Index; ** Delta Cardiac Output. # Statistically significant.

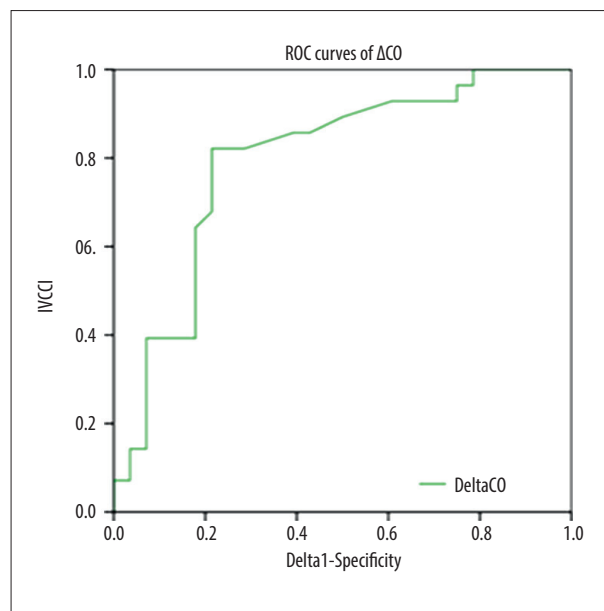


Figure 6. ROC curves for ΔCO: AUC for ΔCO=0,794. Delta CO=ΔCO – delta cardiac output; ROC – receiver operator characteristics curve; AUC – area under the curve.

Inferior vena cava is a primary vein that is highly collapsible and its diameter changes with respiration, blood volume, and right heart function. It also reflects the patient's fluid status [18,19]. Although the literature describes cutoff values ranging from 39% to 42% for the IVCCI in terms of response to fluid expansion [7–9], the cutoff value of 40% is most commonly reported [10–12]. In our study, we considered IVCCI values of 40% or more as hypovolemia.

Changes in stroke volume due to changes in respiration can be echocardiographically evaluated by Doppler analysis of the VTI [4]. SV is calculated by using the aortic diameter and VTI values in the following formula: $SV (ml) = \pi \times (\text{diameter}/2)^2 \times \text{VTI}$ [17]. When we consider the aortic valve area to be constant, changes in VTI can be used instead of changes in SV [7]. In PLRT, the head is raised 45 degrees from the hip joint while the patient is in the supine position and kept in this position for 2 minutes to record systolic arterial pressure in terms of mmHg. The patient is placed in the supine position again. The legs are then raised 45 degrees from the waist and kept in this position for 1 minute, after which the systolic arterial pressure is recorded in terms of mmHg [18]. In PLRT, an increase in CO is seen as a result of the increase in preload. Fluid response can thus be determined without any liquid being administered [14]. This maneuver quickly moves approximately 300–500 mL of blood from the lower extremities into the intrathoracic compartment, creating fluid bolus-like effects. This maneuver is fully reversible and lacks any risk of liquid expansion [3]. In their study, Monnet et al. observed a 12% increase in SAP measured by PLRT, which they considered in favor of hypovolemia (sensitivity 60% and specificity 85%) [17]. In their review, Mesquida et al. reported that PLRT is an easy and reliable method for assessing fluid responsiveness [20]. PLRT is a promising method to assess fluid responsiveness of patients and can be applied in almost all critically ill patients, but it also has some limitations [14]. It might be unsafe in conditions such as insufficient increase in central venous pressure and intraabdominal hypertension [9]. It might not be performed on patients with lower extremity amputation, on patients in prone position, and on acute lower extremity fractures due to risk of advanced trauma [14]. In 2 studies, aortic VTI, SV, and CO were recorded during passive leg raising using transthoracic echocardiography in patients with spontaneous breathing [21,22]. Lamia et al. showed that an increase of 12.5% or more in SV caused by PLRT would predict a 15% or more increase in SV after volume expansion with 77% sensitivity and 100% specificity [21]. In the aforementioned study, patients had spontaneous breathing and were intubated. In a study on

34 patients with spontaneous breathing, Maizel et al. reported that >12% increase in CO or SV during PLRT could predict volume response with a high degree of accuracy [22]. The sensitivity and specificity values were 63% and 89%, respectively. In our study, we used a different and more practical method than PLRT. After measuring CO_1 in the supine position, the patient's legs were raised 45 degrees from the hip joint, kept in this position for 45 seconds, and CO_2 was then measured. ΔCO was calculated through the percent increase between CO_1 and CO_2 [$\Delta CO = (CO_2 - CO_1 / CO_1) \times 100$]. We took the IVCCI cutoff value in response to fluid expansion as 40%, and we found the cutoff value for ΔCO to be 29.5%. This method has not been described in the literature before; it was applied in this study based on the reasoning that it would be more objective than PLRT. In this study, this method was found to be correlated with IVCCI, and can be further tested in future studies.

There was a moderately statistically significant positive correlation between IVCCI and CO values. This situation makes us think that IVCCI and CO values can be used interchangeably. We considered patients to be hypovolemic when patients had an IVCCI of 40% or more. Based on this value we found that the cutoff value for ΔCO was 29.5. ΔV_{peak} (11.4) less than an increase ΔCO (29.5) for more and 40% of VCCI.

Limitations

This study had some limitations. This study has no immediate clinical consequences, but it offers a new parameter. Findings of the present study need to be confirmed in further and larger studies in order to have operative value for everyday clinical practice. We recommend conducting prospective multicenter studies with larger populations.

Conclusions

In conclusion, we found that IVCCI, which is one of the dynamic parameters used in the diagnosis of hypovolemia, was correlated with ΔCO created by the leg raising method, which we used for the first time in our study. When an IVCCI of 40% or more was accepted as hypovolemia, we found the cutoff values of 29.5 for ΔCO . We believe that, based on a clinician's experience, looking at 1 of these 2 parameters is sufficient for the diagnosis of hypovolemia in patients with septic shock. This provides more freedom to the clinicians, allowing them to diagnose hypovolemia with only 1 of the parameters in case there is any obstacle in checking the others.

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