

The value of internal jugular vein collapsibility index in sepsis

Murat Haliloğlu, M.D., Beliz Bilgili, M.D., Alper Kararmaz, M.D., İsmail Cinel, M.D.

Department of Anesthesiology and Reanimation, Marmara University Faculty of Medicine, İstanbul-Turkey

ABSTRACT

BACKGROUND: Rapid, accurate, and reproducible assessment of intravascular volume status is crucial in order to predict the efficacy of volume expansion in septic patients. The aim of this study was to verify the feasibility and usefulness of the internal jugular vein collapsibility index (IJV-CI) as an adjunct to the inferior vena cava collapsibility index (IVC-CI) to predict fluid responsiveness in spontaneously-breathing patients with sepsis.

METHODS: Three stages of sonographic scanning were performed. Hemodynamic data were collected using the Ultrasonic Cardiac Output Monitor 1A system (Uscom, Ltd., Sydney, NSW, Australia) coupled with paired assessments of IVC-CI and IJV-CI at baseline, after passive leg raise (PLR), and again in semi-recumbent position. Fluid responsiveness was assessed according to changes in the cardiac index (CI) induced by PLR. Patients were retrospectively divided into 2 groups: fluid responder if an increase in CI (Δ CI) \geq 15% was obtained after PLR maneuver, and non-responder if Δ CI was $<$ 15%.

RESULTS: Total of 132 paired scans of IJV and IVC were completed in 44 patients who presented with sepsis and who were not receiving mechanical ventilation (mean age: 54.6 ± 16.1 years). Of these, 23 (52.2%) were considered to be responders. Responders had higher IJV-CI and IVC-CI before PLR maneuver than non-responders ($p < 0.001$). IJV-CI of more than 36% before PLR maneuver had 78% sensitivity and 85% specificity to predict responder. Furthermore, less time was needed to measure venous diameters for IJV-CI (30 seconds) compared with IVC-CI (77.5 seconds; $p < 0.001$).

CONCLUSION: IJV-CI is a precise, easily acquired, non-invasive parameter of fluid responsiveness in patients with sepsis who are not mechanically ventilated, and it appears to be a reasonable adjunct to IVC-CI.

Keywords: Collapsibility index; fluid therapy; inferior vena cava; internal jugular vein.

INTRODUCTION

Sepsis is associated with decreased effective blood volume, and fluid resuscitation is usually recommended to increase cardiac output and improve tissue hypoperfusion.^[1] However, studies have shown a relationship between positive fluid balance and mortality in patients with sepsis.^[2] Therefore, rapid, accurate, and reproducible assessment of intravascular volume status is crucial in order to predict the efficacy of volume expansion.^[3]

The inferior vena cava collapsibility index (IVC-CI) has been shown to correlate with both clinical and invasive assessment of intravascular volume status and has become increasingly popular.^[4] It is very easy to record and has a short learning curve. However, IVC measurements are not possible in 10% to 15% of patients because of abdominal distension, ascites, bowel gas, tissue edema, complex abdominal wounds, or morbid obesity.^[5] A body of evidence indicates that extrathoracic veins can reflect intrathoracic venous pressure and volume changes.^[6] Based on this association, hypothesis of this study was that internal jugular vein collapsibility index (IJV-CI) could be an alternative sonographic option to IVC-CI. Prospective examination of the efficacy of the IJV-CI as an alternative in the absence of adequate IVC visualization was performed.

MATERIALS AND METHODS

After receiving institutional review board approval, a prospective, observational clinical trial was conducted in the surgical intensive care unit (SICU) at a university hospital. Marmara University ethics committee approval (No: 09.2015.288) was granted, written informed consent was obtained from the pa-

Address for correspondence: Beliz Bilgili, M.D.
Marmara Üniversitesi Tıp Fakültesi, Anesteziyoloji Anabilim Dalı,
Üst Kaynarca, Pendik, İstanbul, Turkey
Tel: +90 216 - 625 45 45 E-mail: belizbilgili@gmail.com

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tients, and the study was conducted in accordance with the Declaration of Helsinki, including current revisions and Good Clinical Practice guidelines. Hemodynamic data obtained from 44 patients presenting sepsis, according to the definition of and treated following the indications of Surviving Sepsis Campaign Guidelines.^[1] All patients were enrolled within 6 hours of the time of admission to SICU and were not receiving mechanical ventilation. The patients signed informed consent form prior to initiation of study-related activities.

Collected data included patient demographics (age, sex), Sequential Organ Failure Assessment (SOFA) score, Acute Physiology And Chronic Health Evaluation (APACHE II) score, laboratory values, hemodynamic parameters, and sonographic measurements of IVC and IJV collapsibility.

Exclusion criteria were age <18 years, pregnancy, severe aortic stenosis, irregular ventricular rhythm (atrial fibrillation or frequent premature ventricular contractions), or any contraindication to performing passive leg raise (PLR) (intracranial hypertension, intraabdominal hypertension, body mass index >40 kg/m², deep venous thrombosis, use of venous elastic compression stockings, or limb and pelvic fracture).

Hemodynamic data and paired sonographic measurements of IVC and IJV were collected simultaneously; measurements were performed by single operator. All patients in this study underwent serial, simultaneous assessments of IVC-CI and IJV-CI using Philips EPIQ 5 ultrasound system (Philips Healthcare, Inc., Andover, MA, USA). Ultrasonographic examination was performed with standard curvilinear phased array transducer via initial B-mode paramedian longitudinal window of the IVC just proximal to the junction of the hepatic veins that lie approximately 0.5 cm to 3 cm proximal to the right atrium.^[4] IJV was visualized with high-frequency linear array transducer via cross-sectional B-mode window of the short axis of the vessel at the level of the cricoid cartilage and recognized by compression, color Doppler, and pulsed-wave Doppler sampling. In order to avoid changes in vein diameter unrelated to respiratory variation, minimal pressure was applied to the probe to ensure that venous occlusion did not occur.^[7] Dynamic diameter changes of the target vein were recorded using M-mode to measure maximum and minimum dimensions over 20-second period of spontaneous respiration. Vein collapsibil-

ity was calculated using the following formula: collapsibility (%) = (max diameter - min diameter) / max diameter.^[8,9] For each scan, time to data acquisition was defined as time from probe placement to vessel measurement recording. Hemodynamic data were collected using Ultrasonic Cardiac Output Monitor (USCOM) IA system (Uscom Ltd., Sydney, NSW, Australia), coupled with paired assessments of IVC-CI and IJV-CI.

The study protocol was performed in 3 sequential stages. Baseline parameters were recorded with the patient in semi-recumbent position. Next, PLR maneuver was performed by placing the patient in supine position and simultaneously raising the patient's legs to 45°, and after 1 minute, second measurement was recorded. Third measurement was performed 2 minutes after the patient had been moved back to semi-recumbent position in order to check that measured parameters had returned to baseline. The study protocol is shown in Figure 1.

Fluid responsiveness was assessed through changes in cardiac index (CI) induced by PLR. Patients were retrospectively divided into 2 groups: fluid responders, if increase in CI (Δ CI) of $\geq 15\%$ was obtained after PLR maneuver, and non-responders if Δ CI was <15%, as previously described.^[10]

Statistical Analysis

R v.215.3 (R Core Team, 2013; R Foundation for Statistical Computing, Vienna, Austria) software was used to perform statistical analyses. Data were reported as mean, standard deviation, median, first quartile, third quartile, frequency, percentage, minimum and maximum. Student's t-test was used to assess difference of normally distributed variables between the 2 groups. Mann-Whitney U test was used to test difference of non-normally distributed variables between groups. Paired t-test was applied to analyze difference between IVC and IJV values. Receiver operating characteristic (ROC) curves were constructed, sensitivity and specificity of variables were calculated for various values, and value with highest Youden index value was taken as cut-off point. Pearson's correlation coefficient was used to test association between variables. Paired, concurrent measurements of IVC-CI and IJV-CI were analyzed using correlation coefficient and Bland-Altman bias plot. Statistical significance was defined as $p < 0.05$.

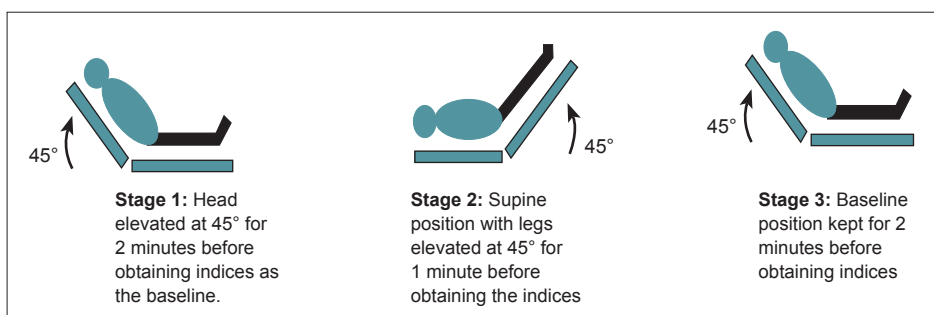


Figure 1. Study protocol.

It was assumed that IVC-CI would be clinically relevant if 95% confidence interval of area under the curve (AUC) was >0.75, corresponding to AUC of good clinical tool as reported by Ray et al.^[11] Inclusion of 39 patients was required to achieve this purpose. Bootstrap analysis was used to calculate precise confidence intervals. Bootstrapping is a method for assigning measures of accuracy to sample estimates and allows estimation of the sampling distribution.^[12] Five patients were added to account for possible missing data.

RESULTS

Total of 44 nonintubated, nonventilated, spontaneously breathing patients with sepsis were examined. Of those, 23 (52.3%) patients were considered to be responders, with increase in CI of 15% or more after PLR maneuver. There were no significant differences between responders and non-responders with regard to demographic or baseline clinical characteristics (Table 1).

Hemodynamic and ultrasonographic measurements are re-

Table 1. Characteristics of the study population

	Responders (n=23)	Non-responders (n=21)	p
Age (years)	64.65±11.28	66.10±16.40	0.734
Gender (% female)	43.47	42.85	0.716
Body mass index	32.22±7.49	33.14±7.56	0.686
APACHE II	16 (15.17)	16 (15.17)	0.875
SOFA	8 (7.10)	9 (8.10)	0.146

Data are presented as median (Q₁, Q₃) where Q₁: first quartile and Q₃: third quartile. APACHE: Acute Physiology And Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

Table 2. Variations in hemodynamic parameters measured in responders and non-responders

	Responders (n=23)	Non-responders (n=21)	p
	Mean±SD	Mean±SD	
Heart rate (beats/minute)			
Stage 1	83.35±5.88	82.43±5.34	0.231
Stage 2	81.78±5.38	81.24±5.25	0.736
Stage 3	84.87±5.83	83.14±5.79	0.342
Mean arterial pressure (mmHg)			
Stage 1	68.22±5.83	70.86±8.44	0.451
Stage 2	76.57±7.23	80.67±8.91	0.100
Stage 3	67.43±5.37	70.90±8.50	0.464
Cardiac index (L/minute/M ²)			
Stage 1	2.26±0.11	2.31±0.18	0.326
Stage 2	3.03±0.17	2.98±0.18	0.287
Stage 3	2.30±0.12	2.32±0.20	0.756
IVC-CI (%)			
Stage 1	37.17±9.02	25.29±8.25	<0.001 ^{***}
Stage 2	17.61±2.74	17.62±2.87	0.812
Stage 3	35.00±8.72	26.05±7.56	<0.001 ^{***}
IJV-CI (%)			
Stage 1	39.04±8.42	26.71±7.04	<0.001 ^{***}
Stage 2	18.83±2.84	18.62±2.89	0.990
Stage 3	38.61±8.74	27.33±6.48	0.001 ^{***}

Data are presented as median (Q₁, Q₃) where Q₁: first quartile and Q₃: third quartile. *p<0.05; **p<0.01; ***p<0.001. IVC-CI: Inferior vena cava collapsibility index; IJV-CI: Internal jugular vein collapsibility index; SD: Standard deviation.

ported in Table 2. In 3 stages, heart rate (HR), mean arterial pressure (MAP), and CI did not differentiate responders from non-responders. Responders had higher IJV-CI and IVC-CI than non-responders at stage 1 ($p<0.001$). This difference was lost after the PLR maneuver at stage 2. Responders also had higher IJV-CI and IVC-CI than non-responders at stage 3 ($p=0.001$, $p<0.001$, respectively).

Total of 132 paired measurements of IJV-CI and IVC-CI were performed. On average, it took 47.5 seconds less to acquire IJV-CI measurements than paired IVC-CI measurements. Mean time to data acquisition was 30 seconds (range: 25-45

seconds) for IJV-CI versus 77.5 seconds for IVC-CI (range: 65-100 seconds; $p<0.01$).

Cut-off values and corresponding sensitivity and specificities of IJV-CI at stage 1 were measured to distinguish responders and non-responders. Cut-off value was determined to be IJV-CI ≥ 36 according to highest Youden index, with 0.78% sensitivity and 0.85% specificity. Area under the ROC curve (AUC) for IJV-CI was 0.872 (Figure 2).

Cut-off values and corresponding sensitivity and specificities of IVC-CI at stage 1 were measured to distinguish responders and non-responders. Cut-off value was determined to be IVC-CI ≥ 35 according to highest Youden index, with 0.78% sensitivity and 0.85% specificity. AUC for IVC-CI was 0.825 (Figure 3).

On linear regression analysis, paired measurements demon-

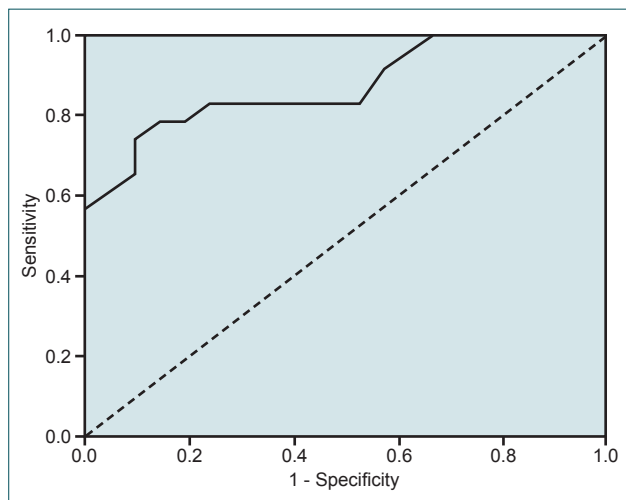


Figure 2. Receiver operating characteristic curve for discriminating responders from non-responders after passive leg raise. The solid line indicates area under curve for internal jugular vein collapsibility index at stage 1 of 0.825; $p<0.001$.

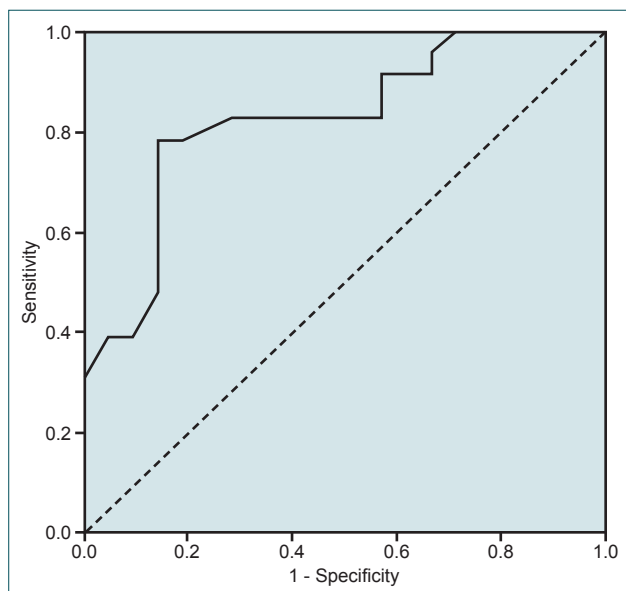


Figure 3. Receiver operating characteristic curve for discriminating responders from non-responders after passive leg raise. The solid line indicates area under curve for inferior vena cava collapsibility index at stage 1 of 0.825; $p<0.001$.

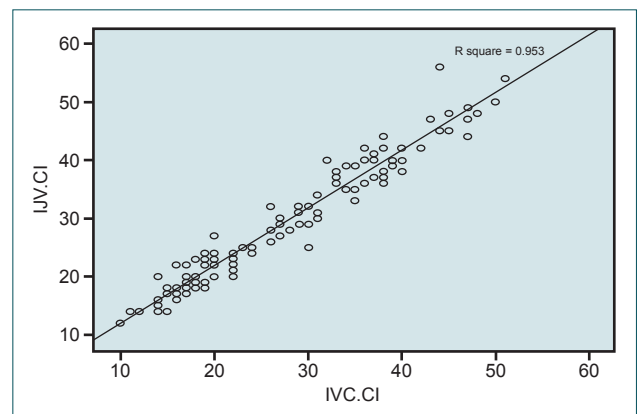


Figure 4. Inferior vena cava collapsibility index versus internal jugular vein collapsibility index. Linear regression demonstrates acceptable correlation between the 2 measurement modalities ($R^2=0.953$). IJV-CI: Internal jugular vein collapsibility index; IVC-CI: Inferior vena cava collapsibility index.

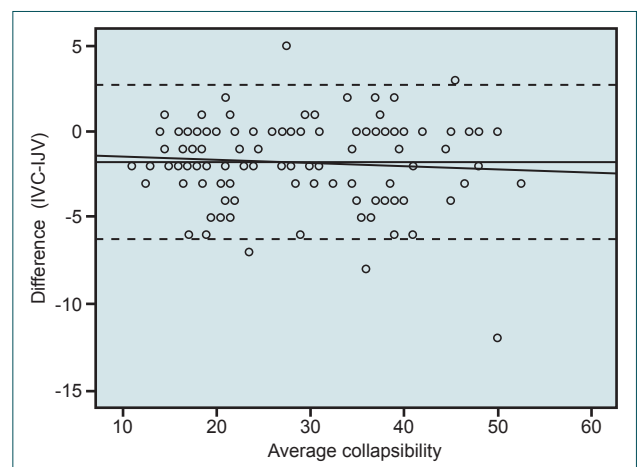


Figure 5. Measurement bias plot comparing inferior vena cava collapsibility index and internal jugular vein collapsibility index across a broad range of collapsibility values. IJV-CI: Internal jugular vein collapsibility index; IVC-CI: Inferior vena cava collapsibility index.

strated acceptable correlation over a broad range of venous collapsibility values ($R^2=0.953$; Figure 4). As a result of the regression analysis, measurement bias was not observed on Bland-Altman graphics. Also, there was a positive correlation between IVC-CI and IJV-CI values ($r=0.976$; $R^2:0.953$) (Figure 5).

DISCUSSION

Results of this study demonstrated that IJV collapsibility was a precise, easily acquired non-invasive parameter of fluid responsiveness in spontaneously breathing patients with sepsis and appeared to be a reasonable adjunct to IVC-CI. Additionally, it took less time to acquire IJV-CI measurements than IVC-CI measurements.

USCOM is a non-invasive continuous-wave (CW) Doppler ultrasound device, temporarily placed in the suprasternal notch to measure Doppler flow at the aortic valve over a cardiac cycle (velocity time integral, VTI). Valve cross-sectional area is determined by applying height-indexed regression equations, and then stroke volume is calculated by multiplying the VTI by the estimate of cross-sectional area.^[13]

The Surviving Sepsis Campaign still recommends central venous pressure (CVP) as a guide for fluid infusion.^[1] However, right-sided filling pressure and CVP measurement require a central venous catheter, which delays resuscitation and is associated with numerous potential complications.^[14] Studies have concluded that there was good correlation between right atrial pressure and IVC respiratory variability in spontaneously breathing patients.^[15,16] Studies that compared IVC measurements and central venous pressure have reported that diameter of the IVC correlated directly to CVP in mechanically-ventilated patients with sepsis, and the IVC-CI correlated with CVP in the setting of low and high CI ranges.^[8,17] Brennan et al. demonstrated that cut-off value of 20% for passive IVC-CI and cut-off value 40% in the sniff test were able to identify patients' right atrial pressure values less than and greater than 10 mmHg.^[18] Additionally, it has been shown that IVC variations were closely correlated with cardiac output increase after fluid infusion.^[19,20] Muller et al. analyzed respiratory variations of IVC to predict fluid responsiveness in spontaneously-breathing patients with acute circulatory failure.^[21] The authors concluded that IVC-CI >40% permitted the prediction of fluid responsiveness, but also IVC-CI <40% did not rule out fluid needs.

A body of evidence shows that extrathoracic veins can reflect intrathoracic venous pressure and volume changes.^[6,22] Based on this association, we hypothesized that IJV-CI could be an alternative sonographic option to IVC-CI. Though several studies have examined IVC-CI and IJV-CI individually to evaluate intravascular volume status and CVP, scarce data exist on the relationship between IVC-CI and IJV-CI. One of our questions was whether IJV-CI and IVC-CI could be used

interchangeably in the setting of spontaneous breathing. Kent et al. studied the feasibility of femoral vein (FV) or IJV collapsibility as options in intravascular volume status assessment and concluded that correlation between IVC-CI and FV/IJV-CI was weak.^[23] However, patients were predominately (72%) mechanically ventilated in their study. Another study from the USA demonstrated that IJV-CI and IVC-CI correlated during spontaneous breathing, but found no statistical correlation during increased thoracic and intra-abdominal pressure.^[24]

PLR maneuver mimics an endogenous fluid challenge by transferring around 300 mL of venous blood from the lower body toward the right heart.^[25] PLR is a reversible maneuver, thereby avoiding the risks of volume overload.^[26] We assessed changes in CI induced by PLR maneuver as an indicator of fluid responsiveness in patients with sepsis who were not receiving mechanical ventilation.

In the present study, IJV-CI was measured to calculate a cut-off of 36%, with sensitivity of 78% and specificity of 86% to predict volume response in spontaneously breathing patients with sepsis. Similarly, we also demonstrated IVC-CI threshold values of 35% to discriminate responders from non-responders with sensitivity of 78% and specificity of 86%. As in our study, the literature has verified that IJV-CI greater than 39% was strongly associated with overall patient hypovolemia.^[27,28]

In the current study, cut-off values of similar parameters are somewhat higher than values reported in mandatory ventilated patients.^[9,20,29] Increased efficiency in patients not mechanically ventilated may result in decreased delta to intrathoracic pressure for comparable tidal volume, and so may require a larger signal to achieve a comparable effect.^[30]

We excluded mechanically ventilated patients because net effect of intrathoracic pressure change may be difficult to assess and collapsibility index may be affected by the amount of diaphragmatic excursion vs. the amount of chest excursion.^[31,32] These data suggest that collapsibility index poorly predicts volume responsiveness in this population.

Our study has several limitations. First, all measurements were performed by a single operator, interobserver variability in sonographic venous diameter measurement remains to be assessed in future studies. Secondly, we did not include patients with cardiac disease. Thirdly, changes in CVP influence IJV diameter and may decrease relative collapsibility. Increased intraabdominal or intrathoracic pressure may increase CVP, which can lead to reduced IJV-CI, independent of preload responsiveness. Of 44 enrolled patients, only 5 patients had CVP catheters. In that case, we did not study the effect of high CVP on IJV-CI and IVC-CI. Therefore, in this study, any confounding conditions, such as cardiac disease, and increased thoracic and intraabdominal pressure were excluded.

IJV-CI is a precise, easily acquired, non-invasive parameter of fluid responsiveness in spontaneously breathing patients with sepsis who are not mechanically ventilated. IJV-CI also appears to be a reasonable adjunct to IVC-CI. Furthermore, obtaining IJV-CI measurements requires less time than IVC-CI measurements, which is another advantage.

Conflict of interest: None declared.

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ORJİNAL ÇALIŞMA - ÖZET

Internal juguler ven kollapsibilite indeksinin sepsisteki değeri

Dr. Murat Haliloğlu, Dr. Beliz Bilgili, Dr. Alper Kararmaz, Dr. İsmail Cinel

Marmara Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, İstanbul

AMAÇ: Septik hastalarda sıvı yanıtını tahmin etmek için volüm durumunun hızlı, doğru ve tekrarlanabilir olarak değerlendirilmesi çok önemlidir. Spontan soluyan septik hastalarda sıvı yanıtının tahmininde inferiyör vena kava kollapsibilite indeksine (IVC-CI) ek olarak internal jugular ven kollapsibilite indeksinin (IJV-CI) etkinliğini araştırmayı amaçladık.

GEREÇ VE YÖNTEM: Sonografik inceleme üç aşamada gerçekleştirildi. USCOM (Ultrasonic Cardiac Output Monitor) sistemiyle hemodinamik verilerle birlikte IVC-CI ve IJV-CI ölçümleri birinci aşamada yarı oturur pozisyonda, ikinci aşamada pasif bacak kaldırma sonrasında (PBK) ve üçüncü aşamada yeniden yarı oturur pozisyona getirildikten sonra ölçüldü. Sıvı yanıtı PBK sonrası kardiyak indeksdeki (CI) değişikliklerle değerlendirildi. Hastalar retrospektif olarak iki gruba ayrıldı: PBK sonrası $\Delta CI \geq 15$ olanlar sıvı yanıtı (R), $\Delta CI < 15$ sıvı yanıtı olarak kabul edildi.

BULGULAR: Mekanik ventilatör desteği almayan 44 sepsis tanılı hastada (ortalama yaş 54.6 ± 16.1 yıl) toplam 132 çift IVK ve IJV kollapsibilite indeksi ölçümü yapıldı. Bu hastalardan 23'ü (%52.2) yanıt alınan (R) olarak kabul edildi. Sıvı yanıtı alınan hastaların IJV-CI ve IVC-CI değerleri sıvı yanıtı olmayan hastalara göre daha yüksekti ($p < 0.001$). İnternal jugular ven kollapsibilite indeksi değeri %36 yüksek olması %78 duyarlılık ve %85 özgüllük ile sıvı yanıtılığını tahmin edebilmektedir. Venöz çap ölçümleri için gereken zaman IJV-CI (30 sn), IVC-CI (77.5 sn) karşılaştırıldığında IJV ölçüm süresi anlamlı olarak kısa bulundu ($p < 0.001$).

TARTIŞMA: Mekanik ventilasyon desteği almayan septik hastalarda sıvı yanıtının tahmininde IJV-CI kolay uygulanabilen, invaziv olmayan bir parametredir, IVC-CI yerine kullanılabilir.

Anahtar sözcükler: İnteriyör vena cava; internal juguler ven; kollapsibilite indeksi; sıvı yanıtı.

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