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Echocardiography Evaluation of the Effects of Midazolam on Passive Leg Raising Test in Critically Ill Patients in the Intensive Care Unit, Diagnosed With Sepsis, Determined to Be Hypovolemic and Responding to Fluid Treatment

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Abstract

Background: In this study, we aimed to investigate the effects of midazolam sedation on intravascular volume in intubated patients diagnosed with sepsis and treated with invasive mechanical ventilation in continuous positive airway pressure mode using Echocardiography (ECHO) parameters.

Methods and Results: One hundred fifty two intensive care unit patients aged 30-50 years with spontaneous breathing, who were intubated, ventilated in continuous positive airway pressure mode via invasive mechanical ventilation, were determined to have fluid deficit. Cardiac index, cardiac out-put and velocity time integral measurements were performed by passive leg rising test before and after midazolam sedation in hypovolemic patients that were determined to respond to fluid treatment and changes in passive leg rising test before and after midazolam were compared. >15% cardiac out-put, >10% cardiac index, and >15% velocity time integral increase in passive leg rising test before midazolam administration showed that patients were hypovolemic and responded to fluid therapy. <15% cardiac out-put, <10% cardiac index, and <15% velocity time integral increase in passive leg rising test after midazolam administration showed that patients were not hypovolemic.

Conclusions: We recommend that passive leg raising test, which is performed to determine the intravascular volume status of critically ill intensive care unit patients determined to be hypovolemic and responding to fluid therapy, should be performed before midazolam sedation.

Keywords:

Cardiac arrest; Echocardiography; Hypovolemic; Sepsis

Introduction

Preservation of intravascular volume, vasopressor treatment and hemodynamic optimization play an important role in preventing morbidity and mortality in ICU patients with sepsis [1-4]. Sepsis has been defined as life-threatening organ dysfunction caused by the irregular host response to infection [2]. Patients with sepsis constitute a majority of critically patients hospitalized in the ICU [5]. While providing hemodynamic stabilization of patients with sepsis, airway control also plays an important role in mortality and morbidity [2]. Providing sedation is also important in patients with sepsis undergoing orotracheal intubation because of airway control [2,6]. Sedative drugs are frequently used in ICU patients [6]. Most of these drugs cause relative hypovolemia as they disrupt compensatory mechanisms [7-15]. Midazolam is one of the sedative drugs frequently used in ICUs [6]. Various animal studies have shown that midazolam can cause vasodilation with its effects on vascular smooth muscle cells and the heart [16-19]. Static and dynamic parameters Central Venous Pressure (CVP), Vena Cava Inferior Collapsibility Index (VCI-CI), Vena Cava Inferior Disability Index (VCI-DI), Delta Velocity Peak (Delta Vpeak), Pulse Pressure Variation (PPV), Stroke Volume Variation (SVV), Passive Leg Raising Test (PLRT)) are used in estimating cardiac preload [2,20]. VCI-CI can also define hypovolemia without performing PLRT. Evaluation with PLRT and hypovolemia can also be defined by Echocardiography (ECHO) parameters.

It is a reliable test to determine whether there is response to fluid in patients who are hypovolemic in PLRT. ECHO is an important tool to identify hypovolemia and monitor fluid resuscitation, especially in critically ill patients, as it is a non-invasive test; it can be performed bedside and frequently repeated. Relative hypovolemia induced by midazolam can change the axis of fluid therapy that is regulated through PLRT, and may cause normovolemic and unresponsive appearance in fluid treatment in patients who have fluid deficit identified with PLRT and normally respond to fluid treatment. In this study, we aimed to investigate the effects of midazolam sedation on PLRT

using ECHO parameters in intubated ICU patients diagnosed with sepsis and proved to have fluid deficit with VCI-CI and PLRT and shown to respond to fluid treatment with PLRT, whose respiration is provided through invasive mechanical ventilation in Continuous Positive Airway Pressure (CPAP) mode at a Positive End Expiratory Pressure (PEEP) of 5cm H2O.

Materials and Methods

This study was carried out between September 2017 and February 2019 in Gazi Yaşargil Training and Research Hospital, Anesthesiology and Reanimation Clinic ICU. The study was designed as an observational prospective study and in accordance with the Strobe statement. Permission was obtained from the local ethics committee hospital ethics committee and written informed consent was obtained from the 1st degree relatives of the patients included in the study. The study was carried out in accordance with the 2008 Helsinki declaration. In the pilot study conducted with 30 patients, CO measurements were performed, and a sample size of N=152 was obtained for Type 1 error 0.05, Type 2 error 0.20, Effect size 0.20, and SD of the change in the outcome 0.88 when mean CO was 8.71 ± 3.37L/min following PLRT prior to midazolam administration and 7.83 ± 3.78L/min following PLRT after midazolam administration. Patients in the pilot study were included in the study.

The patients were diagnosed with sepsis according to the 2016 sepsis guideline [2] Patients with hypoxia or hypercarbia in their Arterial Blood Gas (ABG) and with Glasgow Coma Scale (GCS)<10 were intubated with 1mg/kg propofol and 1μg/kg remifentanil administered intravenously with fluid replacement and vasopressor therapy. Patients with restored spontaneous breathing were connected to the mechanical ventilator in CPAP mode at 5cm H2O PEEP, and all measurements were made after this procedure.

Inclusion criteria

- 30-50 years old patients hospitalized in the ICU
- Intubated patients with spontaneous breathing, ventilated with invasive mechanical ventilation at 5cmH2O PEEP in CPAP mode
- Patients with a Ramsey Sedation Scale (RSS) score of 5-6 at 5 minutes after midazolam administration,
- Patients with fluid deficit. (Patients with >42% VCI-CI and >12% increase in SAP in PLRT)
- Patients who were hospitalized and taken to the emergency department with a blue code, who presented directly to the emergency department, or who developed sepsis while in the ICU.
- Patients with >15% CO, >=10% CI, and >15% VTI increase in PLRT before midazolam administration.

Exclusion criteria

- Patients with serious cardiac disease (cardiac pathology, pulmonary hypertension)
- Patients with intra-abdominal pressure >12mmHg
- Patients with VCI-CI <42%
- Patients with VCI-CI> 42% but without >12% increase in systolic arterial pressure after PLRT
- Hypotensive patients (patients with SAP <90 mmHg despite initiation of fluid replacement and noradrenaline infusion above 1μg/kg/min.
- Patients with arrhythmia
- Patients with a body temperature <37.50C
- Patients without spontaneous breathing
- Patients with APACHE II scores below 25.
- Patients in the supine position from whom five spaces could not be obtained from the 5th intercostal space and images could not be obtained from the parasternal long axis.
- Patients with acute and chronic renal failure.
- Patients with liver failure.

Patients' age, body temperature, height, weight, duration of intensive care stay, Peak Heart Rate (PHR), Peripheral Oxygen Saturation (SpO2), intra-arterial pressures and peripheral body temperatures were recorded before the study procedure was performed. All ECHO (GE Healthcare Vivid S70N made in Germany), Measurements were first performed by the cardiology specialist of the study, and the second measurement was made by the intensive care specialist of the study. Measurement results were obtained by the intraobserver anaesthesiologist and given to the interobserver anaesthesiologist, and all evaluations were made by the interobserver anaesthesiologist. Thus, the experts who made the measurements were blinded to each other. Again, the interobserver anaesthesiologist was also blinded to the experts making the measurements. All data were evaluated by taking the average of the two measurements.

Hemodynamic monitoring

Electrocardiography (ECG), SpO2, intraarterial cannulation followed by continuous invasive arterial pressure measurement, and peripheral body temperature follow-up monitoring were performed in supine position using a bedside monitor (Philips medizin system MX550, made in Germany), as routinely applied to all patients hospitalized in the ICU.

VCI-CI measurement

The positive end-expiratory pressure (PEEP) value was set to 5 mmHg when the mechanical ventilator was in CPAP mode in patients in the supine position. VCI, aorta and vertebra were initially visualized in out-plane position using B-Mode ECHO from the subxiphoid window in a longitudinal section with the ECHO probe **Figure 1**. The ECHO probe was turned counter clockwise without changing its location, and VCI was displayed in the in-plane position **Figure 2**. By visualizing the exit of the VCI from the heart and the hepatic vein, the ECHO cursor was placed approximately 1cm distal to the hepatic vein, and the M-Mode ECHO was turned on. VCI diameter was monitored for several breath periods, and the screen was frozen to measure VCI diameter from the narrowest and widest points.

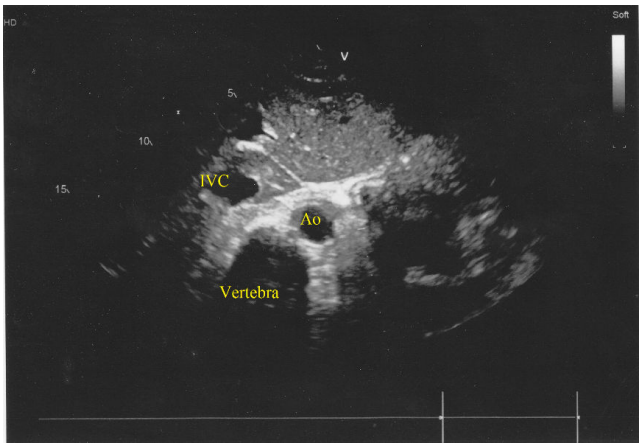

Figure 1: Inferior Vena Cava (ICV), Aorta (AO).

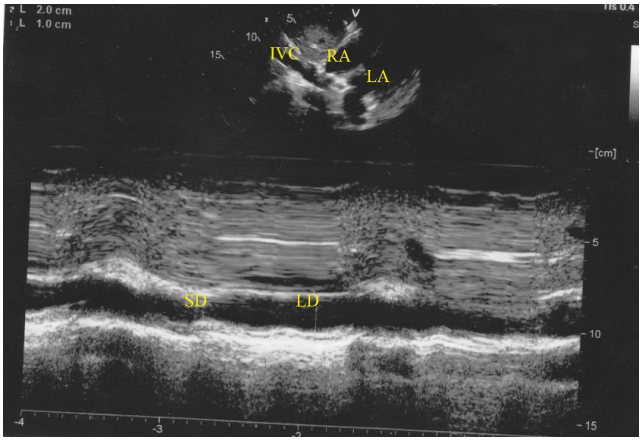

Figure 2: IVC: Inferior Vena Cava (ICV), Right Atrium (RA), Small Diamater (SD), and Large Diameter (LD).

Passive leg raising test

When the patient was lying in supine position, the head was raised 450C above the waist and kept in this position for 2 minutes, and the systolic arterial pressure (SAP) on the monitor was recorded in mmHg. Then, the legs were raised 450C from the waist and the head was restored to its original position, and SAP on the monitor was recorded in mmHg after 1minute. An increase of >12% in the measured SAP was evaluated in favour of hypovolemia and the test was considered positive.

Aortic diameter and VTI measurement

The patient was brought to the supine position, and aortic diameter was measured between the adhesion points of the aortic valve from the aortic annulus line by two-dimensional imaging of the parasternal long axis with the ECHO probe. In the apical window, VTI values of the left ventricular outflow systolic flow velocity were recorded during a single breath cycle with PW (pulsed wave) doppler 1cm below the aortic valve.

Study procedure

1. Patients were diagnosed with sepsis according to the 2016 Sepsis guideline [2].
2. In monitored patients, PHR and SAP were measured in the supine position. The maximum and minimum VCI diameter was measured and recorded. VCI-CI was calculated and the study was continued in patients with>42% VCI-CI.
3. VTI was measured in these patients in supine position by ECHO.
4. SAP and PHR measurements were repeated after PLRT without any medication. The study was continued in patients with>12% increase in systolic arterial pressure in the supine position. In these patients, VTI measurements were repeated by ECHO and recorded.
5. 0.1mg/kg midazolam was administered according to the ideal weight of the patients.
6. No procedure was carried out for five minutes.
7. 5 minutes after midazolam administration, SAP and PHR were measured again and recorded, and VTI was measured again in the supine position by ECHO.
8. PLRT was performed again, and SAP and PHR measurements were recorded. VTI was measured again with ECHO and recorded.

Calculations were made from the recorded data using the following formulas:

With measurements in the supine position:

VCI-CI=(Vmax–Vmin)/Vmax

Aortic area (AA) was calculated as follows: AA=(π x AoD2)/4

Data calculated four times with measurements before and after PLRT before midazolam administration and before and after PLRT after midazolam administration:

- SV: VTI × (πr2)
- CO: SV × HR
- CI: CO/Body surface area (m2)

Statistical analysis

Statistical Package for Social Sciences (SPSS) Mac version 11.5 (SPSS Inc. Chicago, IL, USA) software program was used to evaluate the research data. Normality of distribution of the data was evaluated by Shapiro-Wilk normality test. If $p>0.05$, it was accepted that data was normally distributed, and $p<0.05$ indicated that data was not normally distributed. Data with normal distribution were compared with the Paired Samples t test and the results were given as mean ± SD. Wilcoxon Test was used to compare the data that did not fit normal distribution, and the results were given as median ± Min-Max. $p<0.05$ was considered statistically significant in all analyses.

Result

Demographic and clinical data of the patients are given in **Table 1**.

The source that caused sepsis in patients and the microorganisms grown in the blood are given in **Table 2**. When the effect of PLRT on SAP after the administration of midazolam was examined, it was found that SAP was 114.62 ± 24.40 mmHg before PLRT and 117.72 ± 23.55 mmHg after PLRT. Although

mean SAP increased after PLRT, this increase was not statistically significant (p>0.05). There was a significant difference between SAP before PLRT before and after midazolam administration (128.32 ± 25.30-114.62 ± 24.40 mmHg) and after PLRT before and after midazolam administration (154.03 ± 18.58-117.72 ± 23.55 mmHg). SAP was lower after midazolam administration (p<0.05). A statistically significant increase in PHR was observed in the PLRT performed before midazolam administration (p<0.05).

There was a significant difference between PHR before PLRT before and after midazolam administration (113.53 ± 19.18-101.80 ± 21.62 beats/min) and after PLRT before and after midazolam administration (121.43 ± 16.65-106.45 ± 20.65 beats/min). PHR was lower after midazolam administration (p<0.05). When the effect of PLRT on CI before midazolam administration was examined, it was found that CI was 4.14 ± 1.26L/min/m2 before PLRT, and 5.47 ± 1.28 L/min/m2 after PLRT. The mean CI increase after PLRT was statistically significant (p<0.01). There was a significant difference between CIs before PLRT before and after midazolam administration (4.14 ± 1.26-4.02 ± 1.74) and after PLRT before and after midazolam administration (5.47 ± 1.28-4.39 ± 1.72). CI was lower after midazolam administration (p<0.05).

Parameters	Mean ± SD (Min-Marks)
Age (Year) (n=152)	48,98 ± 10,19 (30-50)
Gender F/M (n=152)	88/74
Weight (kg) (n=152)	67,63 ± 15,89 (50-120)
Height(cm) (n=262)	166,22 ± 9,73 (167-194)
Temperature (ºC) (n=262)	36,61 ± 0,23 (36-37,5)
ICU length of stay (Day) (n=152)	54,28 ± 23,67 (10-157)
SpO_2 % (n=152)	97,70 ± 1,94 (90-100)
Aortic diameter (mm) (n=152)	25,70 ± 3,00(22-34)
VCI-CI % (n=152)	50,95 ± 6,77(44-70)

Female (F), Male (M), Kilogram (Kg), Intensive Care Unit (ICU), Peripheral oxygen saturation (SpO_2), Inferior vena cava-collapsibility index (VCI-CI)

Table 1: Patients' demographic data, temperature, ICU length of stay, SpO_2, Aortic diameter and VCI-CI values (Mean ± SD-Min-Max).

Parameters	Before PLRT (Mean ± SD)	After PLRT (Mean ± SD)	P
SAP before midazolam (mmHg)	128,32 ± 25,30	154,03±18,58	<0,001*
SAP after midazolam mmHg)	114,62 ± 24,40	117,72±23,55	0,051
p	<0,001*	<0,001*	
HR before midazolam (Beat/Minute)	113,53 ± 19,18	121,43±16,65	0,001*
HR after midazolam (Beat/Minute)	101,80 ± 21,62	106,45 ± 20,65	0,509
p	0,049*	0,001*	

Table 2: Comparison of patients SAP and HR values (Mean ± SD).

Discussion

Sedative and anaesthetic drugs are frequently used in critically ill patients in intensive care units. Baroreceptors play a very important role in the regulation of dynamic blood pressure. Baroreceptors are depressed throughout general anaesthesia. Most anaesthetics directly act on myocardial contractility and vascular resistance. This clinical condition contributes to a drop in blood pressure, causes hemodynamic instability, and creates hypovolemia at the same time. One of the sedative agents, propofol reduces systemic vascular resistance and CO, and increases venous capacitance, but does not affect PHR that much. Sedative and anaesthetic drugs prepare the ground for relative hypovolemia by increasing venous capacitance, and as a result, lead to decreased blood volume, CO, inability to meet the oxygen demand in tissues, and potentially hypoxia. Therefore, when using sedative and anaesthetic drugs, drugs with a broad therapeutic index and the least cardiovascular side effects and known antagonists should be used. Midazolam is a benzodiazepine with known effects on cardiac functions that is well tolerated, has a broad therapeutic index and a known antagonist, and its levels can be easily adjusted, especially in patients who will remain intubated for long periods of time.

In the present study, we initially determined that patients were hypovolemic with VCI-CI (>42% significant for hypovolemia), which we performed in supine position and which is an indicator of hypovolemia. We performed PLRT to see if there was fluid response in patients who were considered hypovolemic according to VCI-CI (50.95 ± 6.77 (44-70)) measurement.

Based on SAP measurement results in supine position before PLRT (128.32 ± 25.30 mmHg) and SAP measurement results after PLRT (154.03 ± 18.58mmHg), an increase of 15.3984 (>12%) in SAP before PLRT before midazolam administration is an indication that patients were hypovolemic and responded to fluid. In the present study, the increase in SAP in supine position after PLRT was 25.71 mmHg, which indicated that patients were hypovolemic and responded to fluid therapy.

Conclusion

Our findings show that in hypovolemic patients with sepsis (VCI-CI> 42%) who are determined to be responding to fluid therapy with PLRT (SAP>12%), and demonstrate significant results in CO (>15%), CI (>10%), VTI (>15%) in PLRT in terms of hypovolemia and fluid responsiveness prior to midazolam administration, a significant increase was observed in SAP, CI, CO and VTI values in PLRT after midazolam administration; however, this increase was not enough to diagnose hypovolemia. This shows that the administration of midazolam makes PLRT

meaningless. If PLRT is to be applied to patients, it should be performed before midazolam administration for sedation.

Limitations

In this study, we evaluated the effect of midazolam on PLRT with SAP, CI, CO and VTI in patients diagnosed with sepsis and who were found to be hypovolemic with VTC-CI and responsive to fluid therapy with PLRT. We did not evaluate the effect of midazolam on dynamic parameters during PLRT by thermodilution method independently and objectively, and did not evaluate its correlation with ECHO parameters. We believe that there is a need for further observational prospective studies investigating the correlation between the parameters measured by the thermodilution method and the dynamic parameters viewed by ECHO, and for human studies investigating the effect of midazolam on vascular smooth muscles.

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