

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

Abdulkadir Yektaş (✉ akyektas@hotmail.com)

Research article

Keywords:

Posted Date: June 4th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-29081/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published on September 18th, 2020. See the published version at <https://doi.org/10.37421/jcdd.2020.8.421>.

Abstract

Background

This study used echocardiography parameters to investigate the effects of midazolam sedation on intravascular volume in intubated patients who are diagnosed with sepsis and treated with invasive mechanical ventilation in continuous positive airway pressure mode.

Methods

This study included 152 intensive care unit patients aged 30–50 years with spontaneous breathing; all were intubated, had their lungs ventilated with a positive end-expiratory pressure of 5 cmH₂O in continuous positive airway pressure mode via invasive mechanical ventilation, had a Ramsey sedation scale score of 5–6 at 5 min after midazolam administration, and exhibited a fluid deficit (i.e., inferior vena cava collapsibility index >42% and >12% systolic arterial pressure increase in the passive leg raising test). Cardiac index, cardiac output, and velocity time integral measurements were taken after the passive leg raising test, before and after midazolam sedation, in patients with hypovolaemia who responded to fluid treatment. Changes in passive leg raising test results were compared before and after administration of midazolam.

Results

Cardiac output >15%, cardiac index >10%, and >15% increase in velocity time integral during the passive leg raising test before midazolam administration indicated that patients exhibited hypovolaemia and responded to fluid therapy. Cardiac output <15%, cardiac index <10%, and <15% increase in velocity time integral during the passive leg raising test after midazolam administration indicated that patients did not exhibit hypovolaemia.

Conclusions

We recommend that the passive leg raising test, which is used to determine intravascular volume status of critically ill intensive care unit patients who exhibit hypovolaemia and respond to fluid therapy, should be performed before midazolam sedation.

Background

Preservation of intravascular volume, vasopressor treatment, and haemodynamic optimisation play important roles in prevention of morbidity and mortality in intensive care unit (ICU) patients with sepsis.^(1–4) Sepsis has been defined as life-threatening organ dysfunction caused by an irregular host response to infection.⁽²⁾ Patients with sepsis constitute the majority of critically ill patients hospitalised in the ICU.⁽⁵⁾ Airway control also plays an important role in prevention of mortality and morbidity.⁽²⁾ Provision of sedation is necessary for patients with sepsis who are undergoing orotracheal intubation for airway control.^(2,6) Sedative drugs are frequently used in ICU patients.⁽⁶⁾ Most of these drugs cause relative hypovolaemia, because they disrupt compensatory mechanisms.^(7–15)

Midazolam is a sedative drug frequently used in the ICU.⁽⁶⁾ Various animal studies have shown that midazolam causes vasodilation due to its effects on vascular smooth muscle cells and the heart.^(16–19) Static and dynamic parameters (i.e., central venous pressure, vena cava inferior collapsibility index [VCI-CI], vena cava inferior disability index, delta velocity peak, pulse pressure variation, stroke volume variation, and the passive leg raising test [PLRT]) are used to estimate cardiac preload.^(2,20–23) Notably, the VCI-CI can be used to assess hypovolaemia without performance of the PLRT.^(24–27) PLRT results and hypovolaemia can also be evaluated by echocardiography (ECHO) parameters.^(24,28–37) ECHO is a reliable test to investigate the response to fluid therapy in patients exhibit hypovolaemia on the PLRT.^(28,29) ECHO is an important tool to identify hypovolaemia and monitor fluid resuscitation, particularly in critically ill patients, because of its non-invasive nature, ability to be performed at the bedside, and ability to be repeated frequently.⁽³³⁾

Relative hypovolaemia induced by midazolam can change the axis of fluid therapy regulated through the PLRT; it may cause normovolaemia and unresponsive fluid treatment in patients who exhibit a fluid deficit, as determined using the PLRT, with normal response to fluid treatment. In this study, we investigated the effects of midazolam sedation on PLRT using ECHO parameters in intubated ICU patients diagnosed with sepsis and a fluid deficit, based on VCI-CI and PLRT results, and who responded to fluid treatment, as measured by the PLRT. Respiration was provided through invasive mechanical ventilation in continuous positive airway pressure (CPAP) mode at positive end-expiratory pressure (PEEP) of 5 cmH₂O.

Methods

This study was carried out between September 2017 and February 2019 at the Gazi Yaşargil Training and Research Hospital, Anesthesiology and Reanimation Clinic ICU. The study used an observational prospective study design, in accordance with the STROBE statement. Study approval was obtained from the local ethics committee; written informed consent to participate was obtained from the first-degree relatives of the patients included in the study. The study adhered to the tenets of the 2008 Declaration of Helsinki. In a pilot study conducted with 30 patients, cardiac output (CO) measurements were performed. A sample size of n = 152 was calculated for a Type 1 error of 0.05, Type 2 error of 0.20, effect size of 0.20, and standard deviation of the change in outcome of 0.88; sample size calculations were performed using mean CO of 8.71 ± 3.37 L/min following the PLRT, before midazolam administration, and 7.83 ± 3.78 L/min following the PLRT, after midazolam administration. Patients in the pilot study were included in the main study.

Patients were diagnosed with sepsis in accordance with the 2016 sepsis guidelines.⁽²⁾ Patients with hypoxia or hypercarbia, combined with Glasgow Coma Scale score < 10, were intubated with 1 mg/kg propofol and 1 µg/kg remifentanil administered intravenously. Patients with restored spontaneous breathing were connected to a mechanical ventilator in CPAP mode at 5 cmH₂O PEEP, and all measurements were made after this procedure.

Inclusion criteria:

- 1- Patients (30–50 years of age) hospitalised in the ICU
- 2- Spontaneously breathing intubated patients, whose lungs were ventilated by means of invasive mechanical ventilation at 5 cmH₂O PEEP in CPAP mode
- 3- Patients with a Ramsey sedation scale score of 5–6 at 5 min after administration of midazolam
- 4- Patients with a fluid deficit (i.e., > 42% VCI-CI and > 12% increase in systolic arterial pressure [SAP] on the PLRT)
- 5- Patients who had been hospitalised 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.
- 6- Patients with > 15% CO, ≥ 10% CI, and > 15% increase in velocity time integral (VTI) during PLRT before administration of midazolam.^(38,39,40)

Exclusion criteria:

- 1- Patients with serious cardiac disease (cardiac pathology or pulmonary hypertension)
- 2- Patients with intra-abdominal pressure > 12 mmHg
- 3- Patients with VCI-CI < 42%
- 4- Patients with VCI-CI > 42%, but without > 12% increase in SAP after the PLRT
- 5- Hypotensive patients (i.e., patients with SAP < 90 mmHg, despite initiation of fluid replacement and noradrenaline infusion > 1 µg/kg/min).
- 6- Patients with arrhythmia
- 7- Patients with body temperature > 37.5 °C
- 8- Patients with no spontaneous breathing
- 9- Patients with APACHE II scores < 25.
- 10- Patients in the supine position from whom five images could not be obtained from the fifth intercostal space and no images could be obtained from the parasternal long axis.
- 11- Patients with acute and chronic renal failure.
- 12- Patients with liver failure.

Patient age, body temperature, height, weight, duration of intensive care stay, peak heart rate (PHR), peripheral oxygen saturation, intra-arterial pressures, and peripheral body temperatures were recorded before the study procedure was performed. All ECHO (GE Healthcare Vivid S70N Mannheim, Germany) measurements were first performed by the cardiology specialist; all measurements were repeated by the intensive care specialist. The results were obtained by the intraobserver anaesthesiologist and given to the interobserver anaesthesiologist; all evaluations were then performed by the interobserver anaesthesiologist. Thus, the experts who made the measurements were blinded to each other. The interobserver anaesthesiologist was also blinded to the experts making the measurements. All data were evaluated by recording the average of two measurements.

Haemodynamic Monitoring

ECHO, peripheral oxygen saturation, intra-arterial cannulation, continuous invasive arterial pressure measurement, and peripheral body temperature follow-up monitoring were performed in the supine position using a bedside monitor (Philips Medizin system MX550), as routinely applied to all patients hospitalised in the ICU.

VCI-CI Measurement

The PEEP value was set to 5 mmHg when the mechanical ventilator was in CPAP mode for patients in the supine position. The VCI, aorta, and vertebra were initially visualised in an out-plane position using B-Mode ECHO from the subxiphoid window in a longitudinal section with the ECHO probe (Fig. 1). The ECHO probe was turned counter-clockwise without modifying its location; VCI was displayed in the in-plane position (Fig. 2).

By visualising the exit of the VCI from the heart and the hepatic vein, the ECHO cursor was placed approximately 1 cm distal to the hepatic vein, and M-Mode ECHO was switched on. The VCI diameter was monitored for several breath periods, and the screen was captured to measure VCI diameter at the narrowest and widest points (Fig. 2).

Passive Leg Raising Test

When the patient was lying in the supine position, the head was raised 45° above the waist and kept in this position for 2 min; SAP was then recorded on the monitor in mmHg. Then, the legs were raised 45° from the waist and the head was restored to its original position for 1 min; SAP on the monitor was then recorded in mmHg. An increase of > 12% in the measured SAP was evaluated in favour of hypovolaemia and the test result was considered positive.⁽⁴¹⁾

Aortic Diameter and VTI Measurements

The patient was placed in the supine position and aortic diameter was measured between the adhesion points of the aortic valve from the aortic annulus line, by means of two-dimensional imaging of the parasternal long axis with the ECHO probe (Fig. 3). VTI values of the left ventricular outflow systolic flow velocity (Figs. 4–7) were recorded in the apical window during a single breath cycle with pulsed wave Doppler, 1 cm below the aortic valve.

Study procedure

1- Patients were diagnosed with sepsis in accordance with the 2016 sepsis guidelines.⁽²⁾

2- PHR and SAP were measured in monitored patients who had been placed in the supine position. Maximum and minimum VCI diameters were measured and recorded. VCI-CI was calculated and the study was continued in patients with > 42% VCI-CI.

3- VTI was measured by ECHO in patients with > 42% VCI-CI, with patients in the supine position.

4- SAP and PHR measurements were repeated after the PLRT without any medication. The study was continued in patients with > 12% increase in SAP in the supine position. In these patients, VTI measurements were repeated by ECHO and recorded.

5- Midazolam (0.1 mg/kg) was administered according to the ideal weight of the patient.

No procedures were performed for 5 min.

6- SAP and PHR were measured again 5 min after midazolam administration; VTI was measured again in the supine position by ECHO.

7- The 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:

1- For measurements in the supine position:

a- VCI-CI = (Vmax – Vmin)/Vmax

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

2- Results were calculated four times, using measurements taken before and after the PLRT, before midazolam administration, as well as measurements taken before and after PLRT, after midazolam administration:

a- SV (stroke volume): VTI × (π r²)

b- CO: SV × HR

c- CI: CO/body surface area (m²)

Statistical Analysis

SPSS Statistics for Mac, version 11.5 (SPSS Inc., Chicago, IL, USA) was used to evaluate the data. The normality of the data distribution was evaluated by the Shapiro–Wilk normality test. Normally distributed data were compared with the paired samples *t*-test; results are shown as means ± standard deviations. The Wilcoxon test was used to compare data that did not fit a normal distribution; results are shown as medians (ranges). P-values < 0.05 were considered statistically significant in all analyses.

Results

The demographic and clinical data of the patients are given in Table 1. The source of sepsis in the patients and the microorganisms grown in the blood are given in Table 2.

Examination of the effect of the PLRT on SAP after midazolam administration revealed that SAP was 114.62 ± 24.40 mmHg before the PLRT and 117.72 ± 23.55 mmHg after the PLRT (p > 0.05). A significant difference in SAP was observed between before the PLRT, before and after midazolam administration (128.32 ± 25.30 and 114.62 ± 24.40 mmHg), and after the PLRT, before and after midazolam administration (154.03 ± 18.58 and 117.72 ± 23.55 mmHg); SAP was lower after midazolam administration (p < 0.05) (Table 3). A significant increase in PHR was observed after the PLRT had been performed, before midazolam administration (p < 0.05). A significant difference in PHR was observed between before the PLRT, before and after midazolam administration (113.53 ± 19.18 and 101.80 ± 21.62 beats/min), and after the PLRT, before and after midazolam administration (121.43 ± 16.65 and 106.45 ± 20.65 beats/min); PHR was lower after midazolam administration (Table 3) (p < 0.05).

Examination of the effect of the PLRT on CI before midazolam administration revealed that CI was 4.14 ± 1.26 L/min/m² before the PLRT and 5.47 ± 1.28 L/min/m² after the PLRT; the mean increase in CI after PLRT was statistically significant ($p < 0.01$). A significant difference in CI was observed between before the PLRT, before and after midazolam administration (4.14 ± 1.26 and 4.02 ± 1.74), and after the PLRT, before and after midazolam administration (5.47 ± 1.28 – 4.39 ± 1.72); CI was lower after midazolam administration ($p < 0.05$). While mean CI before the PLRT after midazolam administration was 4.02 ± 1.74 L/min/m², it was 4.39 ± 1.72 L/min/m² after the PLRT after midazolam administration; midazolam significantly enhanced the mean CI after the PLRT ($p < 0.05$) (Table 4).

Examination of the effect of the PLRT on CO before midazolam administration revealed that CO was 6.71 ± 1.40 L/min before the PLRT and 8.37 ± 1.60 L/min after the PLRT ($p < 0.01$). After midazolam administration, CO was 6.22 ± 1.57 L/min before the PLRT and 6.40 ± 1.67 L/min after the PLRT. The PLRT performed after midazolam administration significantly enhanced mean CO ($p > 0.05$). A significant difference in CO was observed between before the PLRT, before and after midazolam administration (6.71 ± 1.40 and 6.22 ± 1.57), and after the PLRT, before and after midazolam administration (8.37 ± 1.60 and 6.40 ± 1.67); CO was lower after midazolam administration (Table 4) ($p < 0.05$).

Examination of the effect of the PLRT on VTI before midazolam administration revealed that VTI was 19.11 ± 4.05 cm before the PLRT and 22.52 ± 4.42 cm after the PLRT; the mean VTI increase after PLRT was statistically significant ($p < 0.01$). Examination of the effect of the PLRT on VTI after midazolam administration revealed that VTI was 18.35 ± 4.28 cm before the PLRT and 19.39 ± 4.95 cm after the PLRT; the mean VTI increase after the PLRT was statistically significant ($p < 0.05$). A significant difference in VTI was observed between before the PLRT, before and after midazolam administration (19.11 ± 4.05 and 18.35 ± 4.28), and after the PLRT, before and after midazolam administration (22.52 ± 4.42 and 19.39 ± 4.95); VTI was lower after midazolam administration (Table 4) ($p < 0.05$).

Discussion

Sedative and anaesthetic drugs are frequently used in critically ill patients in the ICU.⁽⁴²⁾ Baroreceptors play a very important role in the regulation of dynamic blood pressure;⁽⁴²⁾ notably, they are depressed throughout general anaesthesia.⁽⁴²⁾ Most anaesthetics act directly on myocardial contractility and vascular resistance.⁽⁴²⁾ This clinical condition simultaneously contributes to reduced blood pressure, causes haemodynamic instability, and creates hypovolaemia.⁽⁴²⁾ The sedative agent propofol reduces systemic vascular resistance and CO and enhances venous capacitance, but only causes small changes in PHR.⁽⁴²⁾ Sedative and anaesthetic drugs prepare patients for relative hypovolaemia by enhancing venous capacitance, leading to reduced blood volume and CO, as well as the inability to meet tissue oxygen demand and potential onset of hypoxia.^(42,43) Therefore, when using sedative and anaesthetic drugs, drugs with a broad therapeutic index and the lowest numbers of cardiovascular side effects and known antagonists should be used.^(42,43) Midazolam is a benzodiazepine with known effects on cardiac function, which are well tolerated. Midazolam has a broad therapeutic index and a known antagonist, and its levels can be easily adjusted, particularly in patients who will remain intubated for long periods.^(44–50)

In the present study, we initially determined that patients exhibited hypovolaemia when VCI-CI was $> 42\%$ (significant for hypovolaemia),⁽²⁴⁾ which we determined in the supine position. We performed the PLRT to examine whether a fluid response occurred in patients who exhibited hypovolaemia, according to the VCI-CI (50.95 ± 6.77 [44–70]) measurement. Based on SAP results in the supine position before the PLRT (128.32 ± 25.30 mmHg) and SAP results after the PLRT (154.03 ± 18.58 mmHg), an increase in SAP of 15.3984 ($> 12\%$)⁽⁴¹⁾ before the PLRT and before midazolam administration indicated that the patients exhibited hypovolaemia and responded to fluid therapy. In the present study, the increase in SAP in the supine position after the PLRT was 25.71 mmHg, which indicated that patients exhibited hypovolaemia and responded to fluid therapy.

In one study, VCI-CI was measured by transthoracic ECHO, before and 15 min after an infusion of 500 ml (130/0.4) of 6% hydroxyethyl starch. VTI was measured and a 15% increase in VTI after fluid administration was regarded as the fluid response. In the same study, patients were considered to exhibit hypovolaemia when VCI-CI was $> 40\%$.⁽³⁵⁾ In another study, CO was measured by transthoracic ECHO before and after an infusion of 500 ml (130/0.4) of 6% hydroxyethyl starch; the PLRT was also performed. In that study, a 10% increase in CO was considered a positive fluid response; a strong positive correlation with the PLRT was observed. Notably, VCI-CI $> 42\%$ was regarded as the cut-off for hypovolaemia.⁽²⁴⁾ In one study, CO was measured by transthoracic ECHO before and after an infusion of 500 ml (130/0.4) of 6% hydroxyethyl starch; a 15% increase in CO was considered a positive fluid response.⁽³⁶⁾ In another study, CI and SV were strongly correlated with fluid responsiveness.⁽³⁷⁾ In the present study, we performed the PLRT twice. We performed the first assessment before midazolam administration; we evaluated the outcome by means of SAP, CI, CO, and VTI measurements. We detected significant increases in SAP, CO, CI, and VTI after the PLRT. We found that SAP in the supine position was 128.32 ± 25.30 mmHg before midazolam administration and before the PLRT, whereas it was 154.03 ± 18.58 mmHg after the PLRT ($p < 0.05$). A 15.3984 mmHg increase in SAP (12% increase compared to basal value) before PLRT is an indication that patients exhibit hypovolaemia; an increase of 25.71 mmHg was observed in the present study, indicating that our patients exhibited hypovolaemia and responded to fluid therapy. When we evaluated the effect of the PLRT on VTI before midazolam administration, we found that VTI was 19.11 ± 4.05 cm before the PLRT and 22.52 ± 4.42 cm after the PLRT. The increase in mean VTI after the PLRT was statistically significant. An increase of 2.8665 cm in VTI (15% increase compared to basal value) before the PLRT and before midazolam administration is required for diagnosis of hypovolaemia; in the present study, there was an increase of 4.0184 cm, which indicated that our patients exhibited hypovolaemia and responded to fluid therapy. We found that CO was 6.71 ± 1.40 L/min in the supine position before midazolam and before the PLRT, whereas it was 8.37 ± 1.60 L/min after the PLRT ($p < 0.05$). We considered an increase of 1.0065 L/min in CO (15% increase compared to basal value) before the PLRT to be an indicator of hypovolaemia; the CO increase in PLRT before midazolam administration was 2.0706 L/min in our study. This indicated that our patients exhibited hypovolaemia and responded to fluid therapy. We found that CI was 4.14 ± 1.26 L/min/m² in the supine position before midazolam administration and before the PLRT, whereas it was 5.47 ± 1.28 L/min/m² after the PLRT; thus, PLRT caused a significant enhancement in CI. We considered an increase of 0.414 L/min/m² in CI (10% increase compared to basal value) before

the PLRT to be an indicator of hypovolaemia; the increase in CI after the PLRT before midazolam administration was 1.33 L/min/m^2 in the present study, which indicated that our patients exhibited hypovolaemia and responded to fluid therapy.

No significant increase in SAP was observed after midazolam administration; however, there were significant increases in VTI, CO, and CI. SAP in the supine position after midazolam administration and before the PLRT was $114.62 \pm 24.40 \text{ mmHg}$, whereas it was $117.72 \pm 23.55 \text{ mmHg}$ after the PLRT ($p > 0.05$). An increase of 13.7544 mmHg (12% increase compared to basal value) in SAP before the PLRT and after midazolam administration was an indication that the patients exhibited hypovolaemia. In the present study, an increase of 2.7045 mmHg was observed. The increase in SAP decreased during the PLRT, compared to the measurement before midazolam administration; notably, SAP values decreased in some patients compared to pre-PLRT levels. When we evaluated the effect of the PLRT on VTI after administration of midazolam, we found that VTI was $18.35 \pm 4.28 \text{ cm}$ before the PLRT, whereas it was $19.39 \pm 4.95 \text{ cm}$ after the PLRT; this increase in mean VTI after the PLRT was statistically significant. For diagnosis of hypovolaemia, VTI should have increased by 2.7525 cm (15% increase compared to basal value) after the PLRT and after midazolam administration; however, our study revealed an increase of 1.04 cm . This indicated that our patients did not exhibit hypovolaemia. The increase in VTI, caused by the PLRT after midazolam, was smaller than the increase in VTI after the PLRT and before midazolam administration. CO measured in the supine position was $6.22 \pm 1.57 \text{ L/min}$ after midazolam administration and before the PLRT, whereas it was $6.40 \pm 1.67 \text{ L/min}$ after the PLRT. An increase of 0.933 L/min (15% increase compared to basal value) in CO in the PLRT after administration of midazolam would be important in terms of hypovolaemia; however, in the present study, the increase in CO after midazolam was 0.18 L/min . This indicated that our patients did not exhibit hypovolaemia. The increase in CO after the PLRT was reduced after midazolam administration; moreover, CO levels decreased in some patients. There was a significant increase in CO before and after the PLRT after midazolam administration; this increase was insufficient to indicate hypovolaemia. CI measured in the supine position was $4.02 \pm 1.74 \text{ L/min/m}^2$ after midazolam, whereas it was $4.39 \pm 1.72 \text{ L/min/m}^2$ after the PLRT, indicating a significant increase in CI. An increase of 0.402 L/min/m^2 (10% increase compared to basal value) in CI before the PLRT was an indication of hypovolaemia; however, the increase of CI in the PLRT before midazolam administration in our study was 0.37 L/min/m^2 , indicating that our patients did not exhibit hypovolaemia.

Midazolam is frequently used to sedate critically ill patients during the terminal period and is a drug selected for palliative sedation.^(45–48) Midazolam has a two-phase metabolism.⁽⁴⁴⁾ The first phase is hydroxylation via CYP3A; the main metabolite is alpha-hydroxy midazolam and a small amount of 4-hydroxy midazolam.⁽⁴⁴⁾ Alpha-hydroxy midazolam exhibits activity that is 80–100% of the level exhibited by midazolam.⁽⁴⁴⁾ After hydroxylation, alpha-hydroxy midazolam is converted to glucuronate via UDP-glucuronyl transferase; this metabolite exhibits minimal activity (10% of the level exhibited by midazolam).⁽⁴⁴⁾ Peripheral vascular resistance controls blood pressure;^(16,42) it is directly dependent on vascular tone arising from the balance between vasodilator and vasoconstrictor factors that affect vascular smooth muscle cells.^(16,42) Vasodilation depends on the endothelium;^(16,42) endothelial factors (e.g., nitric oxide), reduce endothelial calcium content, leading to relaxation of vascular smooth muscle cells and subsequent vasodilation.^(16,42) Drugs that enhance nitric oxide levels are effective for blood pressure reduction.^(16,42) Benzodiazepines have a direct vascular vasodilator effect on arteries and veins.^(16,42) In addition, benzodiazepines reduce blood pressure indirectly by regulation of the baroreflex system and central inhibition of the autonomic neurocardiac system.^(16,42) Benzodiazepines also regulate chloride ion channels, which may mediate benzodiazepine-induced vascular effects.^(16,42) In addition, vascular calcium channels sensitive to membrane voltage changes may be inhibited by high concentrations of benzodiazepines.^(16,42) At nanomolar concentrations, benzodiazepines bind to non-neurological receptors (i.e., peripheral-type benzodiazepine receptors) in peripheral tissues.^(16,42) In one study, systemic administration of the GABA_A agonist midazolam to *Python molorus* caused significant bradycardia, while the direct cardiac effect of midazolam was not demonstrated; this effect was attributed to midazolam-mediated reduction of cardiac adrenergic tone and enhancement of cholinergic tone.⁽⁵¹⁾ The mean arterial serum concentration of midazolam following intravenous induction (0.2 mg/kg) is 1.36 pg/mL in patients with ischemic heart disease.⁽¹⁸⁾ This is a 95% sufficient dose for unconsciousness.⁽¹⁸⁾ Only high doses of midazolam inhibit noradrenaline release during electrical stimulation, via the alpha-1, alpha-2 agonist contraction effect.⁽¹⁸⁾ Clinical concentrations of midazolam do not inhibit noradrenaline release from sympathetic nerve endings or smooth muscle cell vasoconstriction caused by alpha-adrenoceptors.⁽¹⁸⁾ The results of these animal and human studies suggest that our present findings depended on peripheral vascular vasodilation and the cardiac-depressing effect of midazolam. We presume that the PLRT did not mediate a strong effect after midazolam administration, because fluid responsiveness decreased. To the best of our knowledge, no study has examined the effects of midazolam on intravascular volume status of patients or on the PLRT.

Limitations

We evaluated the effects of midazolam on the PLRT with SAP, CI, CO, and VTI in patients who had been diagnosed with sepsis; all patients exhibited hypovolaemia, according to VCI-CI results, and were responsive to fluid therapy, according to PLRT results. We did not independently or objectively evaluate the effect of midazolam on dynamic parameters during the PLRT by thermodilution, and we did not evaluate correlations with ECHO parameters. Further observational prospective studies are needed to investigate correlations between parameters measured by the thermodilution method and dynamic parameters viewed by ECHO. Human studies are needed to investigate the effect of midazolam on vascular smooth muscle.

Conclusions

Our study revealed significant increases in SAP, CI, CO, and VTI values in the PLRT after midazolam administration in patients with sepsis who exhibited hypovolaemia ($\text{VCI-CI} > 42\%$) and responded to fluid therapy ($\text{SAP} > 12\%$). The results demonstrated significant changes in CO (>15%), CI (>10%), and VTI (>15%) in the PLRT in terms of both hypovolaemia and fluid responsiveness before midazolam administration; however, these increases were insufficient for diagnosis of hypovolaemia. Thus, the PLRT may be unnecessary after administration of midazolam. When the PLRT is applied to patients, it should be performed before midazolam administration for sedation.

Declarations

1. Ethics approval: Republic of turkey, health sciences university, Gazi Yaşargil training and research hospital Ethics committee for clinical research (14.12.2018-179).

Consent to participate: We obtained written informed consent from each the relatives of the patient.

2. Consent to publish: Not Applicable

3. Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

4. Competing interests: The authors declare no competing interests.

5. Funding: Support was provided solely from institutional and/or departmental sources. National Institutes of Health (NIH)

6. Author contribution:

AKY carried out the TTE, participated in the sequence alignment and drafted the manuscript, participated in the design of the study and performed the statistical analysis. Author read and approved the final manuscript.

7. Acknowledgements: Not Applicable

References

- 1-Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, Ranieri VM. et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med* 2006;34(3):589–597.
- 2-Rhodes A, Evans LE, Alhazzani W, Lev MM, Antonelli M, Ferrer R et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock:2016. *Intencive care med* 2017;43(3):304-377.
- 3-Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. *PLoS One*. 2015 Aug 3;10(8):e0129305.
- 4-Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressureare associated with increased mortality. *Crit Care Med*. 2011;39(2):259-65.
- 5-Keijzers G, Macdonald SP, Udy AA, Arendts G, Bailey M, Bellomo R et al. The Australasian Resuscitation In Sepsis Evaluation: Fluids or vasopressors in emergency department sepsis (ARISE FLUIDS), a multi-centre observational study describing current practice in Australia and New Zealand. *Emerg Med Australas*. 2020 Feb 10. doi: 10.1111/1742-6723.13469.
- 6-Ding J, Chen Y, Gao Y. Effect of propofol, midazolam and dexmedetomidine on ICU patients with sepsis and on arterial blood gas. *Exp Ther Med*. 2019 Dec;18(6):4340-4346.
- 7-Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008;108(4):735–48.
- 8-Janssens U, Graf J. [Volume status and central venous pressure]. *Anaesthetist*. 2009;58(5):513-9.
- 9-Lahiry S, Thakur S, Chakraborty DS. Advances in Vasodilatory Shock: A Concise Review. *Indian J Crit Care Med*. 2019 Oct;23(10):475-480.
- 10-Wolff CB, Green DW. Clarification of the circulatory patho-physiology of anaesthesia – implications for high-risk surgical patients. *Int J Surg* 2014;12(12):1348–56.
- 11-Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001;345(8):588–95.
- 12-Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock-part I: physiology. *Crit Care Med* 2013;41(1):255–62.
- 13-Brengelmann GL. Letter to the editor: why persist in the fallacy that mean systemic pressure drives venous return? *Am J Physiol Heart Circ Physiol* 2016;311(5):H1333–5.
- 14-Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care* 2016;20:271.
- 15-Noel-Morgan J, Muir WW. Anesthesia-Associated Relative Hypovolemia: Mechanisms, Monitoring, and Treatment Considerations. *Front Vet Sci*. 2018;5:53.
- 16-Yamaguchi S, Kanmura Y, Yoshimura N. Effects of midazolam on contractions in smooth muscle of the rabbit mesenteric artery. *Anesth Analg*. 1997;84(1):199-205.
- 17-Colussi GL, Di Fabio A, Catena C, Chiuchi A, Sechi LA. Involvement of endothelium-dependent and -independent mechanisms in midazolam-induced vasodilation. *Hypertens Res*. 2011;34(8):929-34.

- 18-Kobayashi Y, Muldoon SM, Kiyose M, Hagiwara T, Kumasaka S, Okabe E. Inhibition by midazolam of the adrenergic function in the isolated canine mesenteric vein. *Acta Anaesthesiol Scand.* 1998;42(10):1157-63.
- 19-Lopes IG, Armelin VA, Braga VHDS, Florindo LH. The influence of midazolam on heart rate arises from cardiac autonomic tones alterations in Burmese pythons, *Python molurus*. *Auton Neurosci.* 2017;208:103-112.
- 20-Vincent JL, De Backer D. Circulatory shock. *N Engl J Med* 2013; 369:1726.
- 21-De Backer D, Cecconi M, Lipman J, Machado F, Myatra SN, Ostermann M, Perner A, Challenges in the management of septic shock: a narrative review. *Intensive Care Med.* 2019;45(4):420-433.
- 22-Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, Cecconi M et al. Current use of vasopressors in septic shock. *Ann Intensive Care.* 2019;9(1):20.
- 23-Cecconi M, Hernandez G, Dunser M, Antonelli M, Baker T, Bakker J, Duranteau J et al. Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force. *Intensive Care Med.* 2019;45(1):21-32.
- 24-Airapetian N, Maizel J, Alyamani O, Mahjoub Y, Lorne E, Levraud M et al. Does inferior vena cava respiratory variability predict fluid responsiveness in spontaneously breathing patients? *Crit Care.* 2015;19:400.
- 25-Corl KA, George NR, Romanoff J, Levinson AT, Chheng DB, Merchant RC, Levy MM et al. Inferior vena cava collapsibility detects fluid responsiveness among spontaneously breathing critically ill patients. *J Crit Care.* 2017 Oct;41:130-137.
- 26-Corl KA, Azab N, Nayeemuddin M, Schick A, Lopardo T, Zeba F, Phillips G et al. Performance of a 25% Inferior Vena Cava Collapsibility in Detecting Fluid Responsiveness When Assessed by Novice Versus Expert Physician Sonologists. *J Intensive Care Med.* 2019;885066619881123.
- 27-Lee CW, Kory PD, Arntfield RT. Development of a fluid resuscitation protocol using inferior vena cava and lung ultrasound. *J Crit Care.* 2016 Feb;31(1):96-100.
- 28-Cherpanath TG, Hirsch A, Geerts BF, Lagrand WK, Leeflang MM, Schultz MJ, Groeneveld AB. Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials. *Crit Care Med.* 2016;44(5):981-91.
- 29-Bou Chebl R, Abou Dagher G, Wuhantu J, Bachir R, Carnell J. Mitral valve velocity time integral and passive leg raise as a measure of volume responsiveness. *Crit Ultrasound J.* 2018;10(1):32.
- 30-Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, Zoric L et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology.* 2011 Sep;115(3):541-7.
- 31-Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, Zoric L et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology.* 2011;115(3):541-7.
- 32-Hu X, Li L, Hao X, Niu N, Tang Y. [Passive leg raising combined with echocardiography could evaluate volume responsiveness in patients with septic shock]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue;* 2019;31(5):619-622.
- 33-Wetterslev M, Haase N, Johansen RR, Perner A. Predicting fluid responsiveness with transthoracic echocardiography is not yet evidence based. *Acta Anaesthesiol Scand.* 2013;57(6):692-7.
- 34-Zhang Z, Xu X, Ye S, Xu L. 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 Med Biol.* 2014;40(5):845-53.
- 35-Muller L, Bobbia X, Toumi M, Louart G, Molinari N, Ragonnet B et al. Respiratory variations of inferior vena cava diameter to predict fluid responsiveness in spontaneously breathing patients with acute circulatory failure: need for a cautious use. *Crit Care.* 2012;16(5):R188.
- 36-Wu Y, Zhou S, Zhou Z, Liu B. A 10 second fluid challenge guided by transthoracic echocardiography can predict fluid responsiveness. *Crit Care.* *Crit Care.* 2014;18(3):R108.
- 37-Audimoolam VK, McPhail MJ, Willars C, Bernal W, Wendon JA, Cecconi M et al. Predicting Fluid Responsiveness in Acute Liver Failure: A Prospective Study. *Anesth Analg.* 2017;124(2):480-486.
- 38-Lamia B, Ochagavia A, Monnet X, Chemia C, Tebeul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007;33(7):1125-1132.
- 39-Maizel J, Airapetian N, Lorne E, Tribolloy C, Massy Z, Slama M. Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med* 2007;33(7):1133-1138

- 40-Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med 2009;37(3):951-6.
- 41-Monnet X, Rienzo M, Osman D et al. Passive leg raising predicts fluid responsiveness in the critically ill passive. Crit Care Med 2006;34(5):1402-1407.
- 42-Sellgren J, Biber B, Henriksson BA, Martner J, Pontén J. The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. Acta Anaesthesiol Scand. 1992;36(8):784-90.
- 43-Seagard JL, Elegbe EO, Hopp FA, Bosnjak ZJ, von Colditz JH, Kalbfleisch JH, Kampine JP. Effects of isoflurane on the baroreceptor reflex. Anesthesiology. 1983;59(6):511-20.
- 44-Franken LG, Masman AD, de Winter BCM, Baar FPM, Tibboel D, van Gelder T et al. Hypoalbuminaemia and decreased midazolam clearance in terminally ill adult patients, an inflammatory effect? Br J Clin Pharmacol. 2017;83(8):1701-1712.
- 45-Franken LG, de Winter BCM, Masman AD, van Dijk M, Baar FPM, Tibboel D, Koch BCP, van Gelder T, Mathot RAA. Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients. Br J Clin Pharmacol. 2018;84(2):320-330.
- 46-Garett F, Cancelli F, Rossi R, Maltoni M. Palliative Sedation for the Terminally Ill Patient. CNS Drugs. 2018;32(10):951-961.
- 47-Bobb B. A Review of Palliative Sedation. Nurs Clin North Am. 2016;51(3):449-57.
- 48-Berg AK, Myrvik MJ, Van Ess PJ. Pharmacokinetics, pharmacodynamics, and tolerability of USL261, midazolam nasal spray: Randomized study in healthy geriatric and non-geriatric adults. Epilepsy Behav. 2017;71:51-59.
- 49-Schaller SJ, Alam SM, Mao J, Zhao Y, Blobner M, Greenblatt DJ et al. Pharmacokinetics cannot explain the increased effective dose requirement for morphine and midazolam in rats during their extended administration alone or in combination. J Pharm Pharmacol. 2017;69(1):82-88.
- 50-Ershoff BD, Machi RY, Navi S, Hong JC. A novel factor influencing perioperative midazolam administration: The effect of presentation dose on administration dose. J Anaesthesiol Clin Pharmacol. 2019;35(2):192-196.
- 51-Lopes IG, Armelin VA, Braga VHDS, Florindo LH. The influence of midazolam on heart rate arises from cardiac autonomic tones alterations in Burmese pythons, Python molurus. Auton Neurosci. 2017;208:103-112.

Tables

Table 1: Patients' demographic data, temperature, ICU length of stay, SpO₂, Aortic diameter and VCI-CI values (Mean±SD-Min-Max).

Parameters	Mean±SD (Min-Maks)
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 (°C) (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)

F: Female

M: Male

Kg: kilogram

ICU: Intensive care unit

SpO₂: Peripheral oxygen saturation

VCI-CI: Inferior vena cava-collapsebility index

Table 2: Microorganisms produced from focus and blood samples taken when the patient was first seen.

sepsis source	Focus +Blood
Pulmonary (n=61)	1- Acinetobacter baumannii (n=21) 2- Klebsiella pneumoniae (n=17) 3- Staphylococcus aureus (n=12) 4- Streptococcus pneumonia (n=2) 5- Candida albicans (n=4) 5- Staphylococcus aureus in focus could not be produced in blood (n=5)
Intra-abdominal (n=34)	1- Escherichia Coli (n=21) 2- Klebsiella pneumoniae (n=7) 3- Candida albicans (n=3) 4- Unclear (n=2) 5- Acinetobacter baumannii (n=1)
Urinary (n=23)	1- Escherichia Coli (n=14) 2- Klebsiella pneumoniae (n=6) 3- Enterobacter spp(n=1) 4- Candida albicans (n=1) 5- Candida albicans in focus could not be produced in blood (n=1)
Skin (n=4)	1- Staphylococcus aureus (n=2) 2- Group A streptococci (n=1) 3- Group A streptococcus in focus could not be produced in blood (n=1)
Central nervous system (n=8)	1- Streptococcus pneumonia (n=6) 2- Neisseria meningitidis (n=1) 3- Escherichia Coli in focus could not be produced in blood (n=1)
Intrauterine (n=5)	1- Escherichia Coli (n=3) 2- Enterobacter faecalis (n=2)
Bone (n=17)	1- Staphylococcus aureus (n=11) 2- Pseudomonas aeruginosa (n=5) 3- Hemophilus influenza (n=1)

Table 3: Comparison of patients SAP and HR values (Mean±SD)

Parameters	Before PLRT	After PLRT	P
	Mean±SD	Mean±SD	
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*	

SAP: Systolic artery pressure

HR: Heart rate

PLRT: Passive leg rise test

Table 4: Comparison of patients CI, CO, VTI values (Mean±SD)

Parameters	Before PLRT mean±SD	After PLRT mean±SD	P
CI before midazolam (L/dk/m ²)	4,14±1,26	5,47±1,28	<0,001*
CI after midazolam (L/dk/m ²)	4,02±1,74	4,39±1,72	0,001*
p	0,034*	<0,001*	
CO before midazolam (L/dk)	6,71±1,40	8,37±1,60	<0,001*
CO after midazolam (L/dk)	6,22±1,57	6,40±1,67	0,001*
p	<0,001*	0,001*	
VTI before midazolam (cm)	19,11±4,05	22,52±4,42	<0,001*
VTI after midazolam (cm)	18,35±4,28	19,39±4,95	<0,001*
p	<0,001*	<0,001*	

CI: Cardiac index

CO: Cardiac output

VTI: Velocity time integral

PLRT: Passive leg rise test

Figures

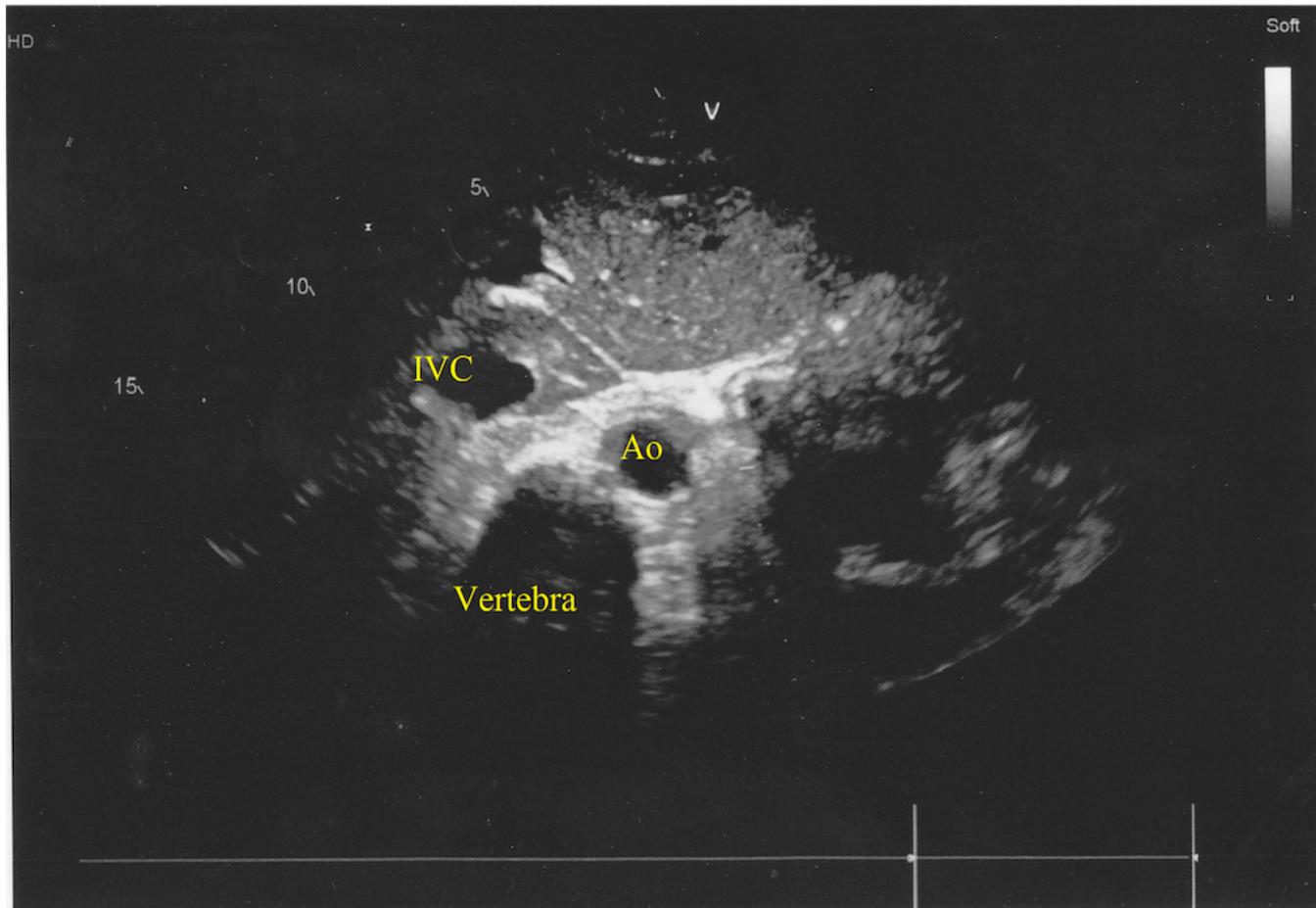


Figure 1

IVC: Inferior vena cava. Ao: Aorta

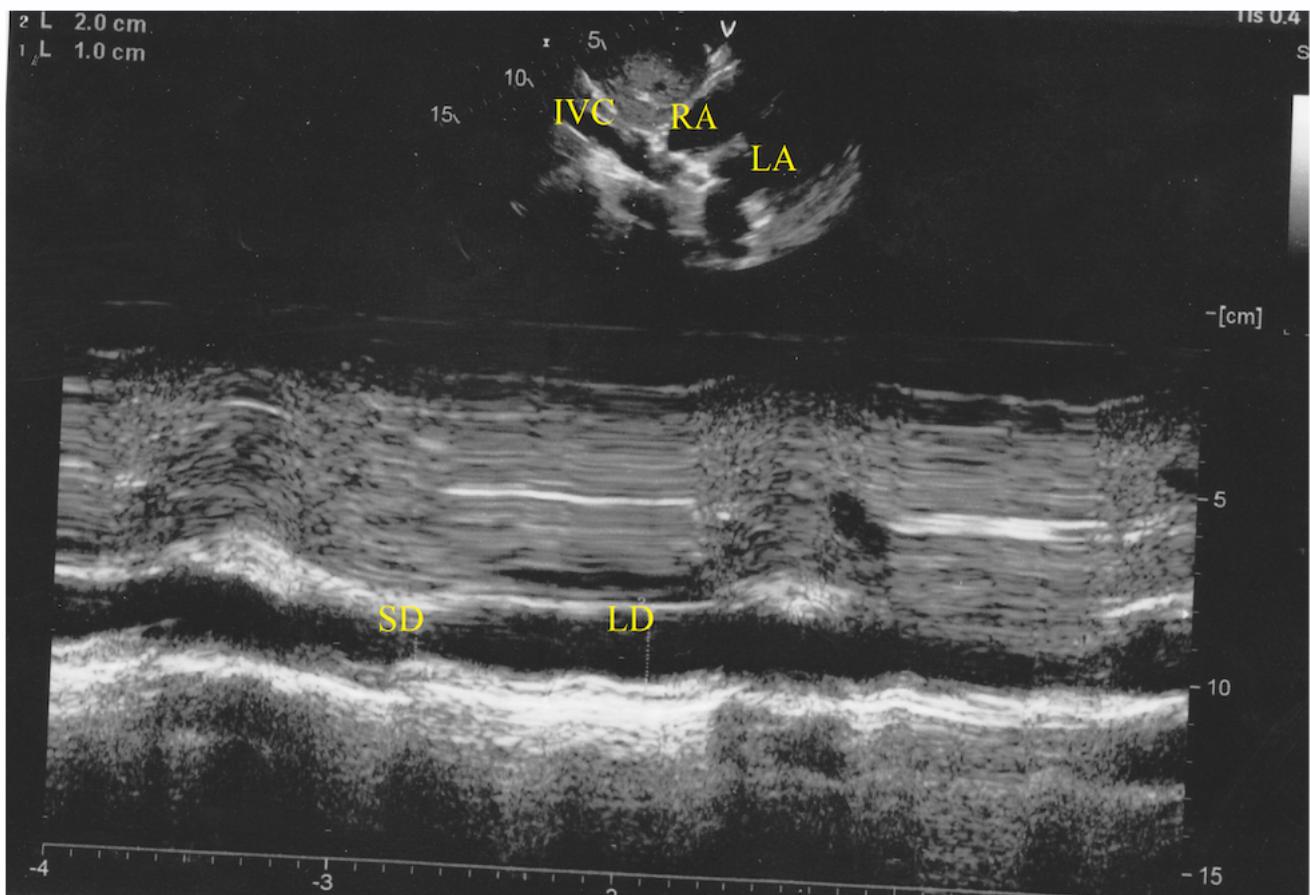


Figure 2

IVC: Inferior vena cava. RA: Right atrium. LA: Left atrium. SD: Small diameter. LD: Large diameter.

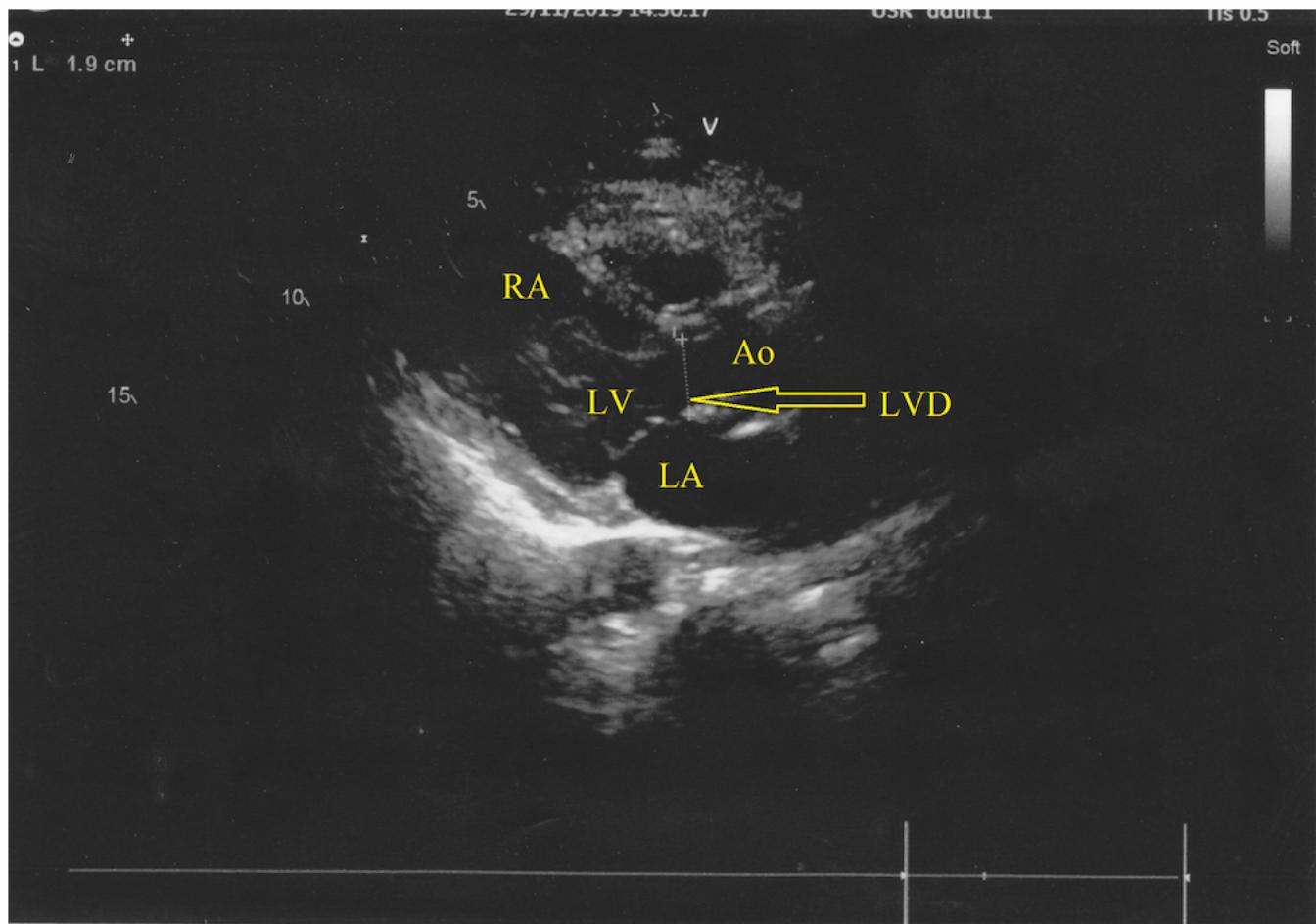


Figure 3

RA: Right atrium. LV: Left ventricle. LA: Left atrium. Ao: Aorta. LVD: LVOT (Left ventricular out flow tract) diamater.

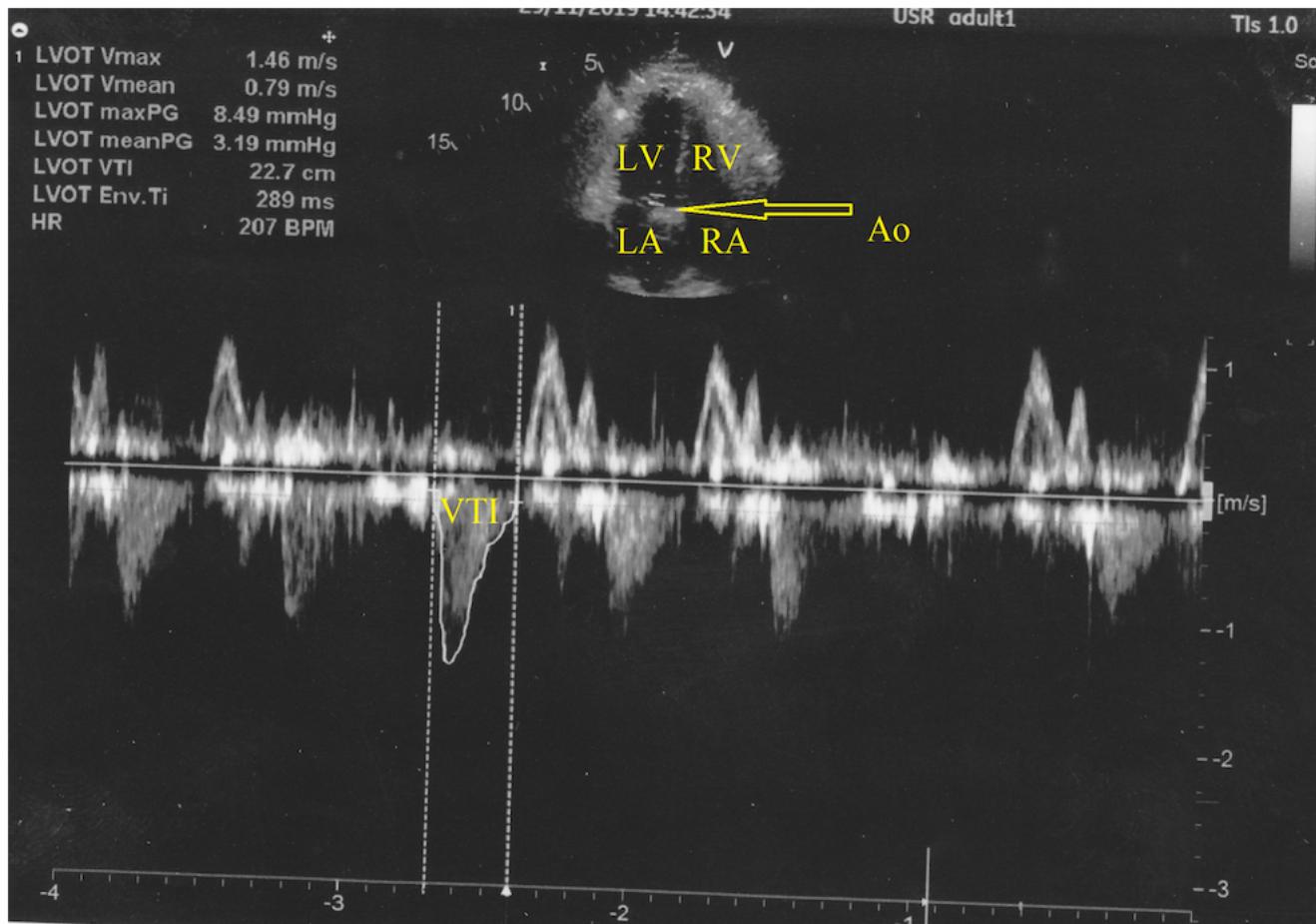


Figure 4

LV: Left ventricle. RV: Right ventricle. LA: Left atrium. RA: Right atrium. Ao: Aorta. VTI: Velocity time integrale.

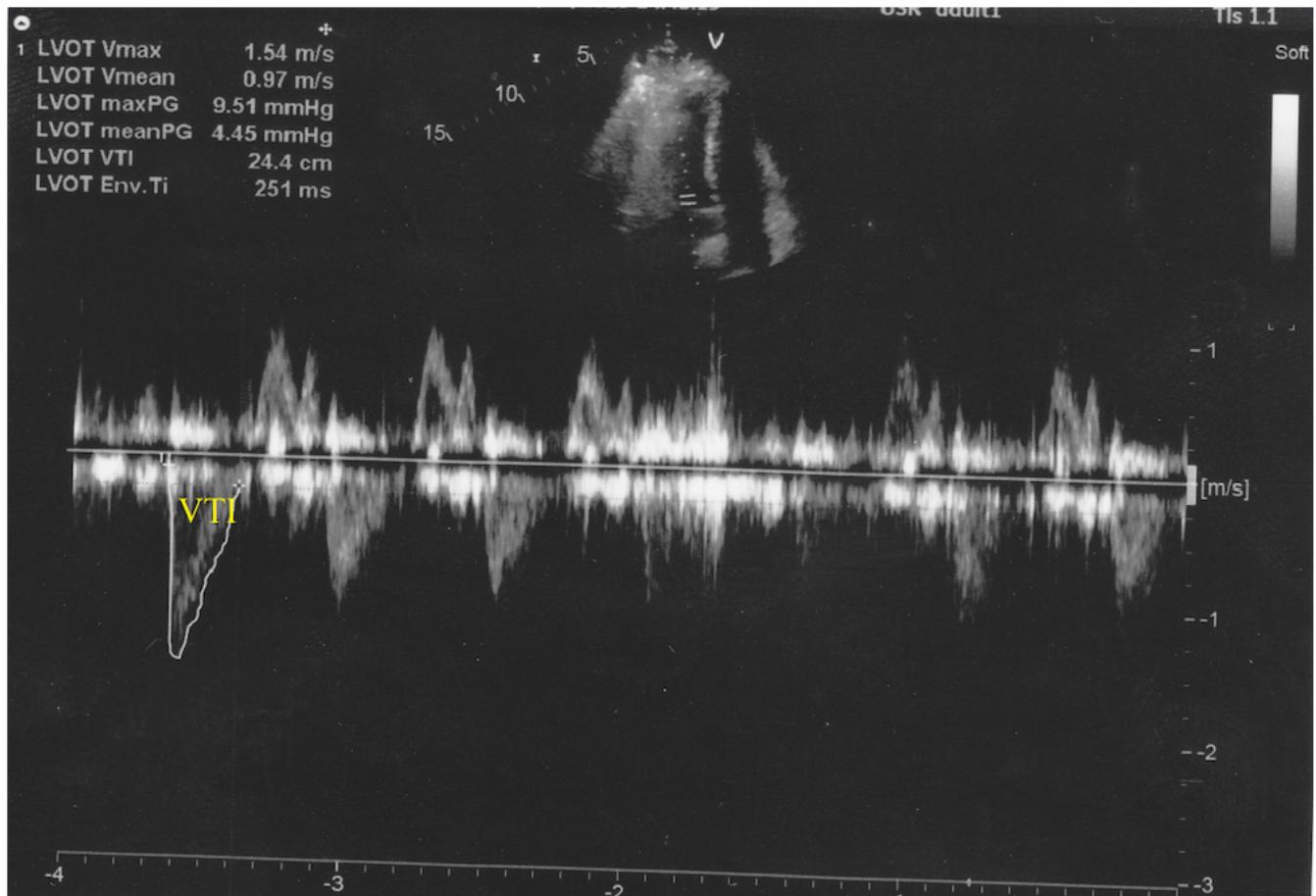


Figure 5

VTI: Velocity time integrale

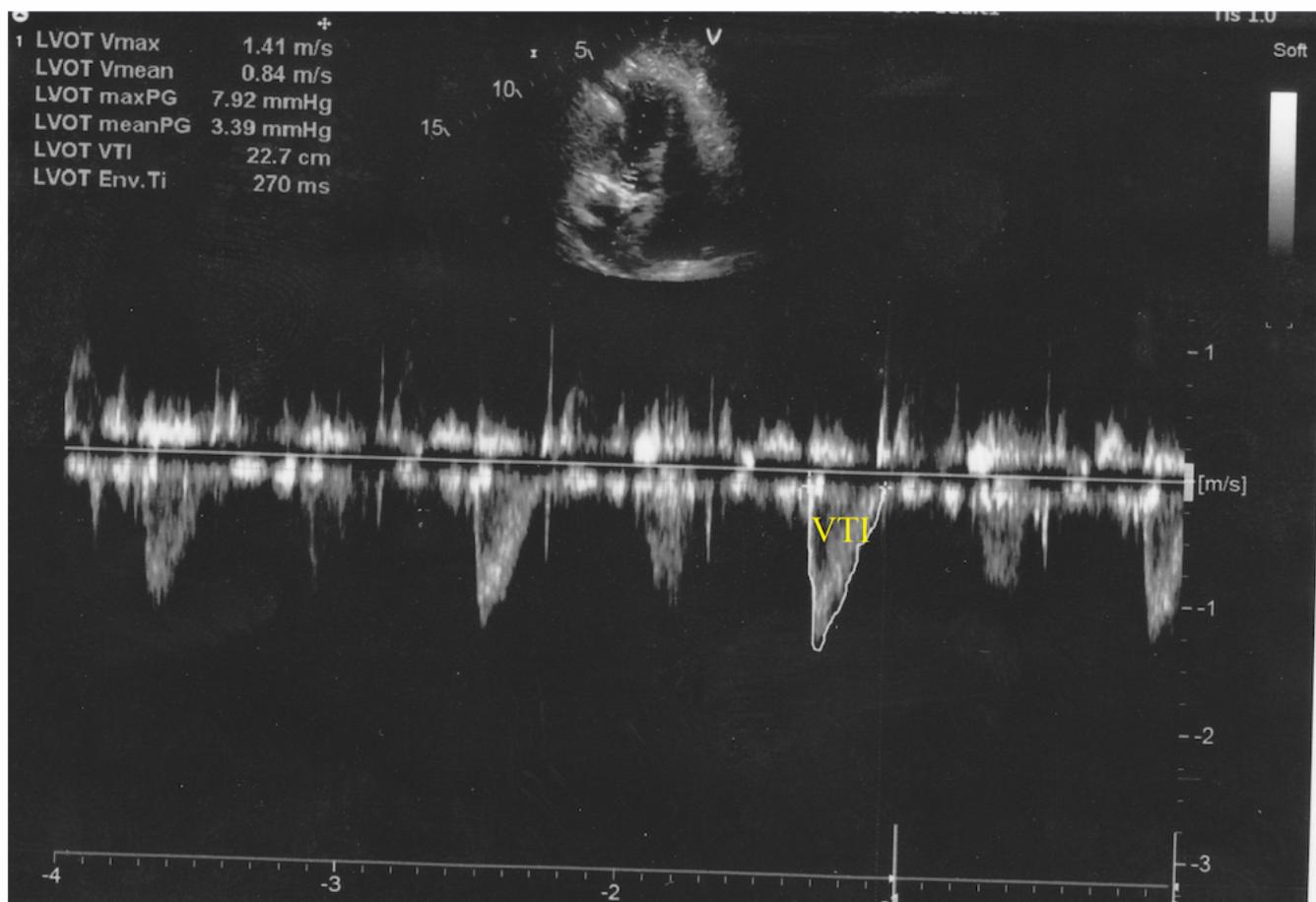


Figure 6

VTI: Velocity time integrale

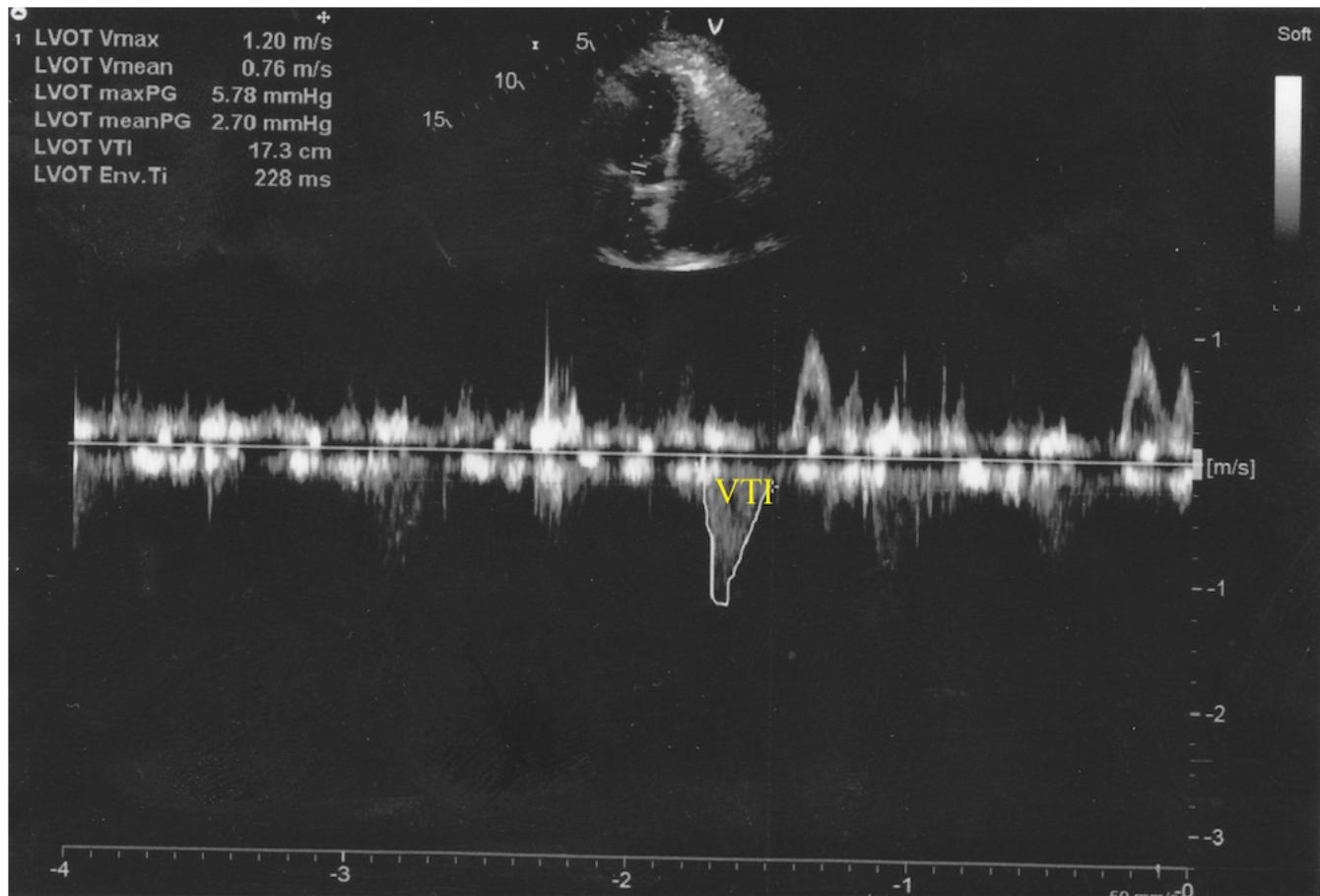


Figure 7

VTI: Velocity time integrale