Variability of left ventricle outflow tract VTI during breathing cycle may predict fluid responsiveness in the postoperative period for non-cardiac spontaneously breathing patients

Introduction: Different studies show controversial results while discussing which echocardiography parameter is the best to assess fluid responsiveness. The aims of the study were to evaluate the feasibility of echocardiography monitoring in postoperative unit and to assess diagnostic value of different parameters obtained by focused assessed transthoracic echocardiography (FATE) to control non-cardiac patients’ postoperative fluid therapy.

Methods: 40 patients who underwent major abdominal surgery and had reduced arterial blood pressure were included in the prospective study. The echocardiography measurements were taken before and immediately after fluid challenge of 500 ml of crystalloids. Positive fluid responsiveness was defined by an increase in stroke volume (SV) of at least 15%.

Results: FATE monitoring is feasible in postoperative unit. The identification of fluid responsiveness by clinical signs was significantly lower compared to echocardiography data (p=0.034). Variability of left ventricle outflow tract (LVOT) velocity time integral (VTI) during breathing cycle prognosis fluid responsiveness AUC of the ROC was 0.881. The mitral E wave, E/A ratio and IVC index prognoses fluid responsiveness in spontaneously breathing patients (p=0.006; p<0.001; p<0.001). CI seemed to be not suitable for prognosis of fluid responsiveness (p=0.214). There was no difference between infusion therapy in responders and non-responders neither during operation 2167 ml and 1678 ml (p=0.13) respectively nor in postoperative period 1500 ml and 1678 ml (p=0.344). After FATE the strategy of infusion therapy was changed in 14 (35%) patients.

Conclusions: LVOT VTI variability of more than 10% in spontaneously breathing patients had the highest sensitivity and comparable specificity among the parameters used for identification of fluid responders by FATE.

KEYWORDS: focused echocardiography, fluid responsiveness, major surgery
Materials and methods
The prospective study was carried out in the Anaesthesiology department of Lithuanian University of Health Sciences (LUHS) from the 1st of May to the 1st of September 2016. Ethical approval for this study was provided by the LUHS Kaunas Region Biomedical Research Ethics Committee according to the protocol No. BE-2-4 on 24 January, 2016 (session protocol no. BE-10-4). Trial was registered in ClinicalTrials.gov. Trial registration No. NCT03044405.

Eligibility criteria of the patients were: age ≥ 18 years old; the written consent to participate in this study; patients undergoing major abdominal surgery (gastric resection, gastrectomy, liver resection, pancreatic-duodenal resection, colorectal surgery); reduced mean arterial blood pressure up to 30% from the baseline during the first hour post-surgery.

Exclusion criteria were: known pregnancy; atrial fibrillation; known severe cardiovascular or renal impairment; poor echo image quality.

Demographic characteristics of the study population (age, gender, body mass index, ASA status) were collected. The following clinical signs for evaluation of fluid responsiveness were registered after the first hour post-surgery: heart rate (HR, t/min), non-invasive arterial blood pressure (ABP, mmHg), mean arterial blood pressure (MAP, mmHg), breathing rate (BR, t/min), and hourly urine flow rate (ml/kg/h). Baseline arterial blood pressure was considered as non-invasive measurement of ABP a day before surgery. The evaluation of fluid responsiveness by clinical signs were defined as urine flow rate less than 0.5 ml/kg/h post-surgery and systolic blood pressure (SBP) increase more than 10 mmHg after fluid challenge [10].

Focused transthoracic echocardiography protocol
All patients received post-operative pain management therapy according to the protocol of our anesthesiology department. Before the examination 0–10 numeric rating scale (NRS) was used to evaluate postoperative pain (0-no pain, 1 to 3 mild pain, 4 to 6-moderate pain, 7 to 10-severe pain) [11,12].

The echocardiography was performed in supine position one hour after abdominal surgery. The standard positions for FATE in all patients were: subcostal four chamber view, apical four chamber view, parasternal long axis view and IVC echo windows.

Transtracheal echocardiography was assessed by two trained investigators. The intra- and inter-observer variability of operators for the stroke volume (SV) was 2.5 and 4%. Positive fluid responsiveness was defined by an increase in SV of at least 15% after the fluid challenge of 500 ml of crystalloids given over 15 minutes. Fluid challenge is stopped when SV is not improving. Calculation of SV included LVOT VTImax and LVOT VTImin during four breathing cycles, IVCmax and IVCmin diameters during breathing cycles. Variability of LVOT VTImax is the product of [(VTImax–VTImin)/(VTImax–VTImin)/2] × 100% [14]. The VTImax and VTImin measurements were recorded during four breathing cycles. The IVC measurements were taken in M-mode 1 cm below the confluence of the hepatic veins [15]. The calculation of IVC variations was made by formula IVC index=(Dmax–Dmin)/Dmax. IVC index was expressed as a percentage [16-18].

The investigators had no influence on intraoperative fluid management. After post-operative evaluation by FATE fluid management was reconsidered. Responders were continuously monitored by FATE.

Statistics
Data were analysed using the SPSS 24.0 software. The Kruskal and Wallis tests were used for comparison of data distributions. Nonparametric, 2 test was used for the analysis of nominal qualitative data. The Mann-Whitney U test was used to compare distributions of two samples. A significance level of 0.05 was considered for all tests. A receiver operating characteristic (ROC) curve was used to determine the threshold value of mitral E and A waves, E/A ratio, LVOT VTI variability, cardiac
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index (CI) and IVC variations to predict fluid responsiveness, taking into account increase of SV more than 15%. We defined the area under the curve (AUC) to be clinically relevant if AUC was more than 0.7. For defining success rate of fluid responsiveness by different methods Cochrane’s Q test was used.

To detect the significant difference in mean values of variability of VTI during breathing cycles for responders vs. non-responders assuming significance level alpha=0.05 and power of the test=0.8, we should have at least 6 patients in each group.

Results

From all the patients who were scheduled for major abdominal surgery at the study period 45 patients were identified as eligible to participate in the study. Five patients were excluded because of the following reasons: one had severe contractility impairment, one had atrial fibrillation and for the rest image quality was not suitable for accurate interpretation. The patient inclusion, follow up and analysis are shown in (FIGURE 1).

Forty patients, 23 (57.5%) men and 17 (42.5%) women, who had reduced MAP from the baseline, were included in the study. The mean age of the patients was 60.8 (56.9-64.78) years. Sixteen patients (40%) had ASA physical status II and 24 (60%) had physical status III. The median pre-investigational VAS measurement was 3 (min 2, max 7).

An adequate apical and parasternal long axes views were obtained in all 40 (100%) patients. An adequate IVC images from subcostal window were obtained in 33 (82.5%) patients, for the rest 7 (17.5%) patients trans-hepatic acoustic window was used. The proportion of adequate view was significantly lower for the IVC echo window while trying to get the image from subcostal long axis view (p=0.046). The lower success rate of obtaining an adequate subcostal view was associated with experienced moderate postoperative pain (p=0.002). Mild pain (pain rating scale score 1-3) was reported in 21 (52.5%) patients, for all these patients echo images were appropriate for further interpretation. Moderate pain (pain rating scale score 4-6) was reported in 19 (47.5%) cases, for 7 (36.8%) of these patients the images from subcostal view were not obtained. The higher body mass index, had no significant influence on obtaining an adequate echo views from subcostal position (p=0.817). Three of seven patients for whom the subcostal echo window was not obtained had normal BMI, for the rest of the patients BMI was above 25 kg/m². Data concerning quality and difficulties of obtaining echo images is shown in (TABLE 1).

The increase of SV of more than 15% after volume expansion was found in 12 patients (30%) while increase of SBP more than 10 mmHg occurred only in 6 (15%) patients. Characteristics of the patients and comparison between responders and non-responders are shown in (TABLE 2).

The identification of fluid responsiveness by the complex of clinical signs was significantly lower compared to echocardiography data (p=0.034).

Variability of LVOT VTI during breathing cycle was significantly higher in responders compared to non-responders 14% (± 5.9) and 6.48% (± 12.9), respectively (p<0.001). ROC analysis showed AUC 0.881 (95% CI 0.744–
The mitral E wave velocity was 72.14 cm/s (± 14.5) in responders compared to 89.7 cm/s (± 17.2) in non-responders. ROC analysis showed AUC was 0.78 (95% CI 0.619–0.941, p=0.006), the best cut off value was 78.5 with 75% sensitivity and 82.1% specificity. The increase of mitral E wave after fluid challenge was bigger in responders compared to non-responders 9.28 cm/s (± 5.9) and 2.64 cm/s (± 2.84) (p=0.003). Calculation of ∆E is suitable parameter to predict fluid responsiveness as AUC under the ROC curve was 0.893 (95% CI 0.794–0.992, p<0.001). The Increase of E wave more than 4 cm/s can predict fluid responsiveness with sensitivity of 91.7% and specificity of 78.6%. The similar results were with A/E ratio: mean
E/A ratio in responders were 0.87 (SD 0.096) and in non-responders 1.086 (± 0.16), AUC was 0.868 (95% CI 0.755–0.98, p<0.001), the best cut off value 0.913 with 75% sensitivity and 89.3% specificity. The increase of E/A ratio after fluid bolus was bigger in responders compared to non-responders 0.07 (± 0.02) and 0.04 (± 0.008) respectively (p=0.001). The AUC under the ROC curve was 0.878 (95% CI 0.76–0.995, p<0.001). The increase of E/A ratio more than 0.07 can predict fluid responsiveness with sensitivity of 83.3% and specificity of 85.7%.

Although cardiac index was lower in responders 2.89 L/min/m² (± 1.06) compared to non-responders 3.35 L/min/m² (± 0.94) the difference was not significant (p=0.214). According to ROC analysis AUC was 0.622 (95% CI 0.424 – 0.82, p=0.82). CI seemed to be not suitable for prognosis of fluid responsiveness.

The variability of IVC was significantly higher in responders 32.29% (± 13.48) compared to 11.03% (± 12.24) in non-responders (p<0.001). The AUC of the ROC curve for IVC variability index was 0.878 (95% CI 0.768 – 0.988, p<0.001) and the best cut off value seemed to be 26.6% with 75% sensitivity and 82.8% specificity.

The results of ROC analysis are show in (FIGURE 2). The individual values of these parameters for responders and non-responders are shown in (FIGURE 3).

The area under the curve (AUC) was considered to be clinically relevant if AUC was more than 0.7.

There was no difference between infusion therapy in responders and non-responders during operation 2167 (± 961) ml and 1678 (± 676) ml (p=0.13) respectively. Before the evaluation by FATE planed postoperative fluid therapy was also similar for responders and non-responders 1500 (± 522) ml and 1678 (± 564) ml respectively (p=0.344). The infusion therapy for non-responders was reduced in average up to 982 (± 120) ml from the primary plan 1678 (± 564) which was before the assessment by FATE (p=0.01).

**Discussion**

It is well known, that the golden standard for overall hemodynamic monitoring is pulmonary artery catheterization. However, because of limitations mentioned above this method is not routinely used for monitoring. Non-invasive methods like echocardiography are also reliable for this purpose [19]. One of the main, but at the same time-banal problems is process of obtaining echo images [20]. Images obtained from apical, parasternal short and long axis view were suitable for interpretation and were informative. We were unable to obtain subcostal view in all cases. For 35 (87.5%) patients, subcostal images were informative. For 7 (30.4%) patients we could not obtain

![FIGURE 2. Receiver operator characteristic (ROC) curves for echocardiographic data defining fluid responsiveness.](image)

The area under the curve (AUC) was considered to be clinically relevant if AUC was more than 0.7.

**Areas under the ROC curve:**
- Mitral E wave velocity - 0.78 (95% CI 0.619 – 0.941, p=0.006);
- E/A ratio - 0.868 (95% CI 0.755 – 0.98, p<0.001);
- Cardiac index - 0.622 (95% CI 0.424 – 0.82, p=0.82);
- VTI variability (%) - 0.881 (95% CI 0.744 – 1.0, p<0.001);
- IVC index (%) - 0.878 (95% CI 0.768 – 0.988, p<0.001).
IVC images from subcostal long axis view. Nevertheless, measurements of IVC diameter were performed for all patients because transhepatic acoustic window was to get missing images. According to our study - different acoustic window did not affect IVC diameter values because the protocol was followed and all measurement of IVC diameter were taken in M mode 2-3 cm from right atrium [16-18,21].

The most common reasons of image quality in subcostal position were postoperative pain and wound dressings.

There are many suggestions for fluid responsiveness monitoring using ultrasound hemodynamic measurement techniques and indices [19,20,22-24]. The identification of fluid responsiveness by LVOT VTI changes more than 15% after volume expansion is not new and widely used [25]. This method is specific and sensitive. Feissel et al. found that aortic velocity changes are specific parameter for predicting hemodynamic response to volume expansion for ventilated patients with septic shock [24]. Similarly, the variations of aortic blood flow velocity predicted fluid responsiveness in mechanically ventilated children [26,27]. Unfortunately, this method requires fluid challenge to identify the increase of the parameter. Variability in aortic blood flow during breathing cycles more than 12% is associated with fluid responsiveness in spontaneously breathing healthy volunteers [14]. However, spontaneous breathing is a limitation of dynamic methods for prediction of fluid responsiveness. There are several factors which have influence on dynamic parameters. Regular variations in intrathoracic pressure, tidal volume and rate are variable in spontaneous breathing patients [28]. Also abdominal muscles contractions are common with spontaneous breathing efforts. What we found new and unexpected in our study was LVOT VTI variability more than 10% during breathing cycle was associated with positive fluid responsiveness in spontaneously breathing patients after major abdominal surgery with high specificity and sensitivity. Even though limitations of dynamic parameter for non-ventilated patients were mentioned, some of them were excluded or minimized. First of all, even though we did not affect the breathing rate of the subjects and did not ask to change the manner of breathing the mean breathing rate was 14 (+/-2) times per minute. There was no difference according to this parameter between responders and non-responders. Of course the deep or forced breathing could affect results more likely. The breathing excursions in postoperative patients are more superficial rather than deep as pain is imminent in postoperative period despite all the efforts of pain management. What is more, the current condition minimizes the abdominal muscles effect on spontaneous breathing. So in this case, one more limitation was excluded. The measurements were taken twice by each investigator to minimize the errors. According to our data LVOT VTI variability during breathing cycles seems to be useful parameter for identification of fluid responders in spontaneously breathing patients. The main advantage of this parameter is that...
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for the stoke volume was assessed and described in methods section.

LVOT VTI variability seems to be suitable parameter for identification of fluid responsiveness; however more studies are needed to confirm our data. Before the evaluation by FATE there were no difference concerning infusion management strategy in responders and non-responders. This supports an idea, that further studies are needed to evaluate the influence of individualized perioperative fluid management based on focused echocardiography data for outcomes after major abdominal surgery.

**Conclusions**

In most cases it was possible to get good quality echocardiographic images after major abdominal surgery. LVOT VTI variability of more than 10% in spontaneously breathing patients had the highest sensitivity and comparable specificity among the parameters used for identification of fluid responders by FATE.

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**Research**

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