의학석사 학위논문

# 개복 간절제술 환자에서 음향 가변성 지수의 유효성을 평가하기 위한 전향적 탐색 임상시험

# Performance of Acoustic Variability Index to predict fluid responsiveness in patients undergoing open abdominal hepatectomy

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2024 년 4 월

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# ABSTRACT


**Background**

For a patient undergoing major abdominal surgery, fluid management is crucial. The non-invasive, continuous measurement offered by phonographic analysis of heart sound can be useful in diagnosing cardiovascular conditions and fluid responsiveness. By comparing the acoustic variability index (AVI) to established parameters, we evaluated its efficacy as a dynamic indicator and predictor of fluid responsiveness in patients having open abdominal hepatectomy.

**Methods**

Forty patients who required volume expansion during an open abdominal hepatectomy were included. 500 mL of crystalloid were given as part of the fluid challenge protocol over the duration of 10 minutes. Applying an esophageal stethoscope and software that evaluates the systolic time interval (STI) as well as the amplitude of S1 and S2 sounds, AVI was measured. After major surgical procedures, and the subjects became hemodynamically stable, the fluid responsiveness indicators, central venous pressure (CVP), stroke volume variation (SVV), pulse pressure variation (PPV), and AVI were obtained for three minutes before and after fluid loading. Subjects who had a cardiac output increase of at least 10% following volume expansion were classified as responders.

**Results**

Overall, 12 of the 37 patients were responders. The baseline hemodynamic variables of the responders and non-responders, that include stroke volume (SV), SVV, PPV, and AVI, demonstrated significant differences. After fluid loading, responders showed significant decreases in AVI (11.4 ± 2.3 % vs. 7.8 ± 2.8 %, $P < 0.01$), whereas AVI in non-responders remained unchanged (7.1 ± 3.1 % vs. 6.3 ± 2.9 %, $P = 0.356$). Fluid responsiveness could be predicted provided the cut-off value was greater than 9.8% AVI from the baseline with an area under the receiver operating characteristic curve of 0.873 (95% confidence interval, 0.722 – 0.959).

**Conclusions**

Intra-operative AVI can predict fluid responsiveness in patients undergoing open abdominal hepatectomy. AVI may be continuously and real-time monitored for fluid management as a useful non-invasive hemodynamic index.

# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# INTRODUCTION

Fluid management is crucial for a patient who undergoes major abdominal surgery. The cardiac output (CO) of the patient fluctuates during this surgery due to intraoperative massive bleeding and individual cardiovascular conditions. In this respect, it is a critical point of perioperative management to estimate cardiac output and optimize stroke volume (SV) of the patient by appropriate fluid challenge (i.e. 250 ml)[1,2]. Monitoring blood pressure alone cannot guarantee optimal tissue perfusion because most of the organs need not only pressure but also flow, and estimating blood flow can theoretically alert physicians earlier than pressure alone[3]. Therefore, in order to optimize fluid management, the concept of fluid responsiveness and the dynamic indices that can reveal the status of cardiac output in real-time have been used increasingly[4,5]. Particularly, when evaluating the incidence of complications, morbidity, and mortality, goal-directed fluid therapy, which utilizes dynamic indices like pulse pressure variation (PPV) and stroke volume variation (SVV), has been shown to be non-inferior in a number of clinical conditions.[2,6,7]. Dynamic indices are currently replacing traditional static indices in clinical settings rapidly. These traditional static indices include central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP), which are invasive and partially reflect the volume status of the patients[8,9].

Auscultation of heart and lung sounds during anesthesia usually provides important information about the patient's condition. Especially, the relaxation and contraction of the ventricles, flow of the blood, and valve movement produce specific heart sounds that can reflect the cardiac condition of the patients. However, it has been considered that the diagnostic accuracy can be affected by the subjective perception and interpretation of individual clinicians. As technology advances, it becomes possible to record heart sounds phonologically, enabling continuous analysis. In fact, various studies have proven that this analysis provides valuable information[10-12]. The use of an esophageal stethoscope for monitoring during general anesthesia appears to have been around for about 70 years[13]. Phonological real-time analysis of cardiac and respiratory sounds during mechanical ventilation under general anesthesia has enabled the evaluation of various patient conditions. In cases of respiratory sound, it has been recognized that utilizing the acoustic spectrum of the sound can assist in evaluating bronchial reactivity or airway narrowing in patients, aiding in monitoring during general anesthesia[14-16]. For heart sounds, measuring the volume of blood flow and the systolic time by esophageal doppler allows for the estimation of the stroke volume[17]. Based on this finding, another study suggested that the systolic time, which can be calculated by analyzing the heart sounds, is applicable to identifying heart diseases including heart failure[18]. Moreover, in patients undergoing liver transplantation, phonographic analysis

of the systolic time interval and its respiratory fluctuation can predict fluid responsiveness, as the variation of the systolic time interval significantly decreases after volume loading[19]. It is being investigated whether this non-invasive and continuous measurement can replace the dynamic indices described earlier. However, given the limited patient population, there is a need for further research to obtain specific and easily assessable hemodynamic indices.

In this thesis, we aim to non-invasively measure the acoustic variability index (AVI) to predict fluid responsiveness and evaluate the efficacy and safety of the biological signal analysis software providing this parameter. Through this, we can determine if the AVI can be used as an auxiliary dynamic index to assist clinicians in diagnosis during fluid therapy. This thesis evaluates biological signal analysis software that allows real-time cardiovascular monitoring using the S1 and S2 indicators of heart sounds. Similar to other dynamic indices (PPV, SVV), heart sounds exhibit variations according to the respiratory cycle in mechanically ventilated patients. The S1-S2 interval encompasses the systolic time intervals, and the intensity of S1 and S2 includes information about myocardial contractility, blood volume, and systemic vascular resistance. The software measures these data and yields the value of AVI. This index could serve as a dynamic indicator of preload, allowing inferences about the overall blood volume and the cardiac output of the patient.

Non-invasive measurement of AVI is expected to result in a lower incidence of side effects and complications compared to invasive and classical methods of obtaining physiological information, such as hemodynamic static indicators (CVP, PCWP) and dynamic indicators (PPV, SVV). Additionally, using an esophageal stethoscope close range to the heart and lungs, the AVI has the potential to be a novel hemodynamic diagnostic tool in clinical settings, assisting clinicians to vigilantly and reliably assess patients' hemodynamic condition. Therefore, this study aims to validate the predictive power and safety of AVI as a dynamic preload indicator through its responsiveness to intraoperative fluid administration.

# METHOD

**Study population**

40 adult patients scheduled for elective major open hepatectomy surgery were enrolled in this study after receiving approval from the Asan Medical Center's Institutional Review Board. Patient with preoperative arrhythmia, esophageal varices or strictures, pulmonary edema, BMI > 30 kg/m2, uncontrolled coagulopathy, intracardiac shunt were excluded. Also, when the massive bleeding was predicted or it was impossible to insert arterial and venous catheter for hemodynamic monitoring, the patient was excluded.

**Equipment description**

In this trial, the medical device used to visualize cardiac and pulmonary sounds provided real-time measurement of the AVI from cardiac sounds and the respiratory rate (RR) from pulmonary sounds. This software outputs the measured cardiopulmonary sounds in real-time as a spectrogram through its own algorithm, which separates cardiac and pulmonary sounds. It calculates heart rate from cardiac sounds, detects the first (S1) and second (S2) heart sounds, and then calculates the time interval between S1 and S2 (systolic time interval, STI) (Fig 1). AVI is calculated using the following formula and displayed on the screen. The data obtained from this device was stored and disposed of according to the regulations approved by the IRB. Digital signal analysis was conducted applying SignalTAB (Signal House Co., Ltd., Seoul, Korea). This Android application can collect and record various biometric signals and waveforms simultaneously (Fig 2).

$$AVI = a \times F(STI)^{\alpha} \times G\left(S1_{amp}\right)^{\beta} \times H\left(S2_{amp}\right)^{\gamma},$$

$$a, \alpha, \beta, \gamma: coefficient$$

A 18 Fr 100% non-PVC esophageal stethoscope (Insung Medical Co., Ltd., Wonju, Korea) was inserted into the esophagus of the subject to accurately transmit cardiopulmonary sound to the software. Additionally, this probe was used to measure the patient's body temperature during surgery. Since the S1 sound is loudest near a depth of 28-32cm from the upper incisor, the attending anesthesiologist placed the esophageal stethoscope based on this[20].

Catheters were inserted into the subjects' internal jugular vein and radial artery to measure CVP, CO, SVV, and PPV for the evaluation of the efficacy of AVI. The FloTrac and EV-1000$^{TM}$ system

(Edwards Lifescience Corporation, Irvine, CA, United States) were applied to analyze arterial blood pressure waveform and measure SVV and CO. The CO of the subjects was derived from non-calibrated pulse contour analysis. PPV was calculated using the arterial pressure measured by the invasive catheter, defined as the difference between the maximum and minimum pulse pressures observed during the respiratory cycle, divided by the mean pulse pressure.

**Anesthesia protocol**

All of the patients were subjected to our institutional standard anesthetic management protocol for major abdominal surgery. Anesthesia was induced with propofol 1.5-2.5 mg/kg, rocuronium 0.6-1.2 mg/kg, and remifentanil 0.05-0.2 μg/kg with continuous basic monitoring (blood pressure, EKG, SpO2) and was maintained using sevoflurane or desflurane, and remifentanil. Mechanical ventilation was performed with a 0-5 cmH2O positive end-expiratory pressure, using a constant tidal volume of 6-8 ml/kg and a constant end-tidal carbon dioxide tension of 35-42 mmHg.

**Study protocol**

This study was designed as a prospective, single-center, single-group, exploratory clinical trial (Fig 3). During the first visit, the investigator provided the subjects with a thorough explanation of the study and conducted screening for those who voluntarily signed consent for the clinical trial. Vital signs, physical examinations, and laboratory tests were obtained from existing medical records including typical pre-operative procedures. Pregnancy tests were conducted for women of childbearing potential. The cardiac output of the patients, the following fluid responsiveness indicators (CVP, SVV, PPV, and AVI) and respiratory rate were collected for three minutes before fluid loading at these times: 1) after laparotomy, 2) after major surgical procedures when the patients were hemodynamically stable and there was no significant bleeding (less than 200 mL). A standardized fluid challenge consisted the administration of 500 mL of crystalloid via central line over 10 minutes. After loading the fluid and achieving hemodynamic stability, the same parameters were collected again for three minutes. The patients' complications and side effects were monitored until they were discharged. In order to identify complications caused by fluid loading, a chest X-ray was performed if necessary based on clinical judgment. Furthermore, the cases of throat discomfort, injury to the oral mucosa, and side effects related to the upper gastrointestinal tract were investigated.

**Data acquisition & Statistical analysis**

This study investigated whether the fluid responsiveness indicators, CVP, SVV, PPV, and AVI, measured before fluid loading can be used as predictors for identifying responders to fluid loading. After a 500 ml fluid loading, subjects with an increase in cardiac output of more than 10% were defined

as the responder group and the others as the non-responder group. The primary efficacy parameter was the value of the AVI, which was a non-invasive indicator obtained when the subjects were hemodynamically stable. The secondary efficacy parameters included CVP, SVV, PPV for each group. The exploratory evaluation parameters were the average of heart rate, stroke volume, and systolic/diastolic/mean arterial pressure measured before and after fluid loading and during surgery for each group. Also, we included average intraoperative values of fluid responsiveness indicators as an exploratory evaluation parameter. The safety parameter was presented as the frequency and number of all adverse events.

The parameters were expressed as the mean ± standard deviation. For comparison of each parameter between the responder and the non-responder groups, the paired t-test or Wilcoxon rank-sum test was used, depending on the normality test. The correlation between AVI and SVV during the baseline period was evaluated in each patient using Pearson correlation coefficients. We also calculated the areas under the curve (AUC) values of receiver operating characteristic (ROC) curves that predict fluid responsiveness. No formal sample size calculation was done as this was an exploratory trial. All data analysis was performed using SPSS version 18 (SPSS Inc., Chicago, United States), MedCalc version 13.1.1 (MedCalc Software, Mariakerke, Belgium), and GraphPad Prism version 5.0 (GraphPad Software Inc., Bostion, United States). A *P* value was considered statistically significant when it was $< 0.05$.

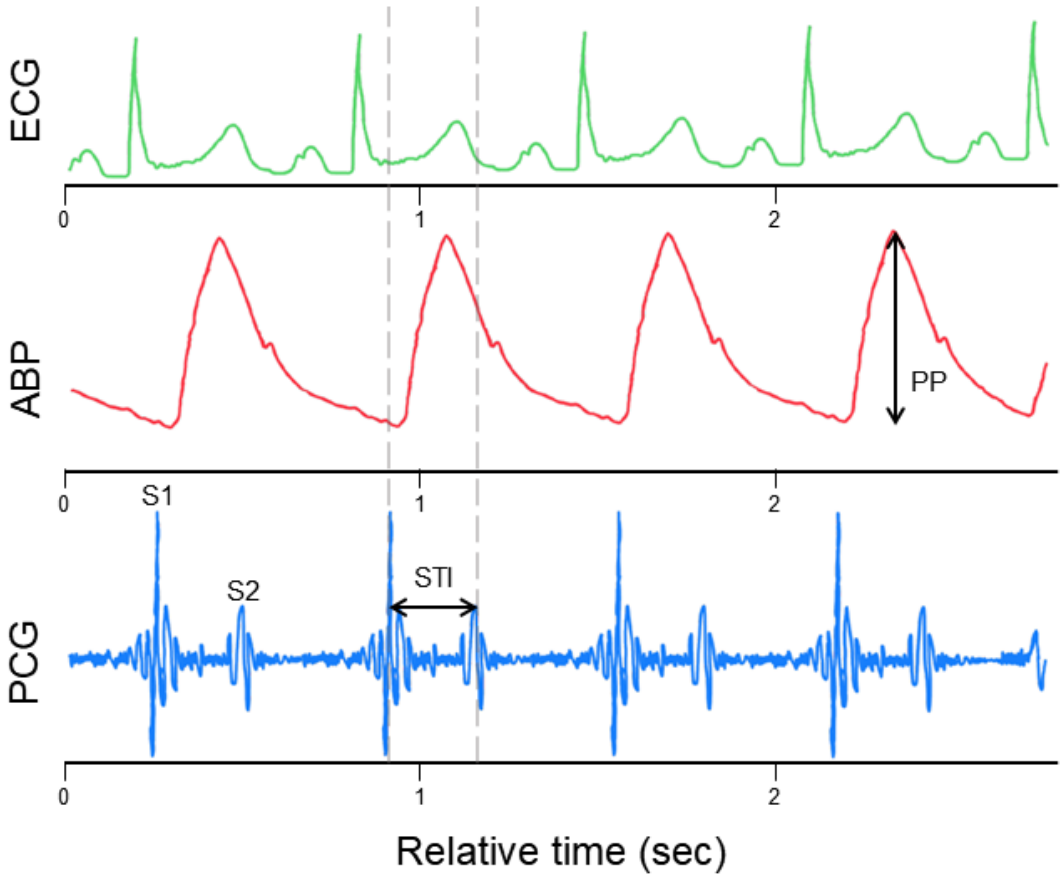



Fig 1. Time-domain measurement of phonocardiographic (PCG), electrocardiographic (EKG), and arterial blood pressure (ABP) parameters; Pulse pressure (PP, difference between systolic and diastolic blood pressure), systolic time interval (STI, interval between first and second heart sounds).

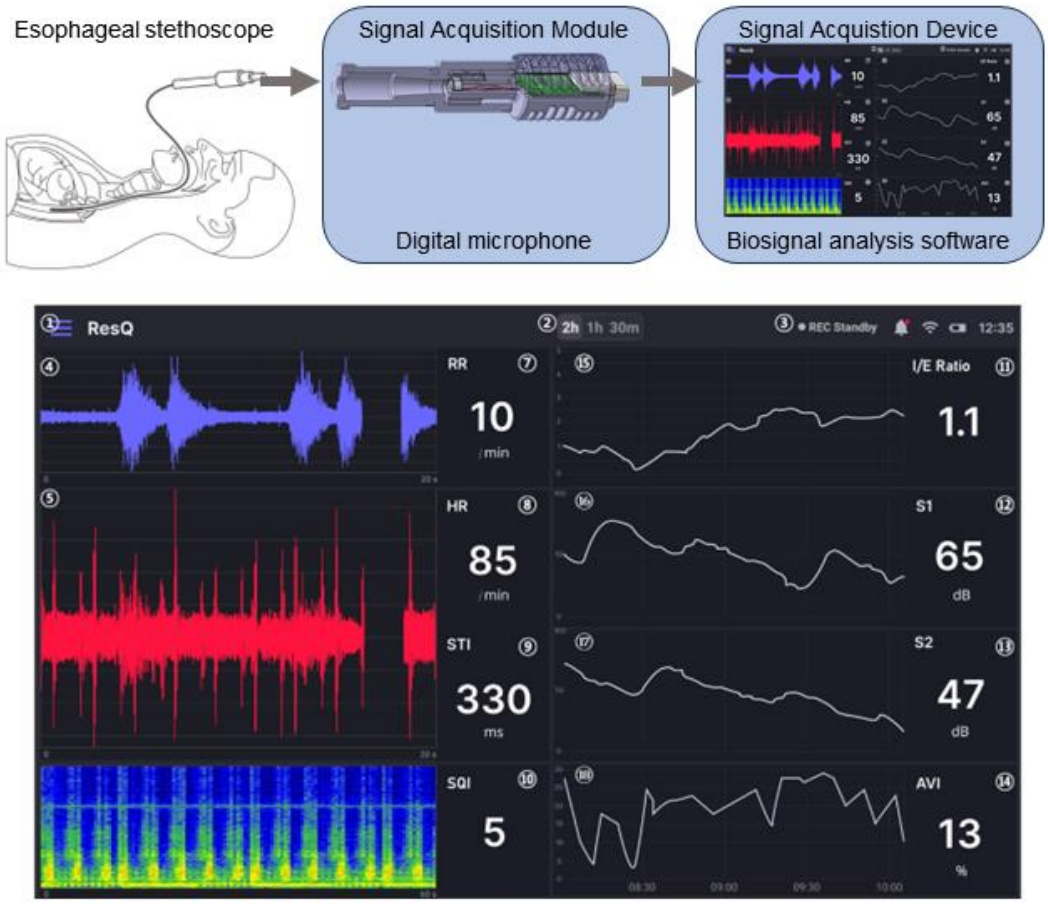



Fig 2. Schematic illustration of the esophageal stethoscope and heart sound signal processing process. The figure below presents a representative display of the application used in this study, SignalTAB (Signal House Co., Ltd., Seoul, Korea); ① Menu; Displays version information, open-source library information, and update functions. ② Trend time; Allows changing the trend graph's time intervals to 2 hours, 1 hour or 30 minutes. ③ Save status; When the cardiopulmonary sound signal is being saved, the save status changes from REC standby to measurement time ④ Heart sound signal; Extracts and displays only the heart sound signal based on filtering specific frequencies from the cardiopulmonary sound. ⑤ Lung sound signal ⑥ Spectrogram ⑦ RR, respiratory rate ⑧ HR, heart rate ⑨ STI, Systolic time interval ⑩ SQI, signal quality index; Evaluates and displays the adequacy of the cardiopulmonary sound signal ⑪ I/E ratio ⑫ S1; Amplitude of S1 heart sound ⑬ S2; Amplitude of S2 heart sound ⑭ AVI, acoustic variability index ⑮ I/E ratio trend graph ⑯ S1 amplitude trend graph ⑰ S2 amplitude trend graph ⑱ AVI trend graph

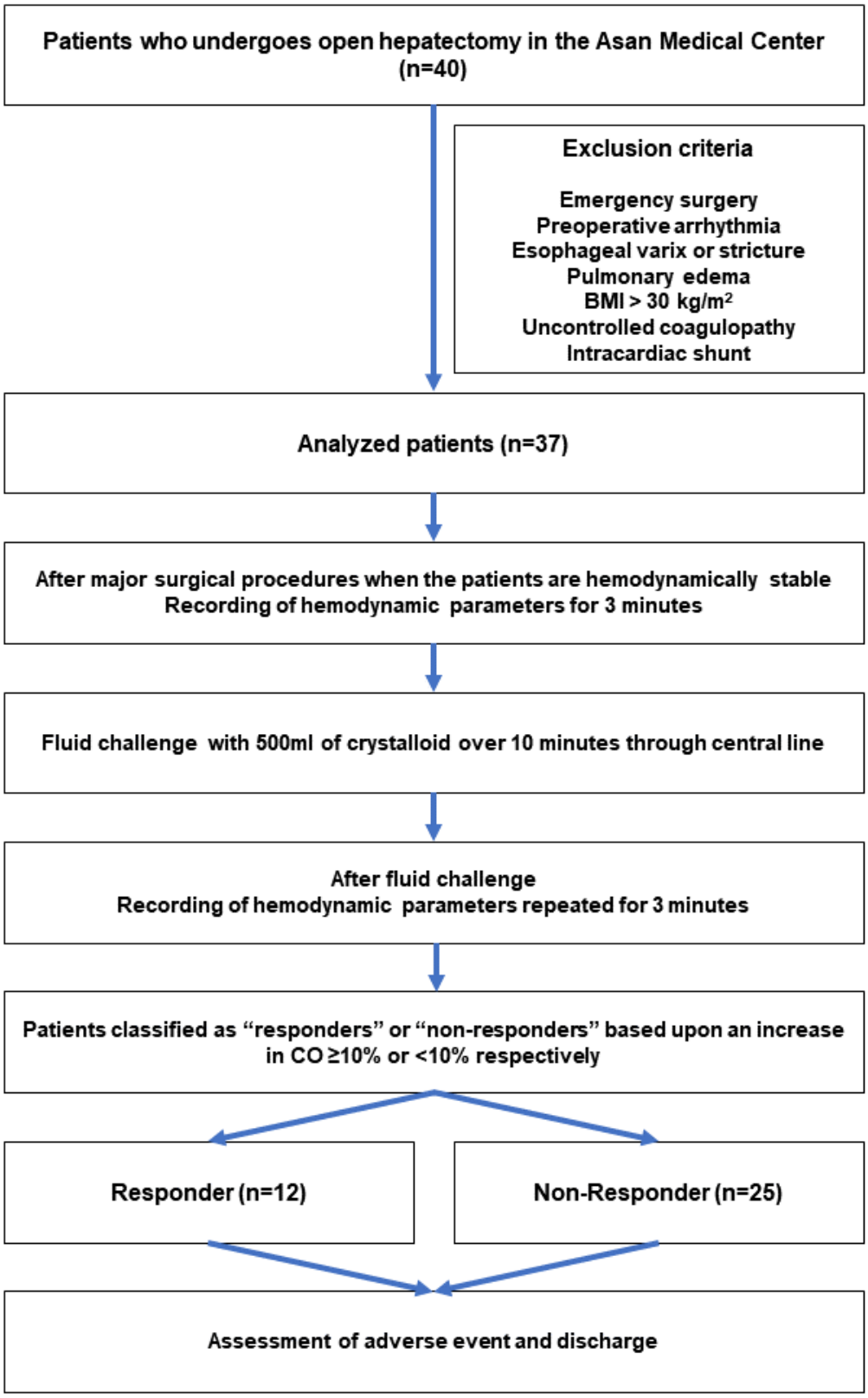



Fig 3. Study design

# RESULTS

In all, 40 patients were screened for this study. Three patients were excluded from the analysis. Due to a surgical procedure, attending medical staff determined that two patients were unsuitable for fluid administration under this protocol. One patient was excluded due to consistently weak signals and severe noises. In total, 37 patients were analyzed (age; 37.2 ± 12.1). The characteristics of patients are presented in Table 1.

Fluid administration was successfully performed in all patients. The responder group consisted of 12 patients (32.4%), while the non-responder group consisted of 25 patients (67.6%). There was no demographic difference between the responder and non-responder group. With the exception of SV, SVV, PPV and AVI, the baseline hemodynamic variables, including mean arterial pressure (MAP), heart rate (HR), CO, and CVP, did not differ significantly between the two groups (Table 2). The responders showed significant increases in SVV and PPV after fluid loading ($P < 0.01$ for SVV, $P < 0.03$ for PPV). The results for AVI are also presented in the same table. In the non-responder group, the baseline AVI was 7.1 ± 3.1 % (range 3.0 – 16.4 %), and after volume expansion, it was 6.3 ± 2.9 % (range 1.8 – 13.4 %), showing no significant difference. In the responder group, the baseline AVI was 11.4 ± 2.3 % (range 7.3 – 16.9 %), and after volume expansion, it was 7.8 ± 2.8 % (range 3.8 – 12.8 %), showing a significant difference ($P < 0.01$) (Fig 4). In the case of CVP, there was no significant difference before and after fluid loading in the responder group, whereas a significant increase (2.9 ± 2.1 mmHg vs. 6.3 ± 2.8 mmHg, $P < 0.001$) was observed in the non-responder group. The correlation analysis of average AVI and SVV values measured before fluid administration in all patients is presented in Fig. 5. The median value of the Pearson correlation coefficient was r = 0.518 ($P = 0.01$). ROC curve analysis showed that >9.8% of AVI from baseline could predict fluid responsiveness with an area under the ROC curve of 0.873 (95% Confidence Interval, 0.722 - 0.959) (Table 3 and Fig 6).

Table 1. Patient Demographic

| | | Responder | Non-responder |
|---|---|---|---|
| N | 37 | 12 | 25 |
| Male | 27 (67.5%) | 8 (66.7%) | 18 (72%) |
| Age (years) | 37.2 ± 12.1 | 34.2 ± 11.4 | 38.6 ± 12.5 |
| BMI ($kg/m^2$) | 23.5 ± 2.8 | 23.7 ± 3.3 | 23.3 ± 2.6 |
| Surgery type | | | |
| Donor hepatectomy | 32 | 11 | 21 |
| Hepatectomy due to tumor | 5 | 1 | 4 |
| ASA classification | | | |
| ASA I | 3 | 1 | 2 |
| ASA II | 34 | 10 | 23 |

Age and BMI are expressed as mean ± standard deviation or number (%).

Abbreviations: BMI, body mass index; ASA, American society of anesthesiologists.

Table 2. Changes In Hemodynamic Variables for Responders and Non-Responders Before and After Fluid Loading

| | Responder (n=12) | | | Non-responder (n=25) | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Volume expansion | P* | Baseline | Volume expansion | P* | P† |
| MAP (mmHg) | 82.2 ± 11.1 | 78.5 ± 5.9 | 0.336 | 76.3 ± 8.0 | 85.6 ± 13.0 | 0.004 | 0.081 |
| HR (bpm) | 87.4 ± 13.3 | 86.5 ± 9.6 | 0.868 | 84.2 ± 12.0 | 80.8 ± 12.9 | 0.352 | 0.480 |
| CO (L/min) | 6.6 ± 1.6 | 9.1 ± 2.0 | 0.003 | 7.6 ± 1.8 | 7.6 ± 1.8 | 0.981 | 0.105 |
| SV (mL/beat) | 75.2 ± 13.9 | 103.7 ± 14.9 | 0.0001 | 90.2 ± 17.8 | 94.1 ± 22.4 | 0.504 | 0.017 |
| CVP (mmHg) | 3.0 ± 3.0 | 3.5 ± 3.0 | 0.701 | 2.9 ± 2.1 | 6.3 ± 2.8 | 0.0001 | 0.931 |
| SVV (%) | 10.5 ± 3.0 | 6.4 ± 2.4 | 0.002 | 6.1 ± 3.3 | 4.2 ± 1.3 | 0.073 | 0.0006 |
| PPV (%) | 10.3 ± 3.9 | 6.6 ± 2.4 | 0.013 | 6.0 ± 3.5 | 3.9 ± 1.5 | 0.008 | 0.002 |
| AVI (%) | 11.4 ± 2.3 | 7.8 ± 2.8 | 0.004 | 7.1 ± 3.1 | 6.3 ± 2.9 | 0.356 | 0.0002 |

All data are expressed as mean ± standard deviation.

*P* value compared with 0.05; *Volume expansion value versus baseline value in each group (responders and non-responders); †Baseline value in responders versus baseline value in non-responders.

Abbreviations: MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; CVP, central venous pressure; SVV, stroke volume variation; PPV, pulse pressure variation; AVI, acoustic variability index.

Fig 4. Changes in acoustic variability index (AVI) after volume loading in responders and non-responders. The columns in this graph represent the mean value of AVI in each period and group. The lines and dots indicate the changes in AVI for each subject. After fluid loading, the AVI in responders showed significant decreases (*$P$ = 0.004), whereas the AVI in non-responders did not significantly change.

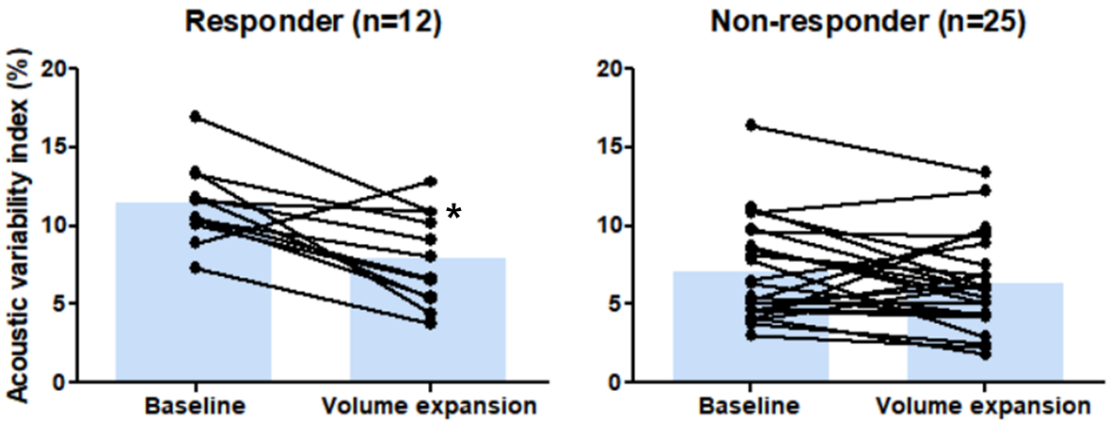


Fig 5. Correlation between stroke volume variation (SVV) and acoustic variability index (AVI) from all patients during the baseline before fluid challenge.

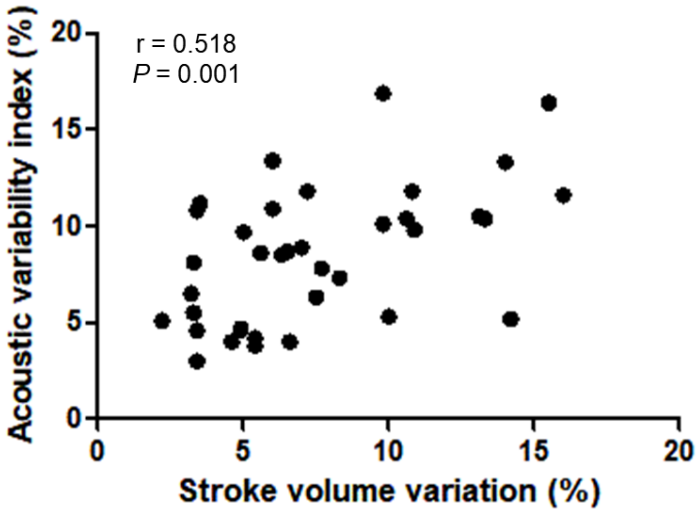


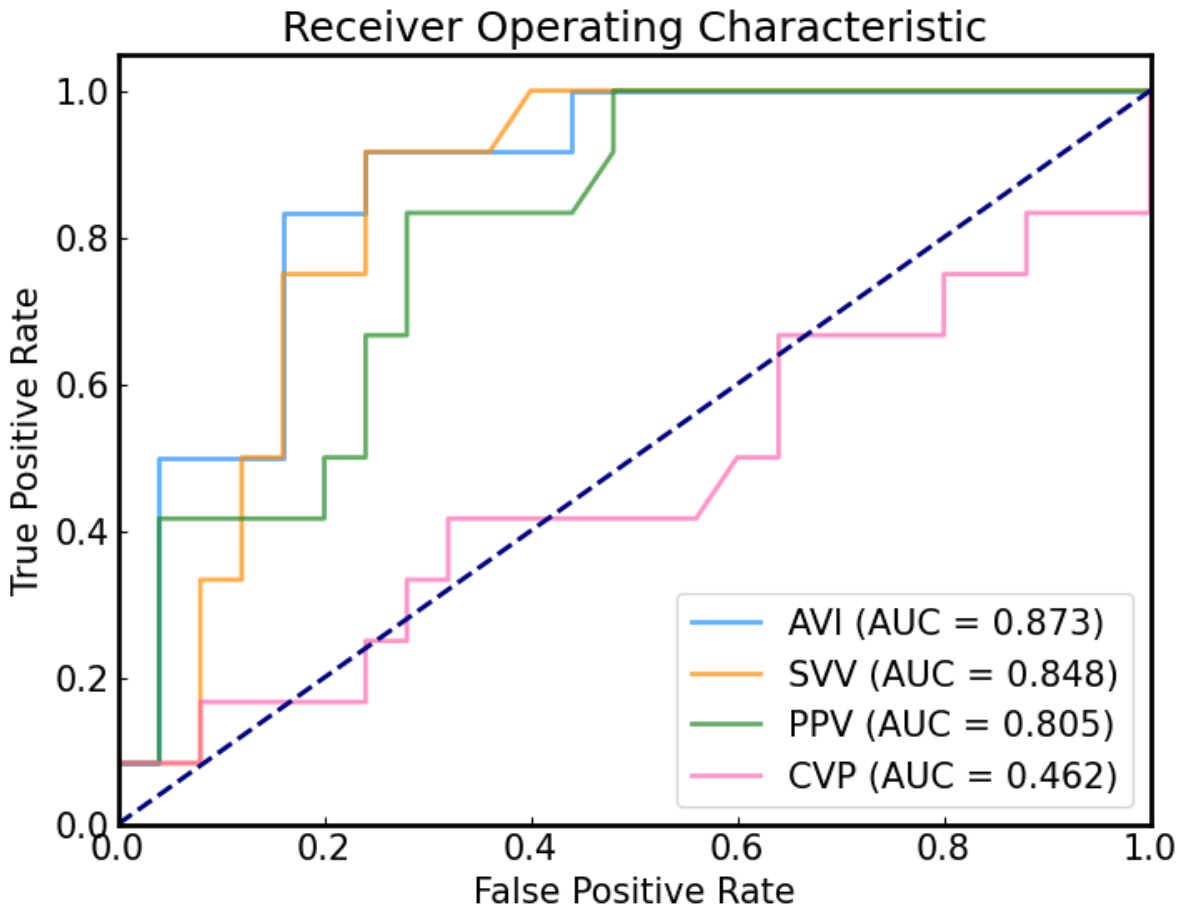
Table 3. ROC curve analysis of baseline AVI, SVV, PPV, and CVP values as predictors of cardiac output increases 10% after fluid loading

| | AUC (95% CI) | Sensitivity | Specificity | Youden index | +PV | -PV | +LR | -LR | P |
|---|---|---|---|---|---|---|---|---|---|
| AVI | 0.873 | 0.833 | 0.840 | 0.714 | 0.714 | 0.913 | 5.208 | 0.198 | 0.002 |
| SVV | 0.848 | 0.917 | 0.760 | 0.677 | 0.647 | 0.950 | 3.819 | 0.110 | 0.006 |
| PPV | 0.805 | 0.833 | 0.720 | 0.553 | 0.588 | 0.900 | 2.976 | 0.231 | 0.002 |
| CVP | 0.462 | 0.417 | 0.680 | 0.097 | 0.385 | 0.708 | 1.302 | 0.858 | 0.931 |

**P* value compared with 0.5.

Abbreviations: ROC, receiver operating characteristics; AVI, acoustic variability index; SVV, stroke volume variation; PPV, pulse pressure variation; CVP, central venous pressure; AUC, area under the curve; CI, confidence interval; +PV, positive predictive value; -PV, negative predictive value; +LR, positive likelihood ratio; LR, negative likelihood ratio.

Fig 6. Receiver operating characteristic curves comparing the abilities of acoustic variability index (AVI), stroke volume variation (SVV), pulse pressure variation (PPV), and central venous pressure (CVP) to predict fluid responsiveness between responders and non-responders. Responders were patients whose cardiac output (CO) increased ≥10% after fluid lading. Parameters are displayed, with AVI showing the highest AUC of 0.873, followed by SVV (0.848), PPV (0.805), and CVP (0.462).



# DISCUSSION

In this study, we presented that non-invasive AVI with an esophageal stethoscope would be a useful index that can predict fluid responsiveness. In specific, ROC curve analysis presented that a 9.8% of AVI with stable hemodynamics could predict a response to the fluid loading. Another traditional hemodynamic parameter, CVP, was not significantly different between responders and non-responders, reflecting the result of the current studies that this classic index cannot predict fluid responsiveness. Also, the correlation analysis revealed an association between AVI and SVV, which is a widely utilized dynamic index. Moreover, it has been revealed that AVI is not inferior to other dynamic parameters, SVV and PPV, when using ROC curve analysis.

Fluid responsiveness is defined as an increase of 10-11% or more in cardiac output or stroke volume upon fluid administration[21]. Physiologically, this can be explained by the Frank-Starling law, which implies that stroke volume is determined by the left ventricle end-diastolic volume and right atrial pressure. According to this law, if the preload increases beyond a certain point (reaches the plateau of the graph), cardiac output cannot increase further with fluid challenge, and this only increases end-diastolic pressure, which can lead to adverse outcomes[22]. For this reason, excessive fluid administration does not help the circulation of end-organ and may instead cause harmful effects such as pulmonary edema or right heart failure[2,6,23]. Thus, assessing a patient's volume status is critical when deciding whether to administer crystalloids and colloids. It is essential to evaluate whether fluid actually contributes to an increase in cardiac output and ultimately to an increase in blood flow to end-organs. Furthermore, with ERAS becoming a significant anesthetic agenda, goal-directed fluid management based on fluid restriction and prediction of fluid responsiveness has been greatly developed[24]. According to a relevant meta-analysis, such goal-directed treatment has been reported to reduce postoperative complications by 57%[1]. In this context, blood pressure alone may not fully reflect cardiac output due to the fluctuation of systemic vascular resistance during surgery and consistently may not represent the blood flow reaching end-organs[3]. As a result, monitoring various indicators to predict a patient's fluid responsiveness has become an important issue. Meanwhile, static indicators, including CVP and PCWP, have been shown not to be good predictors of fluid responsiveness through multiple studies[8,9,25]. Considering the AUC value of CVP (0.462) calculated in this study, it can be seen that previous studies have reproducibility. CVP is a somewhat complex indicator that is difficult to use simply for predicting fluid responsiveness but can be used to assess a patient's volume status. When the CVP value increases without an improvement in cardiac output, volume overload can be suspected[26]. In this study, the non-responder group exhibited the same pattern. Since the measurement of CVP and

PCWP also involves highly invasive catheterization, they cannot be considered free from safety concerns.

Accordingly, the so-called dynamic indices were studied, which involve real-time analysis of the immediate response of the cardiovascular system to changes in respiration and transient increases in preload[27]. Among these dynamic indices, SVV and PPV, based on the arterial waveform analysis used in this study, are prominent. These dynamic parameters analyze variations in stroke volume and pulse pressure during respiratory cycle. Additionally, various studies have been conducted on the passive leg raising test, Valsalva maneuver, and mini-fluid challenge in the intensive care setting[28]. PPV is known to have a very high positive predictive value when the cut-off is set at 13%[29,30]. In the case of SVV, various studies have shown that using a cut-off of 10-15% can serve as a good clinical target for goal-directed therapy[5]. Systematic review and numerous studies have reported a high correlation with changes in stroke volume index and cardiac index (minimum correlation coefficient = 0.72 (SVV), 0.78 (PPV)), making them good clinical options for hemodynamic monitoring[31,32]. Furthermore, the use of these indices in managing patients has been shown to significantly affect the reduction of morbidity and mortality in surgical patients[27,33,34]. The results of this study demonstrate the predictive power of SVV and PPV for fluid responsiveness with consistency compared to previous research. Moreover, considering the previously documented predictive power of SVV, the correlation between AVI and SVV along with the significant changes in SVV, PPV, and AVI within the responders support the predictive efficacy of AVI for fluid responsiveness. However, PPV and SVV are influenced by factors such as arterial compliance and total systemic vascular resistance[35,36]. Therefore, even if fluid administration guided by dynamic indices increases cardiac output, mean arterial pressure may not be improved. To compensate for this, the ratio of SVV to PPV can be used to calculate dynamic arterial elastance, which can then predict the patient's arterial pressure response and assess the need for vasopressors or inotropics[27,37]. Only in certain situations—when the patient does not exhibit spontaneous breathing, irregular heartbeat, an open thorax, or fluctuating intra-abdominal pressure—PPV and SVV are applicable[38]. Along with these limitations, the need for catheter insertion underscores the need for further research about alternative dynamic indices that can be used adjunctively.

In developing and evaluating dynamic indices to predict fluid responsiveness, the most crucial aspect is the estimation and monitoring of patient cardiac output. This enables the classification of patients into responders and non-responders to fluid administration. However, assessing cardiac output presents a tremendous challenge in such research. The gold standard for evaluating cardiac output is intermittent pulmonary artery thermodilution using a pulmonary artery catheter[39]. Nevertheless, not all

patients, as in this study, can be monitored with a Swan-Ganz catheter, which accompanies an invasive catheterization procedure that can cause severe complications. Non-invasive monitoring methods are becoming a growing trend due to advancements in anesthesia techniques, and they should be taken into consideration. Consequently, less invasive methods for estimating cardiac output are now being used in many clinical scenarios. One such method analyzes the arterial waveform to calculate cardiac output. For instance, the VolumeView system (Edwards Lifesciences Corporation, Irvine, CA, United States) uses a three-element Windkessel model for continuous cardiac output estimation[35]. This model divides the systemic vasculature into different components based on resistance level and considers impedance, assuming the human body as an electrical circuit for calculations[40]. Through this assumption, the system can estimate the cardiac output of the patients by analyzing cross-sectional area and pulse wave velocity during the diastolic phase. Additionally, it allows users to calibrate the values of cardiac output closely to actual values through intermittent transpulmonary thermodilution. On the other hand, cardiac output can be assessed without calibration, as demonstrated by the FloTrac System (Edwards Lifesciences Corporation, Irvine, CA, United States) used in this study. This system statistically analyzes changes in pulse pressure on a beat-to-beat basis to estimate cardiac output[41]. A multi-center study showed that this method can predict cardiac output more accurately than the traditional intermittent transpulmonary thermodilution technique in septic patients[42].

According to one meta-analysis, 15% of the studies researching the predictive performance of SVV and PPV categorized responder and non-responder groups based on cardiac output derived from arterial pulse contour analysis[43]. Our study also used non-calibrated pulse contour analysis for cardiac output estimation using the FloTrac system and the EV-1000™ system based on these findings. Although uncalibrated cardiac output estimation can be unreliable when there are significant short-term arterial vascular resistance changes[44], it is still recommended for surgical patients who are not critically ill[45,46]. Also, changes in vascular resistance are not expected to be significant in this study protocol, as a fluid challenge was conducted when the patient became hemodynamically stable after the main procedure of the surgery. Moreover, this study evaluated fluid responsiveness based on changes in estimated cardiac output values rather than the absolute values themselves. Additionally, considering that the AUC values for SVV (0.848) and PPV (0.805) in this study were comparable to those in other research, it can be concluded that the study design was reasonable. Consequently, this study classified patients with a cardiac output change of more than 10% as fluid responders using non-calibrated pulse contour analysis.

In this study, we have demonstrated that the AVI derived from phonocardiogram analysis can be a good predictor of fluid responsiveness. As mentioned above, arterial pulse wave analysis still

requires catheterization and may be limited or inaccurate in certain circumstances. In clinical settings, anesthesiologists often encounter difficulties with arterial catheterization, which may lead to both major and minor complications. In fact, during the experimental procedure, no complication or adverse effect related to the insertion of the esophageal stethoscope or the acquisition of AVI data was reported. In such a situation, the AVI could provide a good alternative or an accurate adjunct diagnostic tool. The mechanism for assessing fluid responsiveness using heart sounds is as follows: First, the amplitude of the heart sounds provides significant information. Heart sounds are generated by the complex interactions of atrial and ventricular contractions, blood flow, and valve movements. S1, the first heart sound, is obtained when the atrioventricular valves close, which is related to the contractility of the ventricular myocardium. S2, the second heart sound, occurs at the end of systole and the onset of diastole when the aortic and pulmonary valves close. The closing of the aortic valve, due to the backflow of systemic blood, generates S2 and it is associated with systemic vascular resistance. The second aspect is the relationship between systolic time and stroke volume. The starting point can be found in the calculation of stroke volume using the esophageal doppler. This method analyzes the blood flow in the aorta, assuming it to be cylindrical, and then uses blood flow velocity and systolic time to estimate cardiac output by integration[47]. The systolic time, or the interval between S1 and S2, can be interpreted as the cardiac emptying time. Intuitively, one might expect that a longer duration would be needed to pump a greater volume of blood. These assumptions suggest that the information contained in the AVI reflects changes in cardiac output.

It is a misconception to think of heart sound analysis in current medicine simply as the subjective assessment of a physician with a stethoscope. There have been attempts for a long time to apply phonocardiographic analysis to diagnose ventricular dysfunction, valvular disease, and cardiomyopathy using the mechanisms previously described[48,49]. However, the development of other diagnostic tools, particularly echocardiography, has relegated heart sound analysis to a secondary tool. Also, phonographic analysis was quite challenging due to its lack of visual and intuitive components. Additionally, there have been several issues that must be considered, such as noise handling, variations depending on the auscultation site, and technical aspects, including digital signal processing techniques like spectral analysis. For these reasons, only few studies have utilized heart sound data as a hemodynamic index[19]. However, with advancements in technology, the precision of signal analysis has improved. The development of pattern analysis has opened up new dimensions in phonocardiographic analysis. Current studies have found that these phonographic analyses of heart sounds can be used as a good real-time hemodynamic index. Systolic duration and its respiratory variations derived phonographically have been shown to reflect pulse pressure in patients undergoing liver transplantation, thereby serving as a hemodynamic index[19,50]. Furthermore, an animal study involving the same

monitoring devices demonstrated that the amplitude of S1 is correlated with myocardial contractility with the administration of inotropic[51]. This could be considered as a rediscovery of heart sounds. Auscultation extends beyond simply analyzing the patient's heart itself to analyzing the hemodynamic status of the entire body.

Additionally, SignalTAB (Signal House Co., Ltd., Seoul, Korea) provides the analysis of both heart sounds and lung sounds. Heart and lung sounds have different frequency ranges, making it possible to separate them. The lung sounds analysis can be used in various clinical situations. Especially, researches have been conducted on children with respiratory diseases such as asthma or bronchial stricture, revealing that phonographic analysis is possible to detect airway narrowing or find changes in response to bronchodilators[14,16]. It is also possible to quickly detect mucus accumulation or blockage in the tubes or trachea during surgeries[15]. It is clear that as signal analysis becomes more precise, the amount of information that real-time analysis of lung sound can provide will be more extensive. An anesthesiologist should be vigilant while monitoring the respiratory system. This sound analysis can provide faster information than traditional monitoring devices such as end-tidal carbon dioxide, arterial blood gas analysis, etc. This could allow its use as an auxiliary or even primary monitoring device for various patients. Furthermore, the use of a signal quality index (SQI) allows for the evaluation of whether appropriate signals are being received, semi-automatically preventing incorrect analysis. In this study, we actually excluded a patient whose SQI values were unstable due to the inability to consistently separate and measure S1 and S2 amplitudes from cardiopulmonary sounds.

This study has several limitations. First, as mentioned above, the measurement of cardiac output was conducted using non-calibrated pulse contour analysis. This may not accurately reflect changes in actual cardiac output. Moreover, in patients undergoing hepatectomy, systemic vascular resistance may fluctuate, and there may be significant bleeding due to surgery. These conditions could also affect the accuracy of this non-invasive analysis[45,46]. In fact, in a meta-analysis, it was pointed out that the results regarding the predictive ability of the dynamic indices (SVV, PPV) vary depending on the method used for measuring cardiac output[43]. Second, this study only included patients undergoing open hepatectomy. In the case of liver transplant patients, who comprise the majority of this study's subjects, they are suitable for this research because fluid is restricted according to an unified protocol until the liver is harvested for donation, and fluid replacement begins thereafter. Additionally, the procedure and level of pain are relatively predictable for these patients. However, various laparoscopic surgeries and minimally invasive surgeries are being performed currently. Additional researches are needed considering that the traditional dynamic indices do not accurately predict fluid responsiveness

in such laparoscopic surgeries. Lastly, this was an exploratory trial with a relatively small sample size in a single center; therefore, further confirmatory trials are needed to confirm these findings.

In conclusion, non-invasive AVI can provide a continuous hemodynamic index that can predict the fluid responsiveness of patients who undergo open abdominal hepatectomy. Anesthesiologist and other clinicians will be able to estimate the volume status of surgical patients through intraoperative monitoring of AVI, which will ultimately contribute to reducing uncertainty in the assessment of preload status. Further research and development of this index is warranted.

# REFERENCE


1. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesthesia and analgesia 2011;112:1392-402.
2. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. Jama 2014;311:2181-90.
3. Miller TE, Myles PS. Perioperative Fluid Therapy for Major Surgery. Anesthesiology 2019;130:825-32.
4. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? Jama 2016;316:1298-309.
5. Meng L, Heerdt PM. Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution. British journal of anaesthesia 2016;117:iii3-iii17.
6. Yang TX, Tan AY, Leung WH, Chong D, Chow YF. Restricted Versus Liberal Versus Goal-Directed Fluid Therapy for Non-vascular Abdominal Surgery: A Network Meta-Analysis and Systematic Review. Cureus 2023;15:e38238.
7. Zhao X, Tian L, Brackett A, Dai F, Xu J, Meng L. Classification and differential effectiveness of goal-directed hemodynamic therapies in surgical patients: A network meta-analysis of randomized controlled trials. Journal of critical care 2021;61:152-61.
8. Bendjelid K, Romand JA. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. Intensive care medicine 2003;29:352-60.
9. Rex S, Brose S, Metzelder S, et al. Prediction of fluid responsiveness in patients during cardiac surgery. British journal of anaesthesia 2004;93:782-8.
10. Wen YN, Lee AP, Fang F, Jin CN, Yu CM. Beyond auscultation: acoustic cardiography in clinical practice. International journal of cardiology 2014;172:548-60.
11. Singh J, Anand RS. Computer aided analysis of phonocardiogram. Journal of medical engineering & technology 2007;31:319-23.
12. Durand LG, Pibarot P. Review: Most Recent Advancements in Digital Signal Processing of the Phonocardiogram. Critical reviews in biomedical engineering 2017;45:453-509.
13. Smith C. An endo-oesophageal stethoscope. Anesthesiology 1954;15:566.

14. Tabata H, Hirayama M, Enseki M, et al. A novel method for detecting airway narrowing using breath sound spectrum analysis in children. Respiratory investigation 2016;54:20-8.
15. Moon YJ, Bechtel AJ, Kim SH, Kim JW, Thiele RH, Blank RS. Detection of intratracheal accumulation of thick secretions by using continuous monitoring of respiratory acoustic spectrum: a preliminary analysis. Journal of clinical monitoring and computing 2020;34:763-70.
16. Tabata H, Enseki M, Nukaga M, et al. Changes in the breath sound spectrum during methacholine inhalation in children with asthma. Respirology (Carlton, Vic) 2018;23:168-75.
17. Lee JH, Kim JT, Yoon SZ, et al. Evaluation of corrected flow time in oesophageal Doppler as a predictor of fluid responsiveness. British journal of anaesthesia 2007;99:343-8.
18. Moyers B, Shapiro M, Marcus GM, et al. Performance of phonoelectrocardiographic left ventricular systolic time intervals and B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc 2007;12:89-97.
19. Kim SH, Moon YJ, Kim JW, Song JG, Hwang GS. Prediction of Fluid Responsiveness by a Non-invasive Respiratory Systolic Time Interval Variation Using Heart Sound Signals in Recipients Undergoing Liver Transplantation. Transplantation proceedings 2017;49:1082-6.
20. Manecke GR, Jr., Poppers PJ. Esophageal stethoscope placement depth: its effect on heart and lung sound monitoring during general anesthesia. Anesthesia and analgesia 1998;86:1276-9.
21. Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Current opinion in critical care 2011;17:290-5.
22. Messina A, Longhini F, Coppo C, et al. Use of the Fluid Challenge in Critically Ill Adult Patients: A Systematic Review. Anesthesia and analgesia 2017;125:1532-43.
23. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. The New England journal of medicine 2018;378:2263-74.
24. Melloul E, Hübner M, Scott M, et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World journal of surgery 2016;40:2425-40.
25. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Critical care (London, England) 2000;4:282-9.
26. De Backer D, Aissaoui N, Cecconi M, et al. How can assessing hemodynamics help to assess volume status? Intensive care medicine 2022;48:1482-94.
27. Cavallaro F, Sandroni C, Antonelli M. Functional hemodynamic monitoring and dynamic indices of fluid responsiveness. Minerva anestesiologica 2008;74:123-35.

28. Alvarado Sánchez JI, Amaya Zúñiga WF, Monge García MI. Predictors to Intravenous Fluid Responsiveness. Journal of intensive care medicine 2018;33:227-40.
29. Michard F, Schmidt U. Prediction of fluid responsiveness: searching for the Holy Grail. Journal of applied physiology (Bethesda, Md : 1985) 2004;97:790-1; author reply 1.
30. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 2002;121:2000-8.
31. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Critical care medicine 2009;37:2642-7.
32. Zhang Z, Lu B, Sheng X, Jin N. Accuracy of stroke volume variation in predicting fluid responsiveness: a systematic review and meta-analysis. Journal of anesthesia 2011;25:904-16.
33. Michard F, Giglio MT, Brienza N. Perioperative goal-directed therapy with uncalibrated pulse contour methods: impact on fluid management and postoperative outcome. British journal of anaesthesia 2017;119:22-30.
34. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. Critical care (London, England) 2014;18:650.
35. Bendjelid K, Marx G, Kiefer N, et al. Performance of a new pulse contour method for continuous cardiac output monitoring: validation in critically ill patients. British journal of anaesthesia 2013;111:573-9.
36. Chemla D, Antony I, Lecarpentier Y, Nitenberg A. Contribution of systemic vascular resistance and total arterial compliance to effective arterial elastance in humans. American journal of physiology Heart and circulatory physiology 2003;285:H614-20.
37. Cecconi M, Monge García MI, Gracia Romero M, et al. The use of pulse pressure variation and stroke volume variation in spontaneously breathing patients to assess dynamic arterial elastance and to predict arterial pressure response to fluid administration. Anesthesia and analgesia 2015;120:76-84.
38. Monnet X, Shi R, Teboul JL. Prediction of fluid responsiveness. What's new? Annals of intensive care 2022;12:46.
39. Saugel B, Vincent JL. Cardiac output monitoring: how to choose the optimal method for the individual patient. Current opinion in critical care 2018;24:165-72.
40. Saugel B, Kouz K, Scheeren TWL, et al. Cardiac output estimation using pulse wave analysis-physiology, algorithms, and technologies: a narrative review. British journal of anaesthesia 2021;126:67-76.

41. Pratt B, Roteliuk L, Hatib F, Frazier J, Wallen RD. Calculating arterial pressure-based cardiac output using a novel measurement and analysis method. Biomedical instrumentation & technology 2007;41:403-11.
42. De Backer D, Marx G, Tan A, et al. Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. Intensive care medicine 2011;37:233-40.
43. Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, Amaya Zuñiga WF, Ospina-Tascón GA, Cruz Martínez LE. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. Annals of intensive care 2021;11:28.
44. Jozwiak M, Monnet X, Teboul JL. Pressure Waveform Analysis. Anesthesia and analgesia 2018;126:1930-3.
45. Scheeren TWL, Ramsay MAE. New Developments in Hemodynamic Monitoring. Journal of cardiothoracic and vascular anesthesia 2019;33 Suppl 1:S67-s72.
46. Bond O, Pozzebon S, Franchi F, et al. Comparison of estimation of cardiac output using an uncalibrated pulse contour method and echocardiography during veno-venous extracorporeal membrane oxygenation. Perfusion 2020;35:397-401.
47. Cholley BP, Singer M. Esophageal Doppler: noninvasive cardiac output monitor. Echocardiography (Mount Kisco, NY) 2003;20:763-9.
48. Sun Z, Poh KK, Ling LH, Hong GS, Chew CH. Acoustic diagnosis of aortic stenosis. The Journal of heart valve disease 2005;14:186-94.
49. Romano M, Carella G, Cotecchia MR, et al. Abnormal systolic time intervals in obesity and their relationship with the amount of overweight. American heart journal 1986;112:356-60.
50. Park YS, Moon YJ, Kim SH, Kim JM, Song JG, Hwang GS. Beat-to-Beat Tracking of Pulse Pressure and Its Respiratory Variation Using Heart Sound Signal in Patients Undergoing Liver Transplantation. Journal of clinical medicine 2019;8.
51. Park YS, Kim HS, Lee SA, et al. Correlations between heart sound components and hemodynamic variables. Scientific reports 2024;14:8602.

# ABSTRACT IN KOREAN

# 국문 초록


## 서론

주요 복강 수술을 받는 환자에서 적절한 수액 요법은 필수적이다. 심음의 음성학적 분석은 환자의 심혈관계 상태를 파악하고 수액 반응성을 예측하기 위해 도움을 주는 비침습적이고 연속적인 측정값을 제공한다. 본 연구의 목적은 음향 가변성 지수(Acoustic variability index)를 기존의 동적 지표들과 비교함으로써 해당 지수가 환자의 수액 반응성을 예측가능한지에 대한 그 유효성을 밝히고 이를 통해 개복 간절제술을 받는 환자에서 기존의 동적 지표를 대체 가능할지에 대해 분석하고자 한다.

## 연구방법

개복 간절제술 시 수액 보충이 필요한 40 명의 환자를 대상으로 실험을 진행했다. 수액 투여는 10 분간 500 mL 의 정질액을 10 분간 투여하는 것으로 표준화 되었다. 식도 청진기를 삽입하고 심실 수축 시간(Systolic time interval)과 S1, S2 심음의 진폭을 계산하는 신호 분석 소프트웨어를 사용하여 음향 가변성 지수를 측정했다. 주요 수술 과정이 종료되어 절제된 간 표본이 체외로 적출되고 환자가 혈역학적으로 안정된 것을 확인한 후 수액 투여를 시행하였다. 수액투여 전후 3 분간 중심 정맥압(Central venous pressure), 일회 박출량 변이(Stroke volume variation), 맥압 변이(Pulse pressure variation), 음향 가변성 지수를 포함하는 수액 반응성 지표를 측정하였다. 수액 투여 이후 10% 이상의 심박출량(Cardiac output) 증가를 보인 피험자를 반응군으로 분류하였다.

## 연구결과

분석 대상이 된 37 명의 환자 중 12 명이 반응군에 해당하였다. 혈역학적 변수 중 일회 박출량(Stroke volume), 일회 박출량 변이, 맥압 변이, 음향 가변성 지수가 수액 투여 전 반응군과 비반응군 사이에서 유의한 차이를 보였다. 반응군의 경우 수액 투여 전후에 음향 가변성 지수의 유의한 감소를 보였으며 (11.4 ± 2.3 % vs. 7.8 ± 2.8 %,

$P$ < 0.01), 반면 비반응군의 경우에는 수액 투여 전후 음향 가변성 지수의 변화가 없었다 (7.1 ± 3.1 % vs. 6.3 ± 2.9 %, $P$ = 0.356). ROC 분석에 따르면 수액 투여 전 음향 가변성 지수 값이 9.8% 이상일 경우 수액 반응성을 예측할 수 있었다 (AUC = 0.873, 95% 신뢰수준에서 오차범위, 0.722 – 0.959).

**결론**

개복 간절제술을 받는 환자에서 수술 중 음향 가변성 지수는 수액 반응성을 예측하는 인자로 사용될 수 있다. 지속적인 실시간 음향 가변성 지수 감시는 수액 요법을 시행하는데 있어 비침습적인 혈역학 지표로서 유용하게 사용될 수 있을 것이다.