Evaluation of fluid responsiveness using liver compression in dogs with experimentally induced hypovolemia

Daeyun Seo, DVM; Seongsoo Lim, DVM; Beomkwan Namgoong, DVM; Ahreum Choe, DVM; Heesung Uhm, DVM; Hyeajeong Hong, DVM; Nanju Lee, DVM; Isong Kim, DVM; Seunghun Heo, DVM; Jiwong Her, DVM, MS, DACVECC; Heesung Uhm, DVM; Hyeajeong Hong, DVM; Nanju Lee, DVM; Isong Kim, DVM; Seunghun Heo, DVM; Jiwong Her, DVM, MS, DACVECC; Min-Su Kim, DVM, PhD*

1Veterinary Emergency Medicine, Department of Veterinary Clinical Science, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Gwanak-gu, Seoul, South Korea
2Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH
*Corresponding author: Dr. Min-Su Kim (minsukim@snu.ac.kr)

OBJECTIVE
To investigate whether liver compression (LC) could increase stroke volume (SV) by more than 15% in healthy, anesthetized dogs with hypovolemia and suggest LC as a novel method to evaluate fluid responsiveness.

ANIMALS
6 healthy Beagles.

METHODS
This prospective, nonrandomized experimental study was conducted from November 2023 to February 2024. The dogs were anesthetized with isoflurane and mechanically ventilated under neuromuscular blockade. After instrumentation, the dogs underwent the following 4 experimental stages in a sequential, nonrandomized manner: stage 1, baseline; stage 2, 30% withdrawal of circulating blood volume; stage 3, 50% infusion of the collected blood; and stage 4, the remaining 50% infusion of the collected blood. At each stage, SV via pulmonary artery thermodilution and hemodynamic variables were measured before, during, and after the LC.

RESULTS
In stage 2, LC significantly increased mean SV by 30%, from 6.9 to 9 mL/beat. Simultaneously, LC significantly increased mean arterial pressure by 11 mm Hg and mean central venous pressure by 2 mm Hg, while pulse pressure variation significantly decreased from 28% to 22%. In stages 1, 3, and 4, LC did not significantly change mean SV, mean arterial pressure, and pulse pressure variation; however, mean central venous pressure significantly increased during stage 3.

CLINICAL RELEVANCE
This study demonstrates that LC at 22 mm Hg for 1 minute could increase SV more than 15% in anesthetized, hypovolemic dogs and LC could be used as a novel method to evaluate fluid responsiveness.

Keywords: liver compression, cardiac output, hemodynamic, blood, dog

Hypovolemia is the most common cause of hypotension in dogs and cats and is an emergency situation that is life threatening if appropriate treatment is not provided.1-3 The primary focus of treatment for patients with hypovolemia is to increase preload through fluid resuscitation, thereby improving cardiac output (CO) and tissue perfusion.4 However, it is known that only about 50% of hemodynamically unstable patients achieve the desired effects through fluid administration.5 In other words, fluid administration may not be appropriate in the remaining patients, and indiscriminate fluid administration in such cases can lead to serious complications such as pulmonary or interstitial edema of various organs. These complications increase morbidity and mortality in both human and veterinary medicine.6-8 Therefore, predicting a patient’s fluid responsiveness (FR) can assist clinicians in evaluating the appropriateness of fluid administration and may also influence the patient’s prognosis.1,5,9
Fluid responsiveness is defined as a state in which CO or stroke volume (SV) increases more than 10% to 15% with volume expansion during a preload challenge. Conversely, if there is no significant change in CO or SV, it is referred to as fluid nonresponsiveness (FNR). In general, preload challenge can be performed in 2 ways; (1) administer a certain amount of IV fluids, or (2) shift fluids within the vascular system without actual fluid administration. However, repeated administration of fluids to predict FR increases the risk of fluid overload. To overcome this limitation, the passive leg raise (PLR) test has been investigated to predict FR. The PLR test predicts FR by raising the legs to induce endogenous autotransfusion from the lower part of the body, thereby increasing preload. In humans, the PLR test has been used to predict FR in various critically ill patients, and recent studies in pigs and dogs have suggested the potential applicability of the PLR test in veterinary medicine. The PLR test has the advantage of being reversible and safe compared with traditional preload challenge, as it does not require external fluid administration, and it can predict FR in spontaneously breathing patients. However, the applicability of PLR may be restricted to certain breeds due to varying leg proportions among dogs. The PLR study in humans has suggested that predicting FR may be challenging in pediatrics with smaller leg proportions compared with adults, as PLR may not sufficiently increase preload.

Recently, a new method for predicting FR through liver compression (LC) has emerged in human pediatrics, and several studies have demonstrated that compression of the mid abdomen with a pressure of 22 to 30 mm Hg for 1 minute can predict FR. Liver compression employs external compression of the liver to redistribute blood from the abdominal organs into the thoracic cavity, rapidly increasing preload to predict FR. Liver compression shares a similar mechanism and advantages with PLR. In addition, it may be practical in clinical settings, as it does not require raising the legs and is not influenced by leg proportions.

This study aimed to (1) evaluate the effect of preload challenge during LC in hypovolemia, and (2) investigate the changes in hemodynamic variables during LC. We hypothesized that (1) LC in dogs could increase SV as observed in human pediatrics, and (2) LC could be used as a novel method to evaluate FR in hypovolemia, if a LC-induced increase in SV is more than 15%.

Methods

Animals
This prospective, nonrandomized experimental study was approved by the Ethics Committee for Experimental Animals of Seoul National University (SNU-230725-2). The study included 6 dogs, all confirmed to be healthy following physical examinations, CBC, serum chemistry panels, as well as thoracic and abdominal radiographic examinations. Based on previous studies identifying FR in the PLR test in veterinary medicine, an a priori power analysis indicated that a sample size of 6 dogs was necessary to show a minimum 15% significant difference in SV assuming a statistical power of 0.8 and an a level of 0.05 (G*Power 3.1; Heinrich-Heine-Universität Düsseldorf).

Anesthesia and instrumentation for standard monitoring
For all dogs, food and water were restricted 12 and 4 hours, respectively, before the induction of anesthesia. A 24-gauge IV catheter was aseptically placed in the cephalic vein with minimal physical restraint. The dogs were preoxygenated with 100% fraction oxygen via flow by method for 5 minutes, and alfaxalone was titrated (2 mg/kg, IV) until orotracheal intubation was possible. After endotracheal tube placement, the dog was positioned in dorsal recumbency and the endotracheal tube was connected to an anesthetic machine with an integrated ventilator. Anesthesia was maintained with isoflurane in oxygen (2 L/min) at an end-tidal concentration of isoflurane of 1.6% to 1.8%, monitored using an infrared gas analyzer included in a multiparameter monitor (Carescape B650; GE HealthCare). Dynamic compliance, peak inspiratory pressure (PIP), and positive end-expiratory pressure were monitored with the same monitor. Volume-controlled mechanical ventilation was initiated with a 13-mL/kg tidal volume, and the respiratory rate was controlled between 10 and 20 minutes to maintain the end-tidal partial pressure of carbon dioxide (PETCO₂) at 35 to 45 mm Hg. Rocuronium was administered (0.4 mg/kg, IV) bolus followed by a continuous rate infusion (0.4 mg/kg/h) to suppress spontaneous breathing. A 24-gauge catheter was aseptically inserted into the dorsal pedal artery to measure the invasive blood pressure and collect blood samples. The catheter was connected to a saline-filled pressure transducer, and the mean arterial pressure (MAP) was measured using a multiparameter monitor (Carescape B650; GE HealthCare). The pulse pressure variation (PPV), heart rate (HR), esophageal temperature, and peripheral oxygen saturation of hemoglobin as measured by pulse oximetry (SpO₂) were recorded using the same monitor. The catheter was periodically flushed with heparinized saline, and esophageal temperature was maintained throughout the anesthesia between 37.0 and 38.0°C using a forced-air warming device. Except for thermodilution (TD) and neuromuscular blockade, maintenance fluids were not administered because of their potential effects on hemodynamic data during the anesthetic procedure.

Instrumentation for CO monitoring
A 5-Fr double-lumen catheter was aseptically inserted into the left jugular vein to induce changes in the volume status. A 6-Fr hemostasis introducer was aseptically placed in the right jugular vein to introduce a 5-Fr thermistor-tipped pulmonary artery TD catheter (Swan-Ganz; Edwards Lifesciences Corp). A Swan-Ganz catheter was advanced until the tip was placed in the pulmonary artery based on the observation
of the characteristic pressure waveform. The catheter was connected to a multiparameter monitor (Carescape B650; GE HealthCare), and mean central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and core blood temperature ($T_{\text{core}}$) were measured. The pressure transducers connected to the central venous and pulmonary artery catheters were placed at the estimated level of the right atrium and zeroed to atmospheric pressure. Cardiac output was measured by TD and automatically calculated using a multiparameter monitor. For each CO measurement, 3 mL of cold (2 to 5°C) 0.9% saline solution was manually injected over < 3 seconds at end expiration into the proximal port of the Swan-Ganz catheter. To reduce bias, injections were performed by the same operator, and the mean of the 3 consecutive CO measurements was recorded within a 10% variation. Stroke volume was calculated by dividing the CO by the HR. Systemic vascular resistance (SVR) was calculated as [(MAP − CVP/CO) X 79.9].

Liver compression technique and FR monitoring

Based on the human literature, the mid abdomen of the dog in dorsal recumbency was compressed with a pressure of 22 mm Hg for 1 minute using a modified compressor connected to a digital force gauge (AMF-50; Aliyiqi Co; Figure 1). An LC-induced increase in SV > 15% defined FR; otherwise, it was defined as FNR.

Experimental design

After the completion of all instruments and a 10-minute stabilization period, a stepwise nonrandomized change in blood volume was performed (Figure 2). Baseline data were collected during stage 1. In stage 2, blood (24 mL/kg, 30% of the estimated total circulating blood volume) was manually collected over 15 minutes through a central venous catheter into 50-mL syringes, prefilled with an appropriate amount of a citrate phosphate dextrose adenine solution, and then transferred from the syringes into a blood transfusion bag. In stage 3, 50% of the collected blood was reinfused through an 18-μm filter for 15 minutes using an infusion pump. In stage 4, the remaining 50% of the collected blood was administered using the same method as in stage 3. Between each stage, 10 minutes elapsed until data collection to stabilize the hemodynamic status. During the stabilization period, arterial blood samples were collected and analyzed using a blood gas analyzer (GEM Premier 5000; Werfen) to evaluate the effects of acute blood loss and transfusion on PCV, arterial partial pressure of oxygen (PaO$_2$), arterial partial pressure of carbon dioxide (PaCO$_2$), oxygen saturation of hemoglobin as measured by pulse oximetry (SpO$_2$), and lactate. Each stage included 3 time points (pre-LC, LC, and post-LC). Liver compression was maintained for 1 minute, and CO was measured from 10 seconds after the initiation of LC until the end of the LC. Hemodynamic variables (PPV, HR, MAP, mean CVP, PAOP, $T_{\text{core}}$, peripheral oxygen saturation of hemoglobin, peripheral partial pressure of carbon dioxide (PaCO$_2$), and lactate) were collected at end expiration following CO measurement. Before data collection at each time point, 5 minutes had elapsed to minimize the volume effect of the TD. One researcher recorded data from the monitors, and researchers who performed LC and TD, other than the recorder, were blinded to the measurements performed.

Recovery from anesthesia

After obtaining the final data, rocuronium was discontinued and reversed by neostigmine (0.08 mg/kg, IV), and glycopyrrolate (0.01 mg/kg, IV) was simultaneously administered to antagonize the side effects of neostigmine. The jugular and arterial catheters were removed, and meloxicam (0.2 mg/kg, SC) was administered as a rescue analgesic. The isoflurane vaporizer was turned off, and recovery was initiated. Spontaneous respiration with an appropriate tidal volume was confirmed before extubation, and the dogs were moved to individual kennels. The hemodynamic variables and catheter sites were periodically monitored for the next 48 hours.

Statistical analyses

All analyses were performed using commercially available software (SPSS Statistics 26; IBM Corp). The normality of hemodynamic variables at each stage was assessed using the Shapiro-Wilk test. For normally distributed variables, the mean and SD were calculated. Repeated-measures 1-way ANOVA was used to compare differences across variables among the 3 time points within each stage and between the 4 experimental stages. Greenhouse and Geisser corrections were applied to the analysis of cases in which a lack of sphericity was observed. A post hoc Bonferroni correction was used when multiple comparisons were performed. Statistical significance was set at $P < .05$.

Results

All the dogs survived after the experiment and recovered without complications. Three intact male and 3 intact female Beagle dogs (aged, 12 to
13 months; body weight, 10 ± 1 kg) were included in this study.

At the pre-LC time point, changes in SV, CO, MAP, HR, PPV, and SVR were demonstrated as blood was withdrawn and reinfused from stage 1 to 4 (Table 1; Supplementary Table S1). Stroke volume significantly decreased in stage 2 compared with stage 1 \((P = .001)\), increased in stage 3 compared with stage 2 \((P < .001)\), and was significantly higher in stage 4 compared with stages 1, 2, and 3 \((P = .003, P < .001, P = .007, \text{ respectively})\). Cardiac output showed a trend similar to that of SV, decreasing from stage 1 to 2 and increasing from stage 2 to 4. Mean arterial pressure significantly decreased in stage 2 compared with stage 1 \((P = .001)\), increased in stages 3 and 4 compared with stage 2 \((P = .003 \text{ for both})\). Heart rate significantly increased in stage 4 compared with stages 2 and 3 \((P = .017, P = .03, \text{ respectively})\). In contrast, PPV and SVR increased with blood withdrawal and decreased with transfusion. PPV significantly increased in stage 2 compared with stage 1 \((P < .001)\), decreased in stage 3 compared with stage 2 \((P = .001)\), and decreased in stage 4 compared with stage 3 \((P = .017)\). Systemic vascular resistance significantly increased in stage 2 compared with stage 1 \((P = .015)\) and decreased in stage 4 compared with stages 2 and 3 \((P = .013, P = .008, \text{ respectively})\). Simultaneously, there were no significant differences among the stages in pH, \(P_{aO_2}\), \(P_{aCO_2}\), and lactate in arterial blood gas analysis (Table 2). However, the PCV was significantly lower in stage 3 than in stage 1 \((P = .028)\).
During LC, changes in SV, CO, MAP, CVP, and PPV were demonstrated compared with pre-LC from stages 1 to 4 (Table 1; Supplementary Table S1). Notably, in stage 2, LC significantly increased SV, MAP, and CVP and decreased PPV compared with pre-LC. Liver compression significantly increased SV by 30% compared with pre-LC ($P = .001$), with the mean SV increasing from 6.9 mL/beat at pre-LC to 9 mL/beat during LC. Post-LC showed a 9% decrease in SV compared with LC; however, the difference was not statistically significant ($P = .08$). Similarly, CO significantly increased by 26% compared with pre-LC ($P = .001$), with the mean CO increasing from 0.8 L/min at pre-LC to 1 L/min during LC. Post-LC showed a 6% decrease in CO compared with LC; however, the difference was not statistically significant ($P = .299$). Mean arterial pressure significantly increased by 11 mm Hg compared with LC ($P = .001$) and decreased by 3 mm Hg post-LC; however, the difference between LC and post-LC was not significant.
During LC, CVP was significantly higher by 2 mm Hg compared with pre-LC (P = .038) and post-LC (P = .031). Liver compression resulted in significantly lower PPV decreasing from 28% to 22% compared with pre-LC (P = .019); however, no significant difference was observed between LC and post-LC.

In contrast to stage 2, during LC, there were no significant differences observed in SV, CO, MAP, CVP, and PPV across stages 1, 3, and 4, except for a significant increase in CVP in stage 3 compared to pre-LC (P = .035). Based on the definition of FR and FNR in this study, dogs in stage 2 were considered FR but were FNR in stages 1, 3, and 4. Liver compression did not significantly affect HR, PAOP, SVR, T_{core}, PIP, SpO_{2}, and PetCO_{2} among all stages compared with pre-LC (Table 1; Supplementary Table S1).

Discussion

This study aimed to evaluate whether LC could increase SV by more than 15% and change hemodynamic variables in hypovolemic, healthy, mechanically ventilated, isoflurane-anesthetized Beagle dogs. Liver compression at 22 mm Hg for 1 minute significantly increased SV by 30%, indicating LC could be used as a novel method to evaluate FR in hypovolemia. In addition, significant changes in hemodynamic variables, including MAP, CVP, and PPV may be helpful in assessing the effects of LC.

Liver compression predicts FR by rapidly redistributing the abdominal organ blood to the central circulation via the hepatic vein, thereby increasing the preload. A study on human pediatric patients with acute circulatory failure reported an increase in the SV index by 12% to 27% with LC. In the present study, LC in stage 2 increased SV by 30%, demonstrating effects similar to those of LC in pediatric patients. The comparable effects of LC in humans and dogs may be attributed to the similarity in hepatic blood flow between the 2 species. In humans, hepatic blood flow is 30 mL/min/kg, accounting for 25% to 30% of CO,20 and in dogs, it is similar at 29.5 mL/min/kg.20,21 However, in contrast to the transient and reversible effects reported in a previous human study on LC, this study did not find a significant difference in SV between LC and post-LC. This can be attributed to differences in the experimental methods. A previous human study focused on patients with congestive heart failure, measuring SV using echocardiography. In contrast, our study experimentally induced hemorrhage in healthy dogs and measured SV using TD. Consequently, physiological compensation for acute hemorrhage and the effects of fluid administration during TD may have influenced the SV after LC.

In this study, LC significantly increased MAP by 11 mm Hg during hypovolemia, but HR and SVR remained unchanged, suggesting that the increase in SV may have contributed to the increase in MAP. A previous study reported that an increase of 7 mm Hg in MAP by LC could discriminate between FR and FNR in human pediatrics. Simultaneously, PPV significantly decreased by LC, but PPV did not change post-LC, likely because there was no significant difference in SV between LC and post-LC.

Liver compression did not affect PAOP and HR across all stages. Pulmonary artery occlusion pressure, traditionally known as the static preload index, remained unchanged regardless of the changes in SV in this study. As PAOP is influenced by various factors beyond preload, including intrathoracic pressure, compliance of heart chambers, transmural pressure, and tone of the venous capacitance vessels, correlation with PAOP and changes in SV may be poor. Although it remains unclear which specific factors LC affected, evaluating the effect of LC through PAOP may not be appropriate. Heart rate did not significantly change during LC; however, it decreased with blood withdrawal and increased with transfusion. This may be attributed to the increased effect of isoflurane-induced by acute hypovolemia or the potential inhibition of the baroreflex due to the moderate depth of anesthesia.22,23

A stepwise transfusion was performed to evaluate the effects of LC on the degree of hypovolemia. Contrary to expectations, no significant differences were observed in SV, CO, and MAP between stage 1 and 3. In stage 4, however, SV and CO significantly increased compared with stage 1. These findings could be explained by several possibilities: (1) decreased capillary hydrostatic pressure during hypovolemia may have caused a fluid shift from the interstitium to the intravascular space; (2) splenic contraction and activation of the renin-angiotensin-aldosterone system induced by acute hemorrhage may have influenced the outcomes; and (3) considering the small size of the dogs, the cumulative effect of the fluid administered during TD may have influenced the increase in intravascular volume in stages 3 and 4.24-25 Despite changes in blood volume, the lack of significant differences in PCV in arterial blood gas analysis, except for stage 3, suggests the possibility of these compensatory mechanisms. In addition, changes in the PCV may not be truly reflected because of the relatively rapid occurrence of blood withdrawal and transfusions. Since inotropy was not measured in this study, the possibility that cardiac contractility influenced the increase in SV in stages 3 and 4 could not be ruled out.

During stages 1, 3, and 4, LC did not induce significant changes in SV and hemodynamic variables. This suggests the possibility that stages 1, 3, and 4 were already positioned on the flat portion of the Frank-Starling cardiac curve, indicating that LC may not have provided sufficient preload effects to increase SV, as suggested in the PLR study conducted in dogs. In addition, some human pediatric patients initially confirmed as FNR with LC showed FR during volume expansion of 10 mL/kg lactated Ringer over 10 minutes, indicating that LC may yield false-negative results, especially in cases of relatively mild hypovolemia (proximal to the plateau of the Frank-Starling cardiac curve), and reassessment through volume expansion may be recommended in such patients. Conversely, fluid administration is not indicated for all patients demonstrating FR. In dogs
with euvoolemia and normotension, volume expansion induced a significant increase in SV with a normal physiological response, indicating FR. Therefore, relying solely on the results of LC to guide fluid administration is not appropriate, and a comprehensive evaluation of the patient’s condition is crucial.

In human pediatric studies, the mid abdomen or right upper abdominal quadrant was compressed at 22 to 30 mm Hg for 1 minute. This provided a sufficient preload increase effect, increasing mean CVP by >2 mm Hg. As the hydraulic principle is fulfilled by midline pressure to the abdomen, indicating that external pressure applied to the abdomen is uniformly distributed across the abdominal cavity, there is no need for direct pressure application to the liver. In addition, direct compression of the liver may induce pain, eliciting the Valsalva response, which increases intrathoracic pressure and reduces venous return. Therefore, the mid abdomen was selected as the compression site in this study for future clinical applications in conscious dogs. In the present study, LC at 22 mm Hg for 1 minute significantly increased mean CVP by 2 mm Hg in stage 2 and significantly increased SV. However, LC with more pressure may be at risk of inducing intra-abdominal hypertension. This can displace the diaphragm forward, causing an increase in intrathoracic pressure and compressing the heart and central venous circulation, potentially decreasing venous return. According to a study conducted on pigs with normal blood pressure, a 10-mm Hg increase in intra-abdominal pressure resulted in an 8% increase in SV, whereas a 30-mm Hg increase led to a 22% decrease in SV. As intra-abdominal pressure was not measured in this study, the influence of LC on intra-abdominal pressure is unclear. However, LC at 22 mm Hg during volume-controlled mechanical ventilation did not affect PIP, and its effect on intrathoracic pressure may be minimal.

This study has some limitations. First, the sample size was small. Due to ethical considerations, the minimum number of dogs necessary to confirm statistical significance was used. Second, the experimental stages were not randomized because this sequential order was critical for evaluating the effects of LC based on changes in blood volume. Despite efforts to blind the recorder to the individuals performing the procedures, inherent bias in recording from the nonrandomized procedure may have influenced the results. Third, this study was conducted in healthy dogs under anesthesia with controlled hemorrhage and transfusion, all positioned in dorsal recumbency. Therefore, the findings of this study may have limitations when applied to clinical situations, such as relative hypovolemia, increased abdominal pressure, obesity, liver diseases, and patients who are critically ill receiving various medications. Furthermore, since dorsal recumbency is not recommended for conscious critically ill dogs, research conducted in sternal or lateral recumbency positions may have been more appropriate. Fourth, the procedures were conducted under mechanical ventilation with the administration of neuromuscular blockade. As intrathoracic pressure differs between spontaneous breathing and mechanical ventilation, LC in dogs with spontaneous breathing may lead to different results compared with this study. Finally, the measurement of SV using a pulmonary artery catheter is not practical in the clinical setting because of the risk associated with invasiveness, the need for specialized skills and equipment, and limitations in real-time and continuous measurement of SV. Studies using minimally invasive or noninvasive SV measurement methods such as pulse contour analysis, bioelectactance, esophageal Doppler, and echocardiography are necessary for the potential clinical application of LC in dogs.

In conclusion, LC at 22 mm Hg for 1 minute significantly increased SV by 30% in anesthetized dogs with hypovolemia. Simultaneously, significant changes in MAP, CVP, and PPV were observed, which may assist in monitoring the effects of LC. These findings suggest that LC could be used as a novel method to evaluate FR in anesthetized dogs with hypovolemia. However, considering that LC may result in false-positive or negative results, relying solely on LC results to determine fluid administration may not be appropriate. Further studies are necessary to determine whether LC could predict FR in various clinical scenarios.

Acknowledgments
None reported.

Disclosures
The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

Funding
This study was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (No. 2022R1F1A1065215).

ORCID
Jiwoong Her https://orcid.org/0000-0003-3150-591X
Min Su Kim https://orcid.org/0000-0002-7467-496X

References


Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.