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Doctoral Thesis in

Comparison of positive end-expiratory pressure-
induced increase in central venous pressure
and passive leg raising to predict fluid responsiveness
in patients with atrial fibrillation

The Graduate School, Ajou University

Major in Medicine

Department of Anesthesiology

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in patients with atrial fibrillation

Supervised by

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A Dissertation Submitted to The Graduate School of Ajou University in
Partial Fulfillment of the Requirements for The Degree of Ph.D. in
Medicine

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Namo Kim

ABSTRACT

Comparison of positive end-expiratory pressure-induced increase in central venous pressure and passive leg raising to predict fluid responsiveness in patients with atrial fibrillation

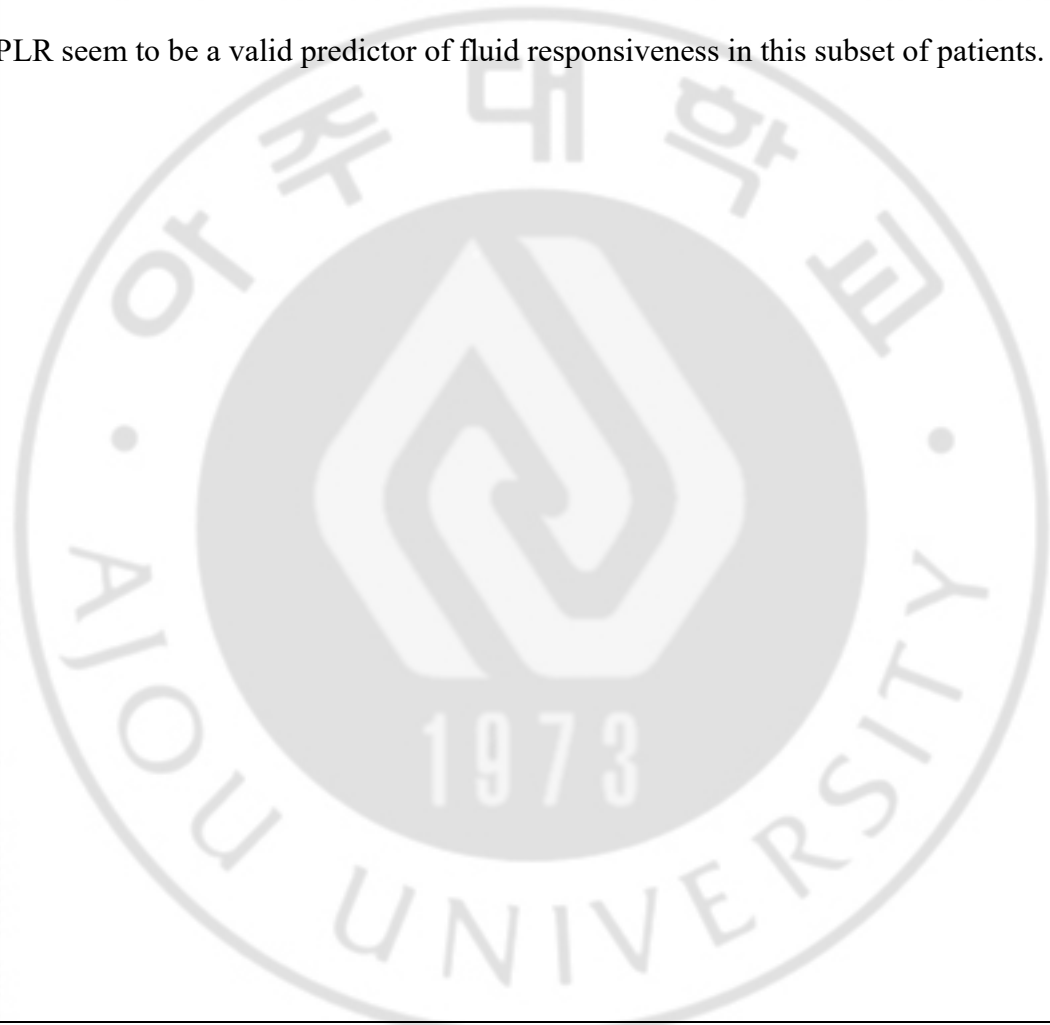
Background: Positive end-expiratory pressure (PEEP)-induced increase in central venous pressure (CVP) has been suggested to be a robust indicator of fluid responsiveness, with heart rhythm having minimal influence. We compared the ability of PEEP induced changes in CVP with passive leg raising (PLR)-induced changes in stroke volume index (SVI) in patients with atrial fibrillation after valvular heart surgery.

Methods: In 43 patients with atrial fibrillation after cardiac surgery, PEEP was increased from 0 to 10 cm H₂O for 5 min and changes in CVP were assessed. After returning the PEEP to 0 cm H₂O, PLR was performed for 5 min and changes in SVI were recorded. Finally, 300 ml of colloid was infused and hemodynamic variables were assessed 5 min after completion of a fluid challenge. Fluid responsiveness was defined as an increase in SVI $\geq 10\%$ measured by a pulmonary artery catheter.

Results: Fifteen (35%) patients were fluid responders. There was no correlation between PEEP-induced increases in CVP and changes in SVI after a fluid challenge (β coefficient -0.052, P=0.740), whereas changes in SVI during PLR showed a

significant correlation (β coefficient 0.713, $P < 0.001$). The area under the receiver operating characteristic curve of the PEEP-induced increase in CVP and changes in SVI during PLR for fluid responsiveness was 0.556 [95% confidence interval (CI) 0.358–0.753, $P = 0.549$] and 0.771 (95% CI 0.619–0.924, $P = 0.004$), respectively.

Conclusions: A PEEP-induced increase in CVP did not predict fluid responsiveness in patients with atrial fibrillation after cardiac surgery, but increases in SVI during PLR seem to be a valid predictor of fluid responsiveness in this subset of patients.



Key words: atrial fibrillation; central venous pressure; fluid responsiveness; passive leg raising; positive end-expiratory pressure

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I. INTRODUCTION

Before initiating any fluid therapy, proper knowledge of the patient's circulatory status on the Frank-Starling curve should be a prerequisite to prevent harmful fluid excess and edema. During the past decade, dynamic indices derived from the arterial waveform have arisen as the most practical and robust guide to predict fluid responsiveness. [1-3] Due to their dependence on heart-lung interaction, however, the accuracy of these dynamic indices is confounded by ventilatory conditions and their clinical applicability is limited to patients with sinus rhythm. [4]

Evidence remains scarce on a practical and reliable preload index preventing harmful fluid loading in critically ill patients with valvular heart disease and arrhythmia, which is most commonly atrial fibrillation. [5-7] Although passive leg raising (PLR)-induced changes in stroke volume index (SVI) have shown promising results, [8-11] proper PLR testing requires position changes from a semi-recumbent position, [12] which is not always feasible in the critical care setting, and some form of cardiac output measurement. [13] Furthermore, the ability of PLR-induced changes in SVI to predict fluid responsiveness has not been tested prospectively in only cardiac surgical patients with atrial fibrillation.

Recently, positive end-expiratory pressure (PEEP)-induced changes in central venous pressure (CVP) have been shown to be an easy-to-use and valid predictor of fluid responsiveness in mechanically ventilated patients, with minimal risk of being

influenced by ventilatory conditions or heart rhythm. [14] Still, evidence regarding its ability to predict fluid responsiveness in critically ill patients with rhythm other than sinus is lacking. We therefore performed a prospective trial to compare the predictive power of PEEP-induced changes in CVP with that of PLR-induced changes in SVI on fluid responsiveness in patients with atrial fibrillation after valvular heart surgery.

II. METHODS

1. Patients

After approval by the institutional review board of the Yonsei University Health System, Seoul, South Korea, study registration with ClinicalTrials.gov (ref: NCT02224378) and receiving informed consent from all patients, 44 consecutive patients with atrial fibrillation who underwent elective valvular heart surgery were enrolled. Exclusion criteria were left ventricular ejection fraction $<40\%$, systolic pulmonary arterial pressure ≥ 50 mmHg after surgery, history of pulmonary disease, end-stage renal disease, deep vein thrombosis, tricuspid regurgitation grade ≥ 2 after surgery and patients who received concomitant maze procedure. Patients who exhibited hemodynamic instability requiring rapid adjustments of cardiotoxic drugs or with chest tube drainage >200 ml/hr during the immediate postoperative period were also excluded.

2. Protocol and measurements

After induction of anesthesia, a pulmonary artery catheter (Swan-Ganz CCombo, Edwards Lifesciences, Irvine, CA, USA) was inserted in all patients and used for continuous monitoring purposes for 1-2 days after surgery. All measurements were carried out following stabilization and within the first hour after arrival in the intensive care unit (ICU) following valvular heart surgery. During the observation period, the patients remained supine and doses of sedative and vasoactive agents were unaltered. Patients' lungs were ventilated with a tidal volume of 8 ml/kg of the ideal body weight, respiratory rate of 12-16 breaths/min and a PEEP of 0 cmH₂O, at an inspired oxygen fraction of 40-60% with air to maintain the PaO₂ at >100 mmHg. Measurements of heart rate (HR), mean arterial pressure (MAP), CVP, pulmonary artery occlusion pressure (PAOP), cardiac index and SVI were made under four experimental conditions: (1) when PEEP was set to 0 cm H₂O (baseline); (2) 5 min after PEEP was increased to 10 cm H₂O; (3) 5 min after PLR and (4) 5 min after completion of fluid challenge (300 ml of 6% hydroxyethyl starch 130/0.4 [Volulyte, Fresenius Kabi, Stans, Switzerland]). Condition (3) was performed from the semi-recumbent position to ensure maximal endogenous fluid challenge as was recommended. [12] Positional change from the semi-recumbent position to the supine position was done using the automated bed motion followed by immediate leg elevation at 30 degrees, which was done manually using a goniometer. After

performing conditions (2) and (3), all the settings were returned to baseline, adjusting PEEP from 10 to 0 cmH₂O and returning the patient to the supine position, respectively. Every step was done with a sufficient time interval when the patients were hemodynamically stable enough to follow the next step (i.e. with return of hemodynamic variables to their corresponding baseline values without requiring rapid adjustments of cardiotoxic drug delivery or fluid loading, and the absence of excessive bleeding as described above). All pressure transducers were repositioned and zeroed after each positional change of the patients and CVP and PAOP were measured at end expiration. Fluid challenge was performed within 10 min in all patients.

Patients were classified as fluid responders if they showed an increase in SVI $\geq 10\%$ after fluid challenge. Cardiac index and subsequently SVI values were obtained from the pulmonary artery catheter and three consecutive STAT mode values from the continuous cardiac output monitoring device (Vigilance, Edwards Lifesciences, Irvine, CA, USA) were averaged and recorded for analysis.

3. Statistical analysis

All hemodynamic data were analysed as continuous variables and are expressed as mean (sd) or frequency and percentage. Based on previous studies, [14, 15] a difference in the area under the receiver operating characteristics curve (AUROC) of

0.2 was assumed between the null hypothesis of 0.7 and the alternative hypothesis of 0.9, and a sample size of 44 patients was estimated at a two-sided $\alpha=0.05$ with 80% power. Intergroup comparisons of variables between responders and non-responders were conducted using Student's t-test for continuous variables and χ^2 or Fisher's exact test as appropriate for categorical variables. Pearson's correlation was used to evaluate the association between the assessed preload indices of interest and changes in SVI after fluid administration. From the ROC curves, the optimal cut-off value yielding the greatest combined sensitivity and specificity was measured. Statistical analyses were performed using SPSS software (version 20.0, SPSS, Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

III. RESULTS

A total of 44 patients were enrolled in the study. After surgery, one patient was excluded due to unstable hemodynamic condition caused by chest tube drainage >200 ml/hr (Fig. 1). Only 15 patients (35%) were responders exhibiting a $>10\%$ increase in SVI after fluid challenge. Patient characteristics including type of surgery were comparable between responders and non-responders (Table 1). Changes in hemodynamic variables during application of 10 cm H₂O of PEEP and PLR are shown in Table 2 (responders vs non-responders).

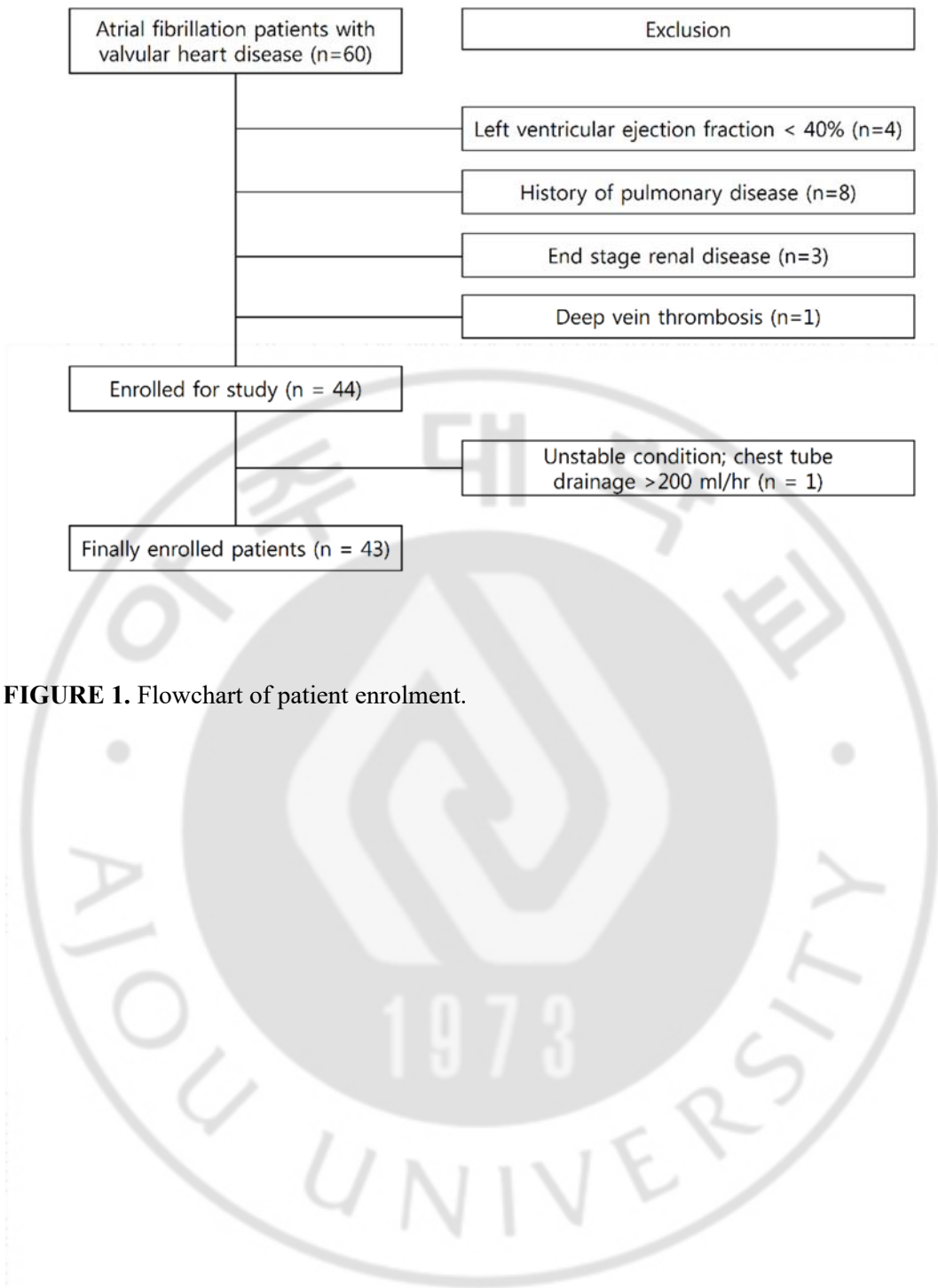


FIGURE 1. Flowchart of patient enrolment.

Table 1. Patients' characteristics and operative data

| | Responder (n=15) | Non-responder (n=28) | P value |
|---|------------------|----------------------|---------|
| Age (yrs) | 62 ± 15 | 66 ± 9 | 0.334 |
| Sex (male/female) | 8 / 7 | 10 / 16 | 0.275 |
| Body surface area (m ²) | 1.61 ± 0.20 | 1.55 ± 0.28 | 0.479 |
| Left ventricular ejection fraction (%) | 60.3 ± 15.4 | 61.0 ± 12.6 | 0.875 |
| Left atrial volume index (ml/m ²) | 96 ± 50 | 110 ± 44 | 0.352 |
| Hypertension | 6 (40.0%) | 12 (46.2%) | 0.702 |
| Diabetes mellitus | 1 (6.7%) | 4 (15.4%) | 0.636 |
| Stroke | 2 (13.3%) | 5 (19.2%) | 1.000 |
| EuroSCORE | 4.6 ± 3.1 | 5.0 ± 3.3 | 0.704 |
| Type of surgery | | | |
| Aortic valve | 3 (20.0 %) | 3 (10.7%) | 0.647 |
| Mitral valve | 4 (26.7%) | 9 (32.1%) | 1.000 |
| Double valve | 7 (46.7%) | 15 (53.6%) | 0.666 |
| Triple valve | 1 (6.7%) | 1 (3.6%) | 1.000 |

Values are expressed as mean ± SD.

Table 2. Hemodynamic data after each experimental condition (responder vs. non-responder)

| | Responder (n=15) | | | | | Non-responder (n=28) | | | | |
|---|------------------|-----------|---------|-----------|---------|----------------------|-----------|---------|-----------|---------|
| | Baseline | PEEP | P-value | PLR | P-value | Baseline | PEEP | P-value | PLR | P-value |
| Heart rate (beats/min) | 90 ± 32 | 91 ± 33 | 0.854 | 86 ± 30 | 0.240 | 86 ± 17 | 87 ± 20.5 | 0.403 | 88 ± 17 | 0.079 |
| Mean arterial pressure (mmHg) | 77 ± 10 | 74 ± 10 | 0.068 | 79 ± 13 | 0.272 | 76 ± 10 | 77 ± 12.6 | 0.545 | 79 ± 13 | 0.079 |
| Central venous pressure (mmHg) | 8 ± 3 | 10 ± 3 | 0.014 | 8 ± 4 | 1.000 | 8 ± 4 | 9 ± 3 | 0.001 | 8 ± 4 | 0.058 |
| Cardiac index (L/min/m ²) | 2.7 ± 0.8 | 2.8 ± 0.8 | 0.284 | 2.8 ± 0.8 | 0.173 | 3.3 ± 0.8 | 3.3 ± 0.8 | 0.491 | 3.2 ± 0.9 | 0.407 |
| Stroke volume index (ml/m ² /beat) | 31 ± 9 | 34 ± 12 | 0.295 | 35 ± 12 | 0.046 | 40 ± 12 | 39 ± 13 | 0.624 | 38 ± 12 | 0.045 |

Values are expressed as mean ± SD. P-values are from intragroup comparisons; PEEP vs. Baseline and PLR vs. Baseline.

Compared with baseline, an increase in PEEP to 10 cmH₂O was associated with a significantly increased CVP and PAOP in both responders and non-responders, while other assessed variables were not significantly affected. Compared with baseline, PLR was associated with a significant increase in SVI in responders, whereas it was associated with a decrease in SVI in non-responders. PAOP in non-responders was significantly increased during application of PLR, whereas it remained constant in responders.

Intragroup comparisons of hemodynamic variables between responders and non-responders after actual fluid challenge are shown in Table 3. After fluid replacement, PAOP, cardiac index, and SVI were significantly increased in responders while other variables remained unchanged. In contrast, MAP, CVP and PAOP were significantly increased in non-responders without any increase in cardiac index or SVI.

A PEEP-induced increase in CVP (β coefficient -0.052, $P=0.740$) and PAOP (β coefficient -0.138, $P=0.379$) did not show any correlation with changes in SVI after fluid challenge, whereas changes in SVI during PLR showed significant correlation (β coefficient 0.713, $P<0.001$). The AUROC for the PEEP-induced increase in CVP and PAOP and changes in SVI during PLR for fluid responsiveness was 0.556 [95% confidence interval (CI) 0.358-0.753, $P=0.549$], 0.621 (95% CI 0.441-0.801, $P=0.194$) and 0.771 (95% CI 0.619-0.924, $P=0.004$), respectively (Fig. 2). The optimal cut-off value for the increase in SVI during PLR was 7.3%, with a sensitivity of 71% and a specificity of 79%.

Table 3. Hemodynamic data before and after fluid replacement

| | Responder (n=15) | | | Non-responder (n=28) | | |
|---|------------------|-----------|---------|----------------------|-----------|---------|
| | Before | After | P-value | Before | After | P-value |
| Heart rate (beats/min) | 90 ± 32 | 84 ± 31 | 0.062 | 86 ± 17 | 87 ± 18 | 0.383 |
| Mean arterial pressure (mmHg) | 77 ± 10 | 79 ± 11 | 0.329 | 76 ± 10 | 82 ± 15 | 0.008 |
| Central venous pressure (mmHg) | 8 ± 3 | 9 ± 4 | 0.100 | 8 ± 4 | 9 ± 4 | <0.001 |
| Cardiac index (L/min/m ²) | 2.7 ± 0.8 | 3.1 ± 0.8 | <0.001 | 3.3 ± 0.8* | 3.4 ± 1.0 | 0.755 |
| Stroke volume index (ml/m ² /beat) | 31 ± 9 | 40 ± 11 | <0.001 | 40 ± 12* | 40 ± 13 | 0.906 |

Values are expressed as mean ± SD. P-values are from intragroup comparisons between Before and After.

*P < 0.05 compared with responder, before fluid replacement.

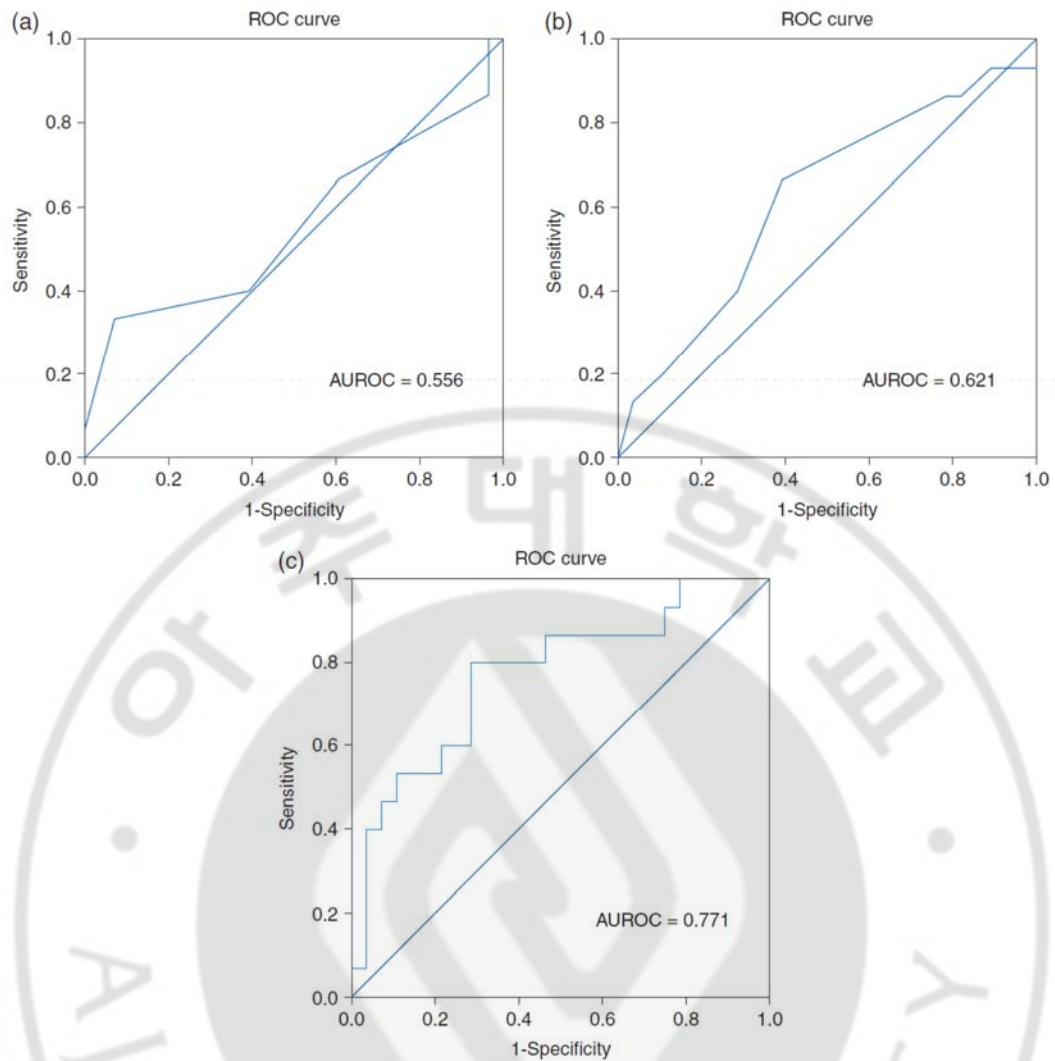


FIGURE 2. Receiver operator characteristics curves of fluid responsiveness. (a) PEEP-induced changes in central venous pressure; AUROC=0.556 (95% CI 0.358–0.753, P=0.549). (b) PEEP-induced changes in pulmonary artery occlusion pressure; AUROC=0.621 (95% CI 0.441–0.801 P=0.194). (c) Changes in stroke volume index during passive leg raising; AUROC=0.771 (95% CI 0.619–0.924, P=0.004).

IV. DISCUSSION

In this study we found that despite its potential for being a robust and practical indicator of fluid responsiveness in patients with irregular heart rhythm, PEEP-induced changes in CVP could not discriminate fluid responders from non-responders among patients with atrial fibrillation following valvular heart surgery. In contrast, a PLR-induced increase in SVI appeared to be a valid predictor of fluid responsiveness in this subset of patients.

In anesthesia and critical care, clinicians are constantly challenged about whether to give fluid or not, knowing that less than half of the critically ill patients are fluid responders and overzealous fluid administration may actually harm patients. [16, 17] Although arterial waveform-derived dynamic indices have gained wide acceptance for guiding fluid therapy, their inherent reliance on heart-lung interaction requires particular conditions such as stable heart rhythm or specific ventilator settings. [3, 18] Subsequently, these drawbacks limit their use in the critical care setting, where arrhythmia, especially atrial fibrillation, is common and lung protective strategies are frequently employed. Thus validation of a practical and reliable preload index in critically ill patients with limited cardiac reserve and arrhythmia would be of high priority to ensure the prevention of harmful fluid loading.

Recently a PEEP-induced increase in CVP was shown to be a simple and robust indicator of fluid responsiveness in patients following cardiac surgery, with an

AUROC of 0.99 (95% CI 0.94–1.00, $P < 0.001$). [14] The latter finding was based on the observation that PEEP application shifts the cardiac function curve toward lower cardiac output and higher CVP in an inverse but proportional relationship, [19] with both changes being larger in patients with hypovolemia than in those with normovolemia. [20] Of interest, a PEEP-induced increase in CVP was speculated to be less dependent on ventilatory conditions and heart rhythm, [14] indicating its more widespread use in the critical care setting. As yet, the ability of PEEP application to predict fluid responsiveness has only been tested in the context of a PLR-induced increase in cardiac output and not against an actual fluid challenge. Moreover, evidence of its predictive power in patients with rhythm other than sinus is lacking.

As the results of the present study indicate, a PEEP-induced change in CVP was not able to predict fluid responsiveness in patients with atrial fibrillation following valvular heart surgery, whereas a PLR-induced increase in SVI could. Although PEEP application was associated with an increase in CVP by 2 mmHg in responders and 1 mmHg in non-responders, in the current trial, the magnitude of increase was less than that reported by Geerts, and colleagues (3.6 mmHg in the responders). [14] Moreover, no subsequent decrease was observed in cardiac index or SVI during PEEP application, indicating that neither changes in CVP nor SVI during PEEP application would predict fluid responsiveness. Plausible explanations for the observed results are as follows. The predominant mechanism of PEEP-induced

changes in CVP to predict fluid responsiveness lies in that it moves the work point of the right ventricle downwards at a given point on the Frank-Starling curve by causing diminished venous return. The resultant backpressure to venous return from the application of brief PEEP, as assessed by an increase in CVP, would be greater under hypovolemia due to higher transmission of the pleural pressure inside the right atrium when it is underfilled and compliant. [21, 22] However, chronic atrial fibrillation leads to an enlarged and less compliant atria. Of note, it has been shown that interstitial fibrosis is more prominent in the right than the left atrial appendage in atrial fibrillation patients with structural heart disease undergoing cardiac surgery. [23, 24] Therefore transmission of the pleural pressure induced by PEEP may not be enough to elicit any meaningful changes of the work point of the right ventricle on the Frank-Starling curve in the studied patients. In contrast, PLR produces endogenous challenge of the preload, moving the work point of the right ventricle upwards. Because the right ventricle is more tolerant to volume than pressure overload, an increase in SVI might enable the detection of a potentially present narrow margin of fluid responsiveness due to a blunted Frank-Starling mechanism. [25] Importantly, as the patients of the current trial are likely to have a limited cardiac reserve, PLR might have induced preload augmentation exceeding the point of ventricular interdependence, resulting in a decrease in SVI in non-responders. [25] Together with the observation that only 35% patients were fluid responders, the results of the present study underscore the importance of a proper index to guide

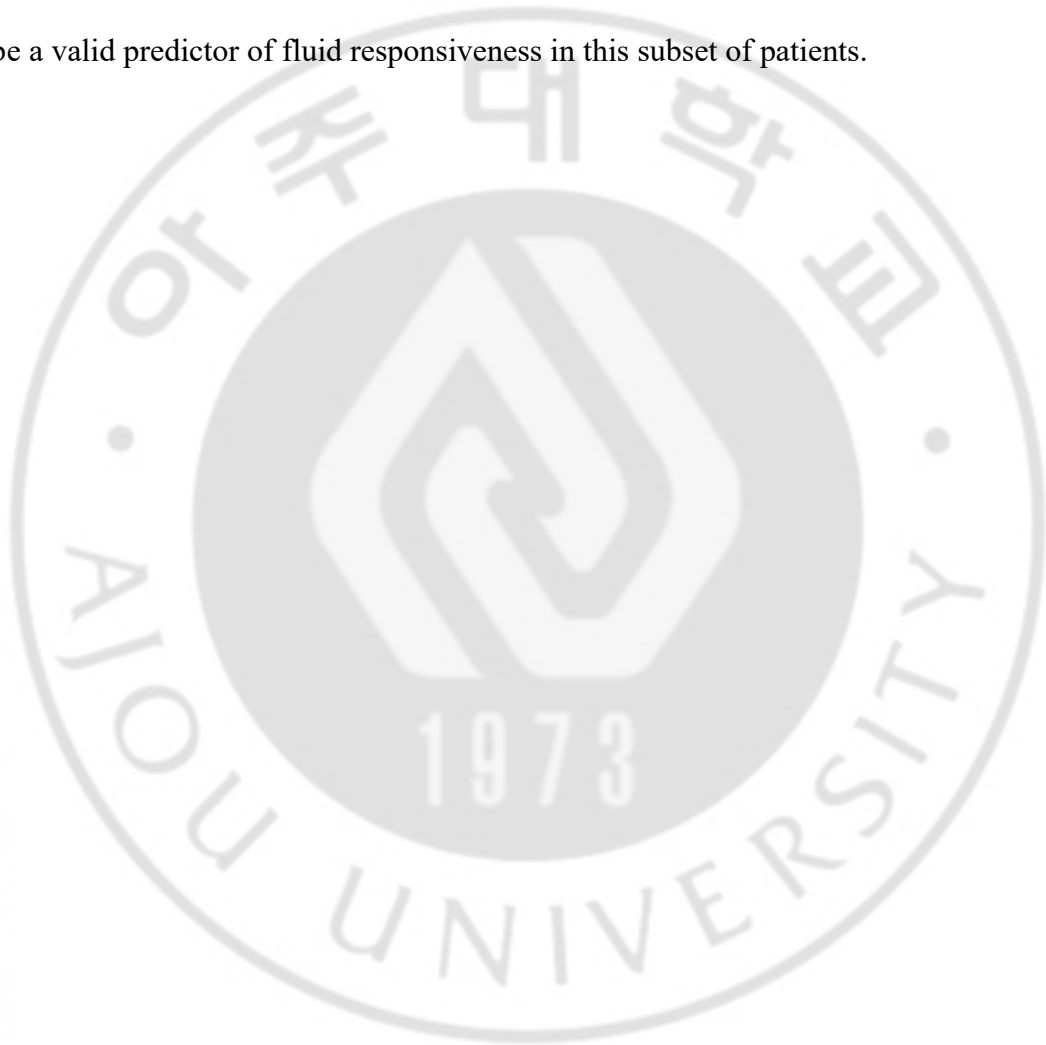
fluid therapy and argue against an empiric fluid challenge in ICU care of cardiac surgical patients with arrhythmia.

In the present study, the PLR maneuver was performed from the semi-recumbent position to maximize endogenous volume augmentation, [12] which may not always be feasible in critically ill patients. In the current trial, the optimal cut-off value of the PLR-induced increase in SVI to predict fluid responsiveness was 7.3%. Thus we may speculate that a modified PLR maneuver from the supine position may suffice to discriminate fluid responders, because it is known to induce an ~7% increase in cardiac output, [12] which merits further studies for validation.

The limitations of this study are as follows. First, although atrial fibrosis would not be as evident as in chronic atrial fibrillation, acute or paroxysmal atrial fibrillation also results in atrial dilatation and consequently less compliance to transmission of increased pleural pressure by PEEP. Nonetheless, because the present study included patients with chronic atrial fibrillation, the predictive power of PEEP-induced changes in CVP may be different in patients with acute or paroxysmal atrial fibrillation, limiting the generalization of the observed results of the current study. Second, to minimize the introduction of operator dependent bias, SVI was measured using the STAT mode of continuous cardiac index measurement instead of the bolus thermodilution method, which is known to be able to detect changes in the cardiac index after approximately 270 s. [26] Although it would have been suitable in the present study to measure the cardiac index after 5 min of PLR application, the effect

of PLR might have been underestimated since it can diminish after even 1 min in certain clinical conditions such as septic shock or vasoplegia. [8] Therefore the effect of PLR may have been underestimated.

In conclusion, brief application of PEEP and monitoring of subsequent changes in CVP could not predict fluid responsiveness in patients with atrial fibrillation following valvular heart surgery, whereas a PLR-induced increase in SVI proved to be a valid predictor of fluid responsiveness in this subset of patients.



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ABSTRACT (IN KOREAN)

심방세동 환자에서 호기말양압에 의해 유도되는 중심정맥압의 변화와
수동적 다리 들어올리기의 수액 반응성에 대한 예측력 비교

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환자에게 수액을 투여하였을 때 반응성 여부를 평가하는 것은 쉽지 않은 일이다. 본 연구자는 최근에 수액반응성의 신뢰할만한 지표로 발표된 바 있는 호기말양압 (Positive end-expiratory pressure, PEEP) 적용에 의한 중심정맥압 (Central venous pressure, CVP)의 변화와 수동적 다리 들어올리기 (Passive leg raising, PLR)에 의한 박출량지수 (Stroke volume index, SVI)의 변화를 심장 판막 수술을 한 심방세동 환자들을 대상으로 비교하고자 하였다.

총 43명의 환자들을 대상으로 연구가 진행되었고, 교질액 300ml 를 투여한 후 박출량지수가 10% 이상 상승하는 대상자들을 수액반응성이 있는 환자들로 정의하였다. 5분 동안 10 cmH₂O 의 호기말양압을 적용하여 발생하는

중심정맥압 변화와 5분 동안 수동적 다리들기를 적용하여 발생하는 박출량지수 변화를 측정하여 비교하였다.

전체 43명의 환자 중에서 15명의 환자들이 수액반응성이 있는 환자였다 (35%). 호기말양압 적용에 의한 중심정맥압 변화는 수액 투여 후 박출량지수 변화와 연관성을 보이지 않았고 (β coefficient -0.052 , $P=0.740$), 수동적 다리들기에 의한 박출량 지수 변화는 연관성이 있었다 (β coefficient 0.713 , $P<0.001$). 호기말양압의 적용에 의한 중심정맥압 변화와 수동적 다리들기에 의한 박출량 지수 변화의 수액반응성에 대한 반응자 작용특성 공간(area under the receiver operating characteristic curve, AUROC)은 각각 0.556 [95% confidence interval (CI) $0.358-0.753$, $P=0.549$] 과 0.771 (95% CI $0.619-0.924$, $P=0.004$) 으로 나타났다.

결론적으로 심장 판막 수술을 한 심방세동 환자에서 호기말양압에 의한 중심정맥압 변화로는 수액반응성을 제대로 예측하지 못하는 것으로 생각된다. 반면, 수동적 다리들기에 의한 박출량지수 변화는 의미있게 수액반응성을 예측할 수 있었다.

핵심어: 심방세동; 중심정맥압; 수액반응성; 수동적 다리들기; 호기말 양압