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A comparative study of pulse pressure variation, stroke volume variation and central venous pressure in patients undergoing kidney transplantation

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ABSTRACT

Introduction: Optimal intraoperative fluid management guided by central venous pressure (CVP), a traditional intravascular volume status indicator, has improved transplanted graft function during kidney transplantation (KT). Pulse pressure variation (PPV) and stroke volume variation (SVV) – dynamic preload indexes – are robust predictors of fluid responsiveness. This study aimed to compare the accuracy of PPV and CVP against SVV in predicting fluid responsiveness in terms of cost-effectiveness after a standardised empiric volume challenge in KT patients.

Methods: 36 patients undergoing living-donor KT were analysed. PPV, SVV, CVP and cardiac index (CI) were measured before and after fluid loading with a hydroxyethyl starch solution (7 mL/kg of ideal body weight). Patients were classified as responders ($n = 12$) or non-responders ($n = 24$) to fluid loading when CI increases were $\geq 10\%$ or $< 10\%$, respectively. The ability of PPV, SVV and CVP to predict fluid responsiveness was assessed using receiver operating characteristic (ROC) curves.

Results: SVV and CVP measured before fluid loading were correlated with changes in CI caused by fluid expansion ($\rho = 0.33$, $p = 0.049$ and $\rho = -0.37$, $p = 0.026$) in contrast to PPV ($\rho = 0.14$, $p = 0.429$). The ROC analysis showed that SVV and CVP predicted response to volume loading (area under the ROC curve = 0.781 and 0.727, respectively; $p < 0.05$).

Conclusion: Under the conditions of our study, SVV and CVP exhibited similar performance in predicting fluid responsiveness and could inform fluid management during KT as compared with PPV.

Keywords: central venous pressure, fluid therapy, kidney transplantation, pulse pressure variation, stroke volume variation

INTRODUCTION

Kidney transplantation (KT) is the treatment of choice in patients with end-stage renal disease (ESRD) because it reduces the rates of overall morbidity and mortality.⁽¹⁾ KT recipients usually have one or more comorbid conditions, including hypertension, diabetes mellitus, congestive heart failure, coronary artery disease and pulmonary disease.^(2,3) Moreover, KT recipients have a narrow margin of safety in terms of volume expansion, which may widely fluctuate between hypo- and hypervolaemia.⁽⁴⁾ Accordingly, balanced fluid management is necessary to guarantee optimal graft function and reduce recipient mortality during KT.

The continuous monitoring of central venous pressure (CVP) has conventionally been recommended to assess intravascular volume status, although there is still some debate regarding the routine use of CVP monitoring during clinical anaesthesia for KT.⁽⁵⁾ Furthermore, fluid management based on specific CVP values has been suggested to ameliorate transplanted graft perfusion and achieve higher rates of long-term graft survival in patients with ESRD undergoing KT.^(1,6,7)

As technology has advanced, dynamic preload parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV), which are easily measured using pulse contour analysis, have been proposed for volume status monitoring and predicting preload responsiveness in mechanically ventilated patients.^(8,9) In fact, a previous study documented that SVV could be used as an alternative to CVP monitoring to guide fluid therapy for the enhancement of graft perfusion during KT.⁽¹⁰⁾

However, few published trials have validated the reliability of these preload indexes for predicting fluid responsiveness using a standardised empirical volume challenge in KT recipients. Regarding the measurement of intravascular volume status, PPV and CVP are more cost-effective than SVV because the additional transducer required for SVV measurement is costly. This study was, therefore, designed to investigate whether PPV and CVP could be

suitable substitutes for SVV as preload indicators after administration of a standardised fluid bolus in patients undergoing living-donor KT.

It was also our objective to explore whether preoperative recipient characteristics, including already initiated long-term dialysis treatment before transplantation, dialysis modality, and duration between last pretransplant dialysis and transplant surgery, are associated with fluid responsiveness.

METHODS

This prospective study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Republic of Korea (2013-03-180), and all patients provided informed consent. This study was registered at <http://www.clinicaltrials.gov> (NCT02459470). A total of 42 patients scheduled for living-donor KT between December 2012 and December 2013 were consecutively enrolled in this study. Patients with a history of arrhythmia, significant valvulopathy, intracardiac shunt or pulmonary hypertension, left ventricular ejection fraction less than 40%, and respiratory disorders resulting in high peak airway pressure were excluded.

Upon arrival in the operating room, standard monitoring including pulse oximetry, three-lead electrocardiography, noninvasive arterial pressure and bispectral index monitoring (BIS VISTA™ Monitoring; Aspect Medical Systems, Norwood, MA, USA) was applied. If there were no contraindications, a single spinal block was performed using intrathecal morphine 400 mcg for intra- and postoperative analgesia. General anaesthesia was induced with 4–5 mg/kg thiopental, and a neuromuscular block was achieved using 0.5 mg/kg atracurium.

Mechanical ventilation was initiated with tidal volumes of 7 mL/kg of predicted body weight (determined as $X + 0.91$ [height in centimetres] – 152.4, where $X = 50$ for males and 45.5 for females) and a 50:50 oxygen to medical air ratio using the volume-controlled mode.⁽¹¹⁾

The respiratory rate was adjusted to maintain end-tidal carbon dioxide between 35 mmHg and 40 mmHg. The inspiratory-to-expiratory ratio was fixed to 1:2. Mechanical ventilation was maintained with 6 cm H₂O positive end-expiratory pressure and peak inspiratory pressure of \leq 25 mmHg. Anaesthesia was maintained with infusion of remifentanyl and inhalation of sevoflurane to maintain the bispectral index (BIS) value between 40 and 60 throughout the study. After anaesthetic induction, the radial artery was cannulated with a 20- or 22-gauge arterial catheter. Arterial pressure was calculated using the FloTrac transducer (Edwards Lifesciences, Irvine, CA, USA) connected to both a Philips IntelliVue MP70 monitor (Philips Medical Systems, Böblingen, Germany) and a Vigileo™ monitor (Edwards Lifesciences, Irvine, CA, USA).

Automated PPV was measured using a Philips IntelliVue MP70 monitor, as previously described.⁽⁸⁾ In addition, PPV was determined using the arterial pressure waveform alone with no need for airway pressure acquisition. The maximum pulse pressure (PPmax), minimum pulse pressure (PPmin) and mean pulse pressure (PPmean) were measured over a window of eight seconds, and the values from four consecutive windows (32 seconds) were used to calculate the average PPV (%) as $(PP_{max} - PP_{min})/PP_{mean}$. In addition, the FloTrac/Vigileo system displayed the automated calculation of SVV in real time. The algorithm applied in our study was introduced in previously published trials.^(12,13) As pulse pressure is proportional to stroke volume, it was estimated by analysing the standard deviation of the immediate arterial pressure (100 values per second over 20 seconds) around its mean value. The formula $SVV (\%) = (SV_{max} - SV_{min})/SV_{mean}$, where SV_{max} , SV_{min} , and SV_{mean} are the maximum, minimum, and mean stroke volume (SV), respectively, was used to determine the SVV value during a time window of 20 seconds. The FloTrac/Vigileo system continuously monitors SV without external calibration as follows: $SV = x \times \text{std (BP)}$, where x factor compensates for the difference in vascular compliance and resistance, and std (BP) is the standard deviation of the

arterial blood pressure.⁽¹⁴⁾ After the placement of the arterial catheter, a triple lumen central venous catheter (7 Fr, 20 cm; Arrow International, Reading, PA, USA) was inserted through the right internal jugular vein in cases where patients did not have a central venous haemodialysis catheter. The catheter was connected via low-compliance tubing directly to a pressure transducer (Abbott Critical Care Systems, North Chicago, IL, USA), calibrated and zeroed at a level corresponding to a horizontal line extending four-fifths of the anterior-posterior diameter of the thorax from the skin on the back for an accurate measurement of CVP without any influence of hydrostatic pressure, as described in a previous study.⁽¹⁵⁾ CVP measurements were obtained after halting the positive pressure ventilation. Cardiac output (CO) was calculated using the Vigileo device. The cardiac index (CI) was calculated as follows: $CI = CO / \text{body surface area (BSA)}$, and BSA was calculated using the Dubois formula ($BSA = \text{body weight [kg]}^{0.425} \times \text{body length [m]}^{0.725} \times 0.20247$). The CI values were used to discriminate between responders (Rs) and non-responders (NRs) after fluid loading.

No patients received fluid bolus from induction of anaesthesia to commencement of the surgery, in accordance with routine practice during KT surgery in our centre. And there were no significant differences in the fluid management and the use of vasoactive drug method between Rs and NRs groups during this period.

After starting surgery and establishing haemodynamic stabilisation, baseline haemodynamic data including heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, PPV, SVV, CVP and CO were simultaneously recorded. After documenting the baseline haemodynamic variables, an empiric fluid bolus of 6% hydroxyethyl starch solution (HES 130/0.4, Voluven®, Fresenius Kabi, Halden, Norway) at 7 mL/kg of ideal body weight was administered. In all patients, fluid challenge was conducted for ten minutes. Within five minutes after completion of the fluid challenge, the aforementioned haemodynamic data were recorded again. In all patients, two sets of measurements of haemodynamic

parameters were acquired when the haemodynamic status was stable without the use of vasopressors or inotropic drugs. Fluid loading was stopped, and data were excluded from analysis when CVP increased more than 10 mmHg before the completion of fluid loading.

In addition, the numbers of patients who already had initiated long-term dialysis before transplantation, the mode of dialysis, and the duration between pretransplant dialysis and transplantation were compared between the two groups.

All haemodynamic data were analysed as continuous variables and are presented as the mean \pm standard deviation. The Shapiro–Wilk test was performed to assess the normality of the continuous data. Primary indicators of fluid responsiveness were the percentage differences in CI before and after volume challenge. Thus, recipients were divided into Rs and NRs according to the change in CI ($\geq 10\%$ and $< 10\%$, respectively) after a volume challenge. Comparisons of haemodynamic variables before fluid loading between Rs and NRs were performed using an independent *t*-test or Mann–Whitney *U* test, as appropriate. All haemodynamic variables before and after fluid loading within each group were compared using a paired *t*-test or Wilcoxon signed rank test, as appropriate. Correlations between changes in CI responses to fluid loading and haemodynamic variables before fluid loading (PPV, SVV and CVP) were analysed using Spearman’s rank correlation coefficient. Additionally, categorical data were reported as numbers and analysed using a chi-square test or Fisher’s exact test, as appropriate. In addition, the ability of SVV, PPV and CVP to predict fluid responsiveness after fluid challenge was determined using areas under the receiver operating characteristic (ROC) curves of Rs (area under the curve [AUC] = 0.5: no prediction possible; AUC = 1.0: best possible prediction). These AUCs were compared using the Hanley–McNeil test⁽¹⁶⁾; values of $p < 0.05$ were considered statistically significant. IBM SPSS Statistics version 21.0 (IBM Corp, Armonk, NY, USA) and MedCalc version 11.6.1.0 (MedCalc Software, Ostend, Belgium) were used for the aforementioned statistical analyses.

Sample size calculations were performed based on a previous study.⁽¹⁷⁾ An ROC curve with $AUC \geq 0.8$ was generally considered a clinically valid indicator of preload responsiveness and was compared with other ROC curves with an AUC of 0.5, which means that the probability of a positive instance ranking higher than a negative instance is 0.5 and hence random. Assuming that the number of Rs was similar to that of NRs, each group was to have a sample size of 13 patients to detect a 0.3 difference in the AUC with a type 1 error of 0.05 and a probability power of 0.8. To compensate for patients who might drop out of the study, we planned to enrol 30 or more patients.

RESULTS

A total of 50 patients were consecutively screened; 42 patients fulfilled the inclusion criteria and were enrolled in this study. Of these, six patients were withdrawn from the study: five because of an increase in CVP of more than 10 mmHg and one because of newly developed ventricular arrhythmia. Finally, 36 patients were included in the final analysis. After fluid loading, 12 patients were defined as Rs and 24 as NRs (Fig. 1). The demographic data and preoperative findings of the patients are shown in Table I. The demographic data were comparable between the Rs and NRs. There were no significant differences in the number of patients who received dialysis before transplantation between the Rs and NRs (83.3% vs. 70.8%, respectively; $p = 0.685$). In addition, the mode of dialysis and duration from last pretransplant dialysis to transplantation were comparable between the Rs and NRs (100% vs. 94% haemodialysis and 1.1 days vs. 1.0 day, respectively; $p > 0.05$ for both groups).

Table I. Patient characteristics and preoperative findings.

Characteristic	Mean \pm SD/No.		p-value
	Responders (n = 12)	Non-responders (n = 24)	
Age (yr)	48.1 \pm 11.7	45.0 \pm 9.7	0.346
Gender			0.151
Male	9	12	
Female	3	12	
Height (cm)	165.7 \pm 7.5	164.3 \pm 8.8	0.497
Weight (kg)	63.1 \pm 13.1	59.0 \pm 13.1	0.381
BMI (kg/m ²)	23.0 \pm 3.6	21.5 \pm 3.3	0.254
Dialysis			0.685
Yes	10	17	
No	2	7	
Mode of dialysis	10/0	16/1	0.434
HD	10	16	
PD	0	1	
Duration of dialysis before KT (days)	1.1	1.0	0.343

Responders were patients whose cardiac index (CI) increased greater than or equal to 10% after fluid loading; non-responders were patients whose CI increased less than 10% after fluid loading. BMI: body mass index; HD: haemodialysis; PD: peritoneal dialysis; KT: kidney transplantation; SD: standard deviation

Before fluid loading, PPV and SVV were significantly higher five minutes after anaesthesia induction than at the beginning of the study in both Rs and NRs (PPV in Rs: 17.9% \pm 14.6% vs. 9.3% \pm 6.7%; PPV in NRs: 10.9% \pm 4.6% vs. 5.4 \pm 2.0 %, respectively; $p < 0.05$ for both groups; SVV in Rs: 15.3% \pm 10.0% vs. 8.4% \pm 4.3%; SVV in NRs: 10.2% \pm 4.3% vs. 4.5% \pm 1.8%). In addition, CVP was significantly lower five minutes after anaesthesia induction than at the start of physiological study in both Rs and NRs (CVP in Rs: 1.6 mmHg \pm 1.4 mmHg vs. 3.3 mmHg \pm 1.7 mmHg, respectively; $p < 0.05$ for both groups; CVP in NRs: 2.6 mmHg \pm 1.8 mmHg vs. 4.8 mmHg \pm 1.8 mmHg, respectively; $p < 0.05$ for both groups).

Haemodynamic parameters for Rs and NRs before and after fluid challenge are presented in Table II. Before fluid loading, SVV was significantly higher and CVP was significantly lower in the Rs than in the NRs (8.4% \pm 4.3% vs. 4.5% \pm 1.8%, and 3.3 mmHg \pm 1.7 mmHg vs. 4.8 mmHg \pm 1.9 mmHg, respectively; $p < 0.05$ for both groups), whereas the

other baseline haemodynamic variables did not significantly differ between the two groups. After fluid challenge, the Rs showed significant decreases in PPV and SVV, and significant increases in CVP, and these findings were associated with significant increases in CI after fluid loading. However, despite the similar changes in PPV, SVV and CVP after fluid loading in NRs, CI responses to fluid challenge decreased. As presented in Fig. 2, both SVV and CVP measured before fluid loading was significantly correlated with changes in CI caused by a volume challenge in contrast to PPV (Spearman's correlation coefficient $\rho = 0.14$, $p = 0.429$), even though the degree of correlation was weak ($\rho = 0.33$ and -0.37 , respectively, $p < 0.05$ for both groups).

Table II. Haemodynamic variables Before and After fluid loading in responders and non-responders.

Variable	Responders (n = 12)			Non-responders (n = 24)			p-value 3
	Mean \pm SD		p-value 1*	Mean \pm SD		p-value 2	
	Before volume expansion	After volume expansion		Before volume expansion	After volume expansion		
Heart rate (beats/min)	94.9 \pm 16.1	91.6 \pm 11.2	0.256	94.0 \pm 13.3	83.5 \pm 12.2	0.000 [†]	0.857
MAP (mmHg)	96.2 \pm 6.4	99.6 \pm 12.0	0.319	101.4 \pm 18.7	92.3 \pm 14.9	0.006 [†]	0.225
CI (L/min)	3.9 \pm 0.8	4.8 \pm 0.8	0.000*	4.5 \pm 1.0	4.2 \pm 1.0	0.022 [†]	0.075
PPV (%)	9.3 \pm 6.7	4.2 \pm 2.0	0.008*	5.4 \pm 2.0	4.1 \pm 1.4	0.009 [†]	0.070
SVV (%)	8.4 \pm 4.3	3.7 \pm 1.2	0.001*	4.5 \pm 1.8	3.7 \pm 1.7	0.029 [†]	0.009 [‡]
CVP (mmHg)	3.3 \pm 1.7	7.3 \pm 2.0	0.000*	4.8 \pm 1.9	7.6 \pm 1.9	0.000 [†]	0.024 [‡]

p-value 1: before and after volume expansion in responders. p-value 2: before and after volume expansion in non-responders. p-value 3: before volume expansion in responders and non-responders. * $p < 0.05$ compared with values before fluid loading in responders. [†] $p < 0.05$ compared with values before fluid loading in non-responders. [‡] $p < 0.05$ compared with responder values before fluid loading. CI: cardiac index; CVP: central venous pressure; MAP: mean arterial pressure; PPV: pulse pressure variation; SD: standard deviation; SVV: stroke volume variation

Furthermore, data on the AUC and ROC curves for PPV, SVV and CVP, showing the ability of the haemodynamic parameters to discriminate between Rs and NRs, are presented in Table III and Fig. 3. The ROC analysis indicated that SVV and CVP before fluid loading were both able to predict fluid responsiveness (AUC = 0.781 and 0.727, respectively; $p < 0.05$),

whereas PPV before fluid loading was not (AUC = 0.622, $p = 0.315$). Further, there was no statistical significance between the AUC data for SVV and CVP ($p > 0.05$). An SVV greater than 6.0% discriminated between Rs and NRs with a sensitivity of 58.5% and a specificity of 87.5%, and a CVP less than or equal to 3.0 mmHg discriminated between Rs and NRs with a sensitivity of 66.7% and a specificity of 70.8% (Fig. 4).

Table III. Receiver operating characteristic analysis of baseline pulse pressure variation (PPV), stroke volume variation (SVV) and central venous pressure (CVP) as predictions of CI increase $\geq 10\%$ after fluid loading in patients undergoing kidney transplantation.

Predictor	AUC	Standard error	p-value	95% CI
PPV	0.622	0.121	0.315	0.445–0.777
SVV	0.781	0.088	0.015*	0.612–0.901
CVP	0.727	0.091	0.012*	0.554–0.862

* $p < 0.05$ was considered significant. AUC: area under the curve; CI: confidence interval; CVP: central venous pressure; PPV: pulse pressure variation; SVV: stroke volume variation

DISCUSSION

In the present study, we compared CVP and arterial waveform-derived dynamic variables like PPV and SVV in terms of their capacity to predict fluid responsiveness after the empiric administration of a fluid bolus in patients undergoing living-donor KT. The results of our study found that CVP and SVV before volume challenge had comparable ability of predicting fluid responders, in contrast to PPV. In addition, no significant associations were observed between cardiac changes according to fluid challenge and perioperative recipient characteristics, including long-term dialysis treatment that was already initiated before KT, and the mode of dialysis and the duration from last pretransplant dialysis to transplant surgery.

Despite advancements in KT, patients undergoing KT are still at risk of several complications affecting postoperative morbidity and mortality; numerous trials focused on measures to provide goal-directed haemodynamic management and improve outcomes after KT. Several studies on KT recipients have documented that maintenance of adequate hydration and proper arterial blood pressure during the intraoperative period is essential for early

functionality of the transplanted kidney.^(18,19) Furthermore, another trial suggested that volume expansion throughout KT is preferred over the administration of a fluid bolus just before graft reperfusion, although there is ongoing debate about the optimal timing of fluid therapy.⁽¹⁾ In addition, inadequate intravascular volume is associated with poor urine output after reperfusion, resulting in early graft failure, whereas aggressive intravascular volume expansion increases the risk of pulmonary or tissue oedema, and cardiac deterioration in ESRD patients with pre-existing uncompensated cardiovascular disease.^(5,20) Accordingly, a study of indicators of intravascular volume status relevant for maximising transplanted kidney perfusion, a primary concern during anaesthesia for KT, was performed to discriminate patients who might benefit from volume expansion from those who would not.

In the present study, we investigated whether PPV, SVV or CVP, used as preload indexes, could predict preload responsiveness using empiric fluid administration. We found that both CVP (a static indicator) and SVV (a dynamic indicator) successfully identified who would benefit from fluid loading. These findings were in close agreement with the results of Chin et al,⁽¹⁰⁾ who documented that SVV could be used as an alternative to CVP monitoring to guide fluid therapy for enhanced perfusion of the transplanted graft during the critical periods of KT. Another study found that CVP and SVV have a statistically significant relationship with the right ventricular end-diastolic volume index (RVEDVI), although a discrepancy in the correlation coefficient during liver transplantation was present.⁽²¹⁾ Wang et al⁽²²⁾ documented that fluid therapy guided by SVV and CVP led to similar outcomes, including acute kidney injury and 30-day and one-year survival rates after living-donor liver transplantation.

However, a recent prospective observational study demonstrated that SVV accurately represents ventricular volume status, whereas CVP fails to predict the state of intravascular volume in patients undergoing living-donor KT.⁽²³⁾ These findings contrast with the results of our study and might be explained by a discrepancy between the zero reference point of the

pressure measurement and the time of measurement of CVP. The pressure transducer for CVP monitoring was conventionally zeroed at the midaxillary level in the previous study, whereas in our study, the transducer was zeroed at a level corresponding to a horizontal line extending from four-fifths of the anterior-posterior diameter of the thorax from the skin on the back for the accurate measurement of the CVP without any influence of hydrostatic pressure, as described previously.⁽¹⁵⁾ In addition, our measurement of CVP was obtained after halting positive pressure ventilation to minimise its influence on the CVP reading.⁽²⁴⁾

PPV was automatically measured by peripheral arterial line using the Intellivue MP 70 monitor; PPV is regarded as a valid indicator for predicting changes in CO responses to a volume challenge in mechanically ventilated patients under a variety of clinical conditions, including septic shock and major abdominal surgery.^(9,14) However, the results of our study found that the measured automated PPV values, as described in previous studies, failed to predict the effects of a volume challenge. Dynamic preload indicators, such as PPV and SVV, might be affected by alterations in vasomotor tone, which are more prominent in PPV values than SVV values.⁽²⁵⁾ Moreover, the PPV index is not a suitable predictor of fluid responsiveness in cirrhotic patients with low systemic vascular resistance during liver transplantation;⁽²⁶⁾ in contrast, the predictability of SVV as a preload indicator is unaffected, according to systemic vascular resistance.⁽²⁷⁾ Several studies have documented that the endothelial dysfunction that occurs in patients with ESRD and contributes to structural cardiac and vascular remodelling is characterised by left ventricular hypertrophy and increased stiffness of the vessel wall, resulting in decreased vasodilator response of the macro- and microcirculation.⁽²⁸⁻³⁰⁾ Consequently, these properties of vasomotor tone observed in KT recipients might be one of the contributing factors to the lower predictability of PPV compared with SVV.

Interestingly, the correlation between CVP ($\rho = -0.37$) and SVV ($\rho = 0.33$) and changes in CI related to volume expansion, were weak in this study, although ROC analysis

showed a fair predictive accuracy of CVP and SVV (AUC = 0.727 and 0.781, respectively). These findings might be statistically rather than clinically significant. However, these results can be explained by the fact that the preload conditions of our subjects at the initiation of empiric fluid administration were not on the steep portion of the Frank–Starling curve, as documented in a previous study.⁽¹⁷⁾ In our study, the subjects were relatively hypovolaemic during anaesthesia induction because most of them had received preoperative haemodialysis; thus, they showed better volume status at the initiation of the empiric fluid administration than during anaesthesia induction. These findings were confirmed by the significant differences in the values of the preload indicators CVP, PPV and SVV between these two time points (2.2 ± 1.8 vs. 4.2 ± 1.9 , 11.9 ± 7.0 vs. 5.8 ± 3.4 , and 13.2 ± 9.6 vs. 6.7 ± 4.5 , respectively; $p < 0.001$ for all).

Our current results demonstrated that the optimal threshold value in predicting fluid responsiveness was 6% for SVV, which is significantly lower than in most other studies that investigated the validity of SVV for predicting fluid responsiveness.^(9,23) Consequently, a 6% cut-off point for SVV in the present study would be regarded oversensitive with a high false-positive rate. Our lower threshold values discriminating between Rs and NRs in the present study may be explained by the intravascular volume status of the subjects at the initiation of the empiric fluid administration.

Although CVP was considered as a preload indicator for predicting fluid responsiveness in the present study, it is a clinically obvious parameter for congestion, and an excessive increase in CVP after fluid challenge should be considered as a sign of end point to stop fluid loading. Indeed, Campos et al demonstrated that $CVP \geq 11$ mmHg is associated with a twofold greater risk of kidney dysfunction in patients undergoing KT.⁽²⁰⁾ Moreover, low CVP alone should not be used as a decision-making tool for fluid administration. Consequently, the

optimal measurement for evaluating preload response to fluid challenge would be PPV and SVV for the surveillance of perfusion changes and CVP for monitoring congestion.

Dynamic indexes such as SVV and PPV are obtained from cyclic changes of stroke volume and pulse pressure according to the cyclic changes of intrathoracic pressure induced by positive pressure ventilation.⁽³¹⁾ Thus, these dynamic indexes are not only known to be influenced by preload status but also by arterial compliance, administration of vasopressors, cardiac function, arrhythmia, tidal volume, lung and chest compliance, and abdominal pressure.⁽³²⁾ We thereby excluded significant valvulopathy, arrhythmia and respiratory disorders resulting in high peak airway pressure and did not administer vasopressors or inotropic drugs throughout the study period. Clinicians should be conscious of these restrictions when considering the use of SVV and PPV as indicators of volume responsiveness in clinical practice.

Although none of our subjects received fluid bolus anaesthesia induction until the commencement of the study, there were significant differences in PPV, SVV and CVP between the following two time points in both Rs and NRs. Before fluid loading, PPV and SVV were significantly higher 5 minutes after anaesthesia induction than at the beginning of the study in both Rs and NRs (PPV in Rs: $17.9\% \pm 14.6\%$ vs. $9.3\% \pm 6.7\%$; PPV in NRs: $10.9\% \pm 4.6\%$ vs. $5.4\% \pm 2.0\%$, respectively; $p < 0.05$ for both groups; SVV in Rs: $15.3\% \pm 10.0\%$ vs. $8.4\% \pm 4.3\%$; SVV in NRs: $10.2\% \pm 4.3\%$ vs. $4.5\% \pm 1.8\%$). Additionally, CVP was significantly lower 5 minutes after anaesthesia induction than at the start of physiological study in both Rs and NRs (CVP in Rs: $1.6 \text{ mmHg} \pm 1.4 \text{ mmHg}$ vs. $3.3 \text{ mmHg} \pm 1.7 \text{ mmHg}$, respectively; $p < 0.05$ for both groups; CVP in NRs: $2.6 \text{ mmHg} \pm 1.8 \text{ mmHg}$ vs. $4.8 \text{ mmHg} \pm 1.8 \text{ mmHg}$, respectively; $p < 0.05$ for both groups). These increases of CVP and decreases of both PPV and SVV might be explained by surgical stimulation-related vasoconstriction.

In the present study, we performed the fluid challenge using HES for the following reasons. First, in a large number of studies on fluid responsiveness or goal-directed fluid therapy performed in surgical patients, HES has been used during fluid challenge.⁽³³⁾ Second, in perioperative care, current evidence does not suggest that renal injury and HES use are correlated.^(34,35)

Surgery was ongoing during the administration of the fluid challenge in the current study. Although this might affect sympathetic tone and confound the effects of the fluid challenge,^(36,26) the study protocol was performed after the placement of surgical retractor, and anaesthetic administration was titrated to maintain the BIS value between 40 and 60 during the fluid loading in both R and NR groups. There were no differences in method of adjustment of anaesthetic depth and analgesic dosing between the R and NR groups.

KT recipients may present as extremely hypovolaemic or extremely hypervolaemic, depending on whether they receive dialysis before transplantation. Further, the mode of dialysis can affect intravascular volume status; for example, patients receiving peritoneal dialysis generally have a more desirable volume status than patients treated with haemodialysis.⁽³⁷⁾ However, in the present study, we did not find a significant relationship between fluid responsiveness and receiving pretransplant dialysis or between fluid responsiveness and the dialysis treatment modality.

Some limitations of the current trial should be considered. First, we did not measure the RVEDVI, which is regarded as an accurate preload measurement method during KT and obtained with thermo-dilution technique using a pulmonary artery catheter (PAC).⁽²³⁾ However, the use of PAC involves potential risks such as pulmonary artery rupture and arrhythmia. Second, a previous study documented that the predictability of dynamic indicators of respiratory variation of stroke volume and arterial pressure such as SVV and PPV may be lower in patients with right ventricular dysfunction,⁽³⁸⁾ and KT recipients who underwent chronic

haemodialysis usually show impaired or decreased right ventricular function.⁽³⁹⁾ In the present study, we did not evaluate the right ventricular function of the study subjects, although no significant differences were observed between Rs and NRs with regard to the number of recipients who underwent haemodialysis before transplantation surgery. Third, SVV and PPV were measured by different software. Therefore, we can only carefully speculate on clinical significance although there was a statistical significance. Fourth, in the present study, fluid loading was stopped when CVP increased more than 10 mmHg and the subjects were excluded from analysis. This exclusion of an important group of NRs might have influenced the study. Nevertheless, we regarded a CVP increase of more than 10 mmHg before completion of fluid loading as an end point for stopping fluid therapy to prevent adverse events such as right ventricular failure or systemic venous congestion. Lastly, we used colloid fluid administration of 7 mL/kg of ideal body weight over ten minutes instead of a ‘mini-fluid challenge’ of 1–3 mL/kg or 100–200 mL over 1–5 minutes. Recent literature suggests that ‘mini-fluid challenges’ can provide similar information as larger fluid challenges.^(40,41) Further studies are needed to validate the reliability of several preload indexes for predicting fluid responsiveness using ‘mini-fluid challenges’ in KT recipients.

In conclusion, the monitoring of SVV and CVP showed their comparable ability to predict CI responses to volume expansion in ESRD patients undergoing living-donor KT. Based on our current results, their use as indicators of fluid responsiveness would be recommended during KT surgery. However, the routine application of PPV monitoring to assess intravascular volume status might not be considered in patients with characteristics similar to those of our patients. Further research is warranted to determine whether goal-directed fluid therapy based on measurements of SVV and CVP may affect short- or long-term outcomes of KT patients.

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FIGURES

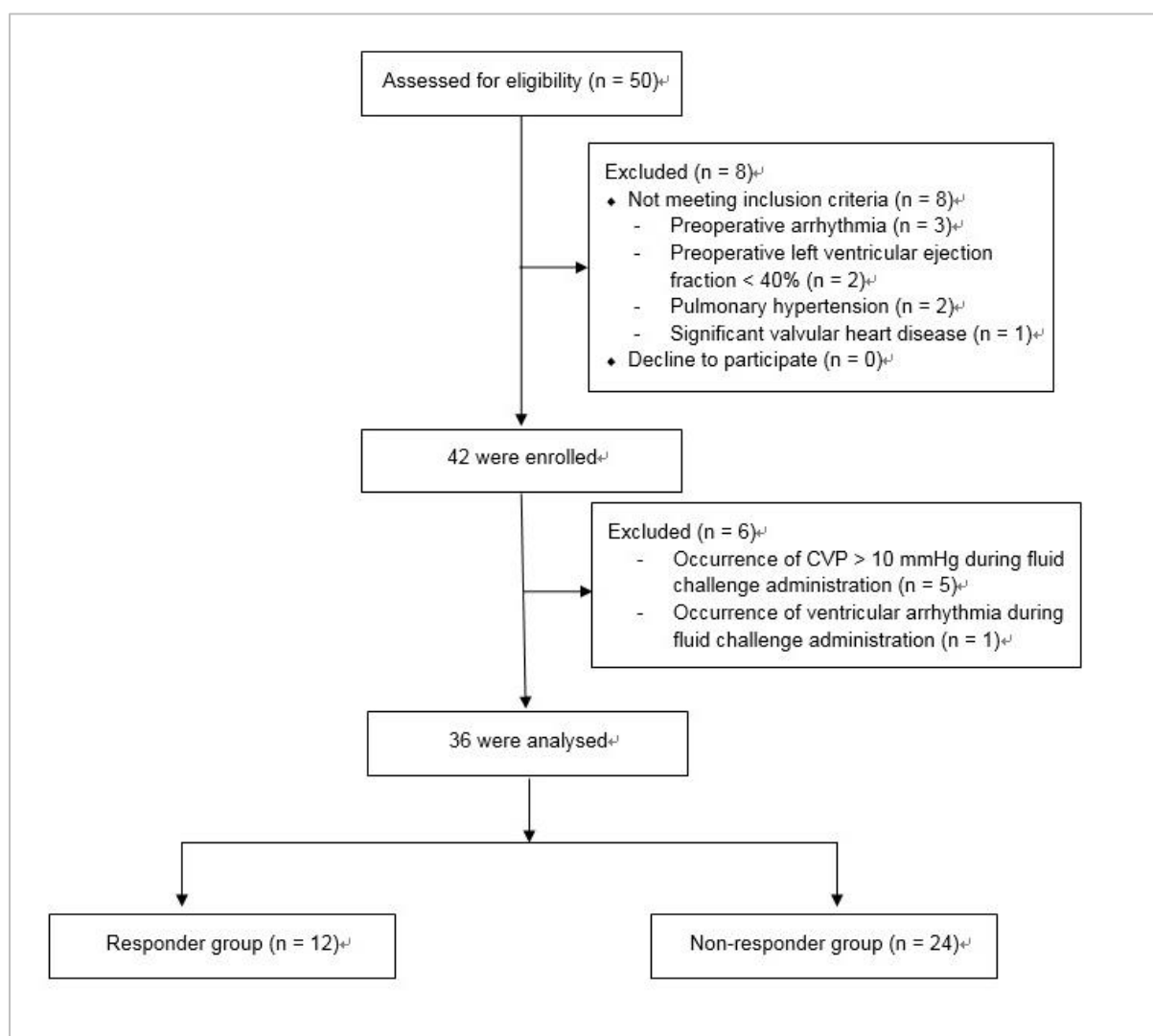


Fig. 1 Flowchart shows the enrolment process for the study.

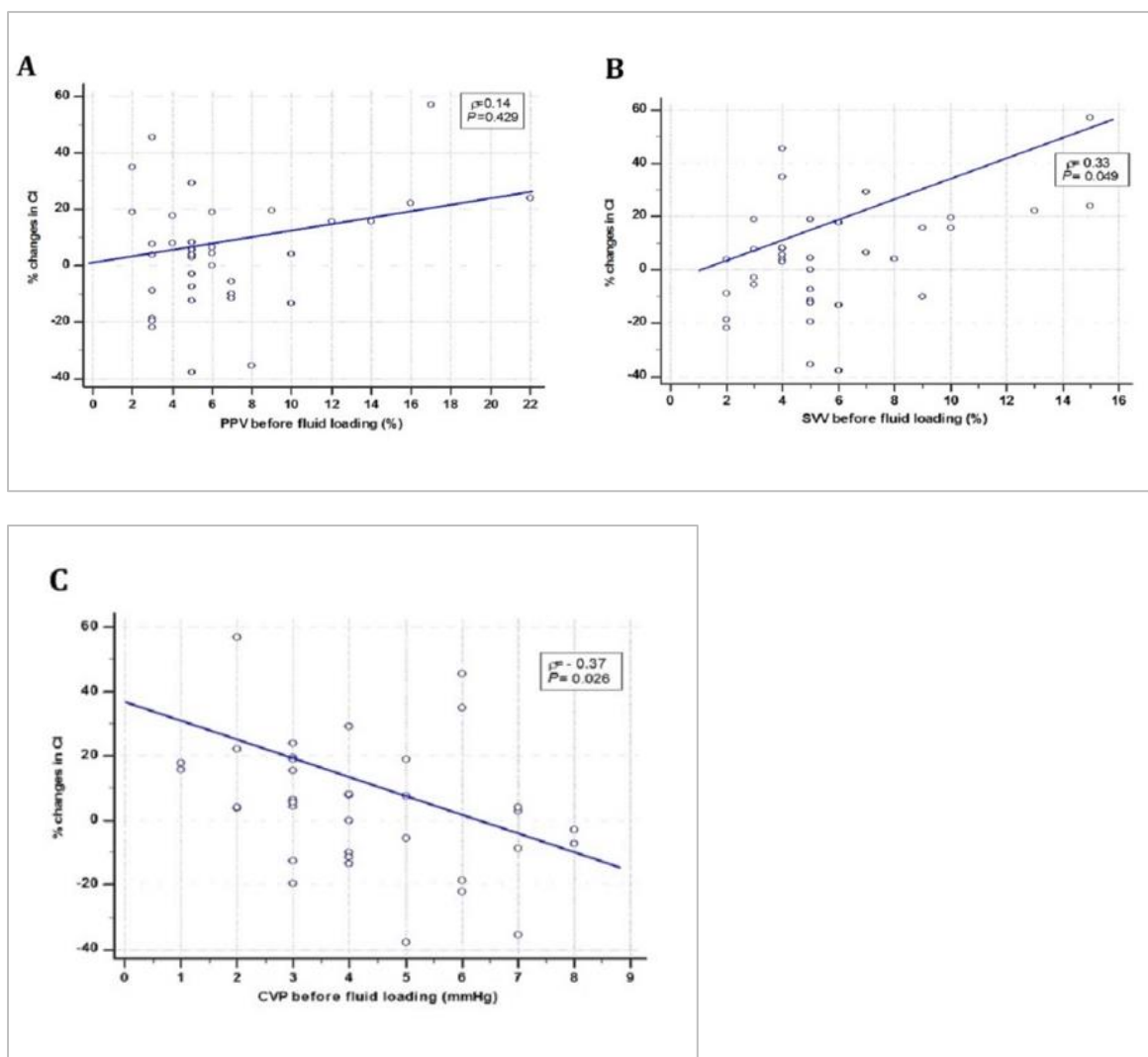


Fig. 2 Graphs show the relationships between the percentage change in cardiac index (CI) and (a) fluid loading and pulse pressure variation (PPV) before fluid loading; (b) stroke volume variation (SVV) before fluid loading; and (c) central venous pressure (CVP) before fluid loading. Spearman's correlation coefficients (ρ) for PPV, SVV and CVP were 0.14, 0.33 and -0.37 , respectively.

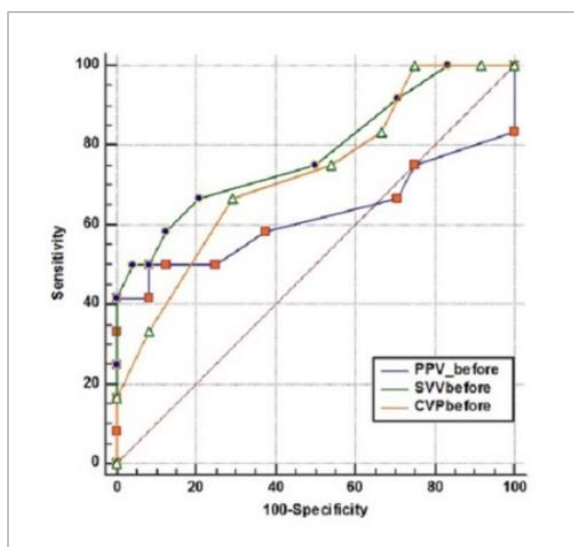


Fig. 3 Receiver operating characteristic curve shows a comparison of the ability of pulse pressure variation (PPV), stroke volume variation (SVV) and central venous pressure (CVP) before fluid loading to discriminate between responders and non-responders.

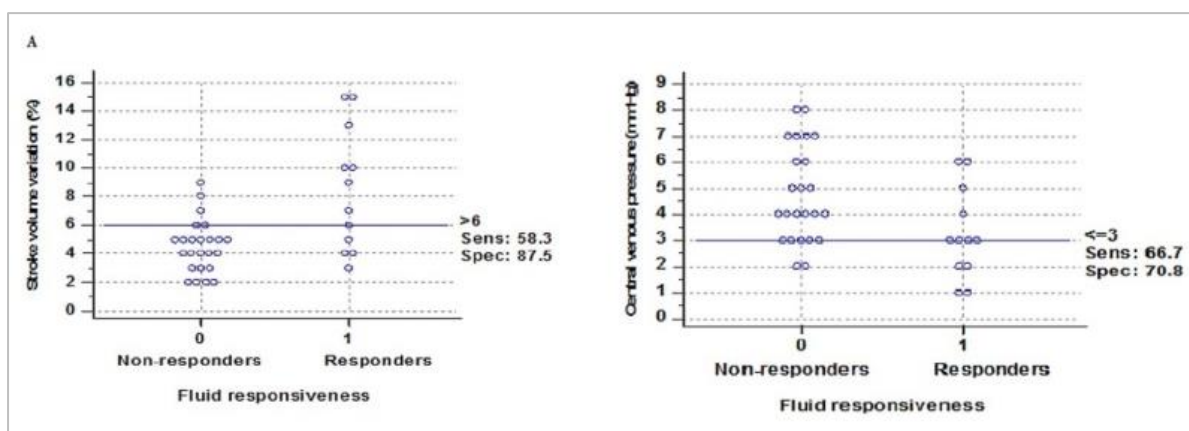


Fig. 4 Dot diagrams show (a) stroke volume variation (SVV) and (b) central venous pressure (CVP) readings of responders and non-responders. The horizontal straight line represents the optimal threshold value in predicting fluid responsiveness. An SVV value $> 6.0\%$ identified responders with a sensitivity of 58.3% and a specificity of 87.5%, and a CVP value $\leq 3.0\%$ identified responders with a sensitivity of 66.7% and a specificity of 70.8%.