ORIGINAL RESEARCH

Effect of fluid loading on left ventricular volume and stroke volume variability in patients with end-stage renal disease: a pilot study

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Purpose: The aim of this study was to investigate fluid loading-induced changes in left ventricular end-diastolic volume (LVEDV) and stroke volume variability (SVV) in patients with end-stage renal disease (ESRD) using real-time three-dimensional transesophageal echocardiography and the Vigileo-FloTrac system.

Patients and methods: After obtaining ethics committee approval and informed consent, 28 patients undergoing peripheral vascular procedures were studied. Fourteen patients with ESRD on hemodialysis (HD) were assigned to the HD group and 14 patients without ESRD were assigned to the control group. Institutional standardized general anesthesia was provided in both groups. SVV was measured using the Vigileo-FloTrac system. Simultaneously, a full-volume three-dimensional transesophageal echocardiography dataset was acquired to measure LVEDV, left ventricular end-systolic volume, and left ventricular ejection fraction. Measurements were obtained before and after loading 500 mL hydroxyethyl starch over 30 minutes in both groups.

Results: In the control group, intravenous colloid infusion was associated with a significant decrease in SVV ($13.8\% \pm 2.6\%$ to $6.5\% \pm 2.6\%$, $P < 0.001$) and a significant increase in LVEDV (83.6 ± 23.4 mL to 96.1 ± 28.8 mL, $P < 0.001$). While SVV significantly decreased after infusion in the HD group ($16.2\% \pm 6.0\%$ to $6.2\% \pm 2.8\%$, $P < 0.001$), there was no significant change in LVEDV.

Conclusion: Our preliminary data suggest that fluid responsiveness can be assessed not by LVEDV but also by SVV due to underlying cardiovascular pathophysiology in patients with ESRD.

Keywords: stroke volume variability, end-stage renal disease, three-dimensional transesophageal echocardiography, hemodialysis, goal-directed fluid therapy

Introduction

End-stage renal disease (ESRD) is a significant global health issue. More than 1.4 million patients are estimated to have ESRD worldwide and the number is steadily increasing.[1] Currently, more than 500,000 patients in the United States and 300,000 patients in Japan are receiving long-term hemodialysis (HD) for ESRD.[2,3]

While HD has extended the life expectancy of patients with ESRD and improved their quality of life, a growing number of these patients are referred to surgery. The majority of patients with ESRD have multiple comorbidities, including diabetes mellitus, hypertension, and coronary artery disease. Hence, these patients are at higher risk for perioperative cardiovascular morbidity and mortality, and perioperative management requires special attention.[4,5]

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Perioperative fluid management is critically important. Persistent fluid overload causes hypertension, pulmonary edema, and congestive heart failure, and is associated with a higher risk of mortality.[6] Therefore, patients with ESRD often receive HD on the day before surgery to achieve their dry weight, at which point they are considered to be euvolemic. On the other hand, these patients often develop significant hypotension in response to the induction of general anesthesia. Recurrent episodes of intra-dialytic hypovolemia are associated with accelerated deterioration of residual renal function,[7] vascular access function loss,[8] brain atrophy,[9] mesenteric infarction,[10] and thus, higher morbidity and mortality.[11,12] Fluid therapy should be administered in an evidence-based, goal-directed manner.[13–15] Surprisingly, however, few published studies address the validity of goal-directed fluid therapy for patients with ESRD.

Among the various parameters, stroke volume variability (SVV) and left ventricular (LV) volume are frequently used to assess fluid status perioperatively to guide goal-directed fluid therapy.[14,15] SVV is calculated as a %change of stroke volume to the mean derived from an arterial pulse contour analysis during a mechanical ventilation cycle. SVV greater than 13% represents fluid responsiveness, the status in which fluid therapy would increase cardiac output.[14,16,17] Findings from previous studies suggest that SVV is a reliable predictor of hypovolemia and fluid responsiveness in various clinical settings.[18–20] On the other hand, left ventricular end-diastolic volume (LVEDV) is frequently measured using transesophageal echocardiography (TEE) as the gold standard indicator of cardiac preload.[21] These two parameters are thought to respond in a coordinated manner to changes in the intravascular fluid status in low-risk patients.[22] Long-term HD, however, is associated with progressive deterioration of the cardiovascular system, including LV hypertrophy, dilatation, and vascular calcification.[23,24] These morphologic changes are frequently accompanied by LV diastolic dysfunction with a preserved ejection fraction (EF).

We have encountered many cases with ESRD in which the patient was hypotensive and the arterial waveform demonstrated a significant fluctuation, and TEE revealed a significantly dilated LV. These findings imply theoretically conflicting information on the fluid status, making the therapeutic decision difficult. How goal-directed fluid therapy should be administered and how fluid loading affects these two hemodynamic parameters in this patient subset are unclear.

We hypothesized that SVV decreases and LVEDV increases after fluid bolus in patients with ESRD, as observed in low-risk patients. We, therefore, conducted the present study to elucidate the effects of fluid loading on SVV and LVEDV in patients with ESRD. The aim of this study was to investigate fluid loading-induced changes in LVEDV and SVV in patients with ESRD using real-time three-dimensional TEE (3D-TEE) and the Vigileo-FloTrac system.

Materials and methods
Study design
This study is a single center, prospective, observational study. The study protocol was approved by the Asahikawa Medical University Research Ethics Committee and registered as a clinical trial (UMIN000007223). We obtained written informed consent from all patients.

Inclusion criteria
Consecutive patients with arteriosclerosis obliterans undergoing scheduled arterial bypass procedure on lower extremity were enrolled. The candidates were screened for eligibility for participation in the study through preoperative assessment. Transthoracic echocardiography and electrocardiogram were performed to assess preoperative cardiac function. Patients with arrhythmia, significant LV systolic dysfunction (left ventricular ejection fraction [LVEF] <50%), or contraindications for TEE probe insertion were excluded.

Interventions
The patients with ESRD requiring HD were assigned to the HD group and those without ESRD were assigned to the control group. Standardized perioperative care was provided for all patients. An arterial line was placed in the radial artery and connected to the Vigileo-FloTrac system (FloTrac™ sensor and Vigileo™ monitor, software version 3.02, Edwards Lifesciences, Tokyo, Japan). Arterial line was placed in the opposite side of the arteriovenous shunt in the HD group. General anesthesia was performed using target-controlled intravenous infusion of propofol (2.0–4.0 µg/mL) and continuous infusion of remifentanil (0.2–0.3 µg/kg/min). Propofol was infused to maintain a bispectral index within the range of 40–60. Rocuronium was administered to facilitate endotracheal intubation and to provide adequate muscle relaxation during surgery when necessary. Phenylephrine (50 µg) was administered, if necessary, to maintain a mean arterial pressure of >50 mmHg. Patients were mechanically ventilated with a tidal volume between 8 and 10 mL/kg to achieve normocapnia and positive end-expiratory pressure was applied at 5 cm H_2O. A 3D-TEE probe (X7-2t, Philips Medical Systems Japan, Tokyo, Japan) was placed in the mid-esophageal position for the LV volumetry.

Once the anesthesia state was stabilized, 500 mL of 6% hydroxyethyl starch with a molecular weight/molar substitution ratio of 70 KDa/0.4 (Fresenius Kabi Japan, Tokyo, Japan) was administered over a 30-minute period in both groups. A full-volume 3D-TEE dataset was obtained before and after fluid bolus for LV volumetry. Simultaneously, the vital signs (heart rate, systolic, and diastolic blood pressure) and hemodynamic parameters by arterial pulse contour analysis (SVV and cardiac output) were recorded.

Data collection and analysis

Patient background, including age, height, weight, sex, and comorbidities, was collected from the medical records. For patients in the HD group, the history of HD and the amount of fluid removed the day before surgery were recorded. Early diastolic inflow (E), early diastolic mitral annular velocity by tissue Doppler imaging (e′), and E/e′ (E/e′ is a parameter of LV diastolic function calculated by dividing E by e′) were collected from the preoperative transthoracic echocardiography (TTE)

record as indices of LV diastolic function. Intraoperative data collection and TEE volumetric analyses were performed by investigators blind to the preoperative TTE results. Volumetric parameters including LVEDV, LV end-systolic volume, cardiac output, and EF were measured using a full-volume 3D-TEE dataset of the LV by quantitative analysis software (QLAB, Philips Medical Systems Japan, Tokyo, Japan, Figure 1). In this study, changes in SVV and LVEDV following fluid bolus were set as primary outcomes.

Statistics

A power analysis using G*Power (software version 3.1.7, University of Düsseldorf, Düsseldorf, Germany) indicated that a sample size of 14 patients per group would result in an approximate chance of obtaining statistical significance via a two-way repeated-measures analysis of variance (ANOVA), assuming a large effect size of 0.4 according to Cohen.[25] Statistical analysis was performed using Prism (software version 5.01, GraphPad Software, La Jolla, CA, USA).
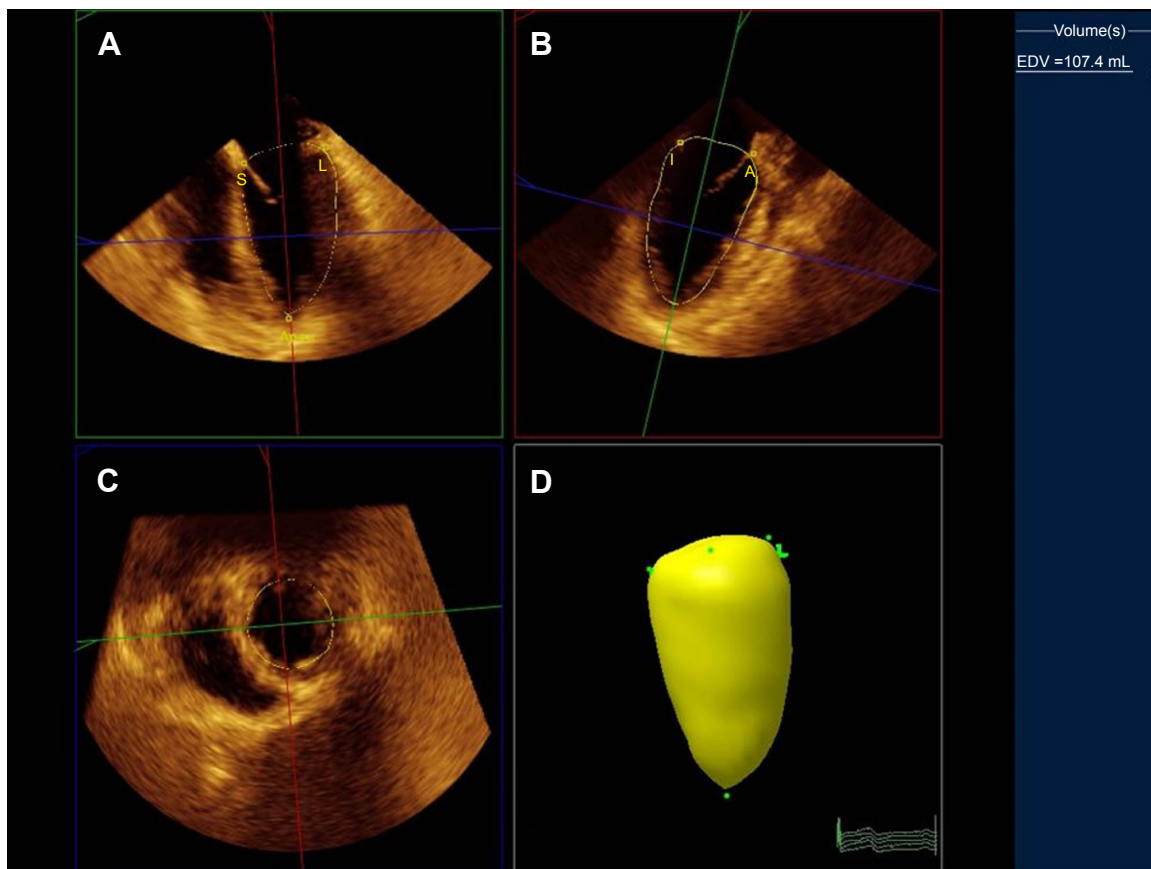

Figure 1 Measurement of left ventricular (LV) end-diastolic volume (EDV).
Notes: After setting five points (S: septal, L: lateral, A: anterior, I: inferior, and apex), the system automatically tracks the complete LV endocardial borders to calculate the LV volume. Figure **A** shows the cross-section of the green lines in figures **B** and **C**. Figure **B** shows the cross-section of the red lines in figures **A** and **C**. Figure **C** shows the cross-section of the purple lines in figures **A** and **B** and represents the midesophageal four chamber view, the midesophageal two chamber view, and the short-axis view, respectively. The green, red, and purple lines in figures **A**, **B**, and **C** indicate three orthogonal lines in the LV; the yellow lines in trace the endocardial borders. Figure **D** is a three-dimensional reconstruction, with the green dots indicating the appointed five points.

Patient backgrounds were compared using Student's *t*-test for continuous data and the chi-square test for categorical data. A two-way repeated-measures ANOVA followed by the Bonferroni post hoc test was performed to assess the patient vital signs and the parameters obtained by the pulse contour analysis and LV volumetry. A *P*-value of <0.05 was considered as statistically significant.

Results

Study cohorts

A total of 35 consecutive patients was enrolled, seven of whom were excluded for the following reasons: atrial fibrillation in four, left ventricular systolic dysfunction in two, and inadequate echocardiography imaging in one. As a result, 28 patients (14 in the HD group and 14 in the control group) were analyzed. There were no perioperative complications related to colloid infusion in both groups. The patient background is summarized in Table 1. The HD group had a significantly lower mean age and a significantly higher prevalence of diabetes. Patients in the HD group received HD and 1,700±675 mL of fluid was removed on the day before surgery. Preoperative TTE revealed that E/e′ was significantly higher in the HD group (16±3.8 vs 9.7±2.8, *P*=0.0012). The vital signs, arterial pulse contour parameters, and LV volumes before and after fluid loading are summarized in Table 2.

Change in SVV

There was a significant effect of time (*F*[1,26] =111.7, *P*<0.0001), but not of grouping on SVV. Post hoc analysis

Table 1 Patient characteristics

	Control group (n=14)	HD group (n=14)	*P*-value
Age (years)	72.4±12.5	64.3±8.6	0.0314
Height (cm)	159±11.9	158±8.1	NS
Weight (kg)	57.7±10.3	54.9±11.0	NS
Men/women (n)	10/4	9/5	NS
Hypertension (n)	11	12	NS
CAD (n)	1	5	NS
DM (n)	2	10	0.0023
Period of HD (years)	NA	8.5±8.2	NA
Fluid removal (mL)	NA	1,700±675	NA
Preoperative TTE			
e′ (cm/s)	5.7±1.0	4.7±0.6	0.0330
E (cm/s)	55±16	76±15	0.0104
E/e′	9.7±2.8	16±3.8	0.0012

Notes: Data are shown as mean ± SD. E/e′ is a parameter of LV diastolic function calculated by dividing E by e′.
Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; E, early diastolic inflow; e′, early diastolic mitral annular velocity by tissue Doppler imaging; HD, hemodialysis; TTE, transthoracic echocardiography; NA, not available; NS, not significant.

Table 2 Effect of fluid loading on hemodynamics, SVV, and LV volume

	HD group (n=14)		Control group (n=14)	
	Pre	**Post**	**Pre**	**Post**
Vital signs				
Heart rate (bpm)	69±12	67±11	68±12	64±11
Systolic BP (mmHg)	125±33#	136±31	105±18	118±19*
Diastolic BP (mmHg)	50±10	53±8	52±11	55±12
Pulse contour analysis				
SVV (%)	16.2±6.0	6.2±2.8**	13.8±2.6	6.5±2.6**
Cardiac output (L/min)	5.1±1.3#	5.9±1.3*	3.9±1.2	4.4±1.3
Volumetric analysis				
LVEDV (mL)	108±34.1#	109±33.8	83.6±23.4	96.1±28.8**
LVESV (mL)	48.7±29.9	49.1±30.2	36.7±12.9	39.6±15.3
Cardiac output (L/min)	4.0±1.3	3.9±1.0	3.4±1.0	3.7±1.3
EF (%)	59.1±7.3	59.3±8.0	53.6±13.0	56.3±15.0

Notes: Data shown as mean ± SD. *P<0.05 vs baseline, **P<0.001 vs baseline, #P<0.05 vs control group.
Abbreviations: HD, hemodialysis; LV, left ventricular; BP, blood pressure; SVV, stroke volume variability; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

revealed that SVV significantly decreased after fluid bolus in both groups (HD group: 16.2%±6.0% to 6.2%±2.8%, *P*<0.001, control group: 13.8%±2.6% to 6.5%±2.6%, *P*<0.001) (Figure 2).

Change in LVEDV

There was a significant effect of time (*F*[1,26] =29.18, *P*<0.0001) on LVEDV. Post hoc analysis revealed that the mean LVEDV in the HD group before infusion was significantly greater than that of the control group (108±34.1 mL vs 83.6±23.4 mL, *P*<0.05). Furthermore, there was no significant change in LVEDV in the HD group (108±34.1 mL to 109±33.8 mL, *P*>0.05), while LVEDV significantly increased in the control group (83.6±23.4 mL to 96.1±28.8 mL, *P*<0.001) (Figure 2).

Discussion

The present study revealed a characteristic response pattern of the SVV and LVEDV associated with colloid infusion in patients with ESRD; SVV significantly decreased after infusion, but there was no change in LVEDV.

Several studies have demonstrated that SVV is a reliable predictor of fluid responsiveness in various clinical settings.[26,27] In our study, patients in HD group underwent HD the day before surgery and a fair amount of fluid was
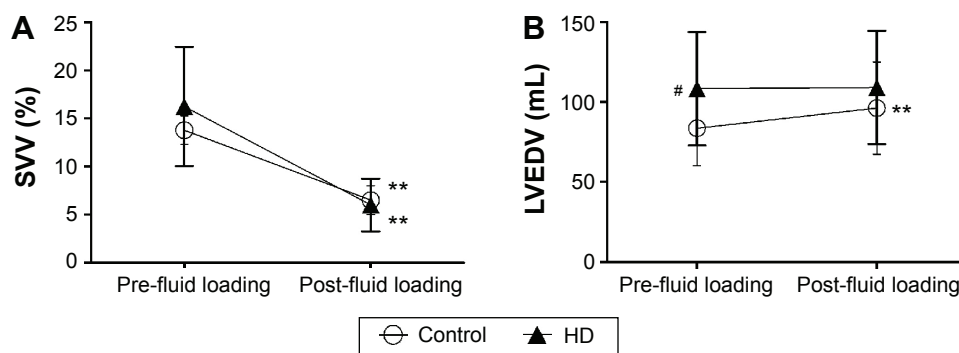
Figure 2 Changes in the SVV (**A**) and LVEDV (**B**) following fluid loading.
Notes: SVV decreased significantly in both groups after fluid loading. There was no significant change in the LVEDV in the HD group despite a significant increase in the control group. Data shown as mean ± SD. **$P<0.001$ vs baseline, #$P<0.05$ vs control group.
Abbreviations: HD, hemodialysis; SVV, stroke volume variability; LVEDV, left ventricular end-diastolic volume.

removed. Therefore, it is reasonable to assume that the patients were in a relatively hypovolemic state on the day of surgery, as reflected by the high SVV. Furthermore, SVV significantly decreased in both patient groups. These findings suggest that the patients in the HD group were responsive to fluid therapy and that SVV can be used to guide intraoperative fluid therapy in HD patients.

LV area or volume is currently considered as the gold standard parameter of cardiac preload.[21] Whether LVEDV predicts fluid responsiveness, however, is a matter of debate because previous studies have demonstrated conflicting results.[28] These conflicting results might be due to the technical limitation of two-dimensional echocardiography to measure an accurate LV volume.[28] Real-time 3D-TEE was therefore used to measure LV volumes in our study, as volumetric analysis by the real-time 3D-TEE is reportedly more accurate than two-dimensional TEE.[29] In the present study, the LVEDV in HD group before colloid infusion was significantly greater than control and, to our surprise, did not increase after infusion despite SVV significantly decreased. This finding implies that there may be a pathophysiologic status in which fluid responsiveness can be assessed by SVV, but not by LVEDV.

Patients on long-term HD develop both morphologic and functional disturbances of the cardiovascular system. A study using magnetic resonance imaging reported that LV hypertrophy is frequently seen in patients with ESRD.[23] Other studies demonstrated that this morphologic change of the LV is associated with LV diastolic dysfunction.[30,31] In this study, E/e′ measured by preoperative TTE was used as a surrogate marker of LV diastolic function, because E/e′ is known to correlate with LV filling pressure and is relatively load independent.[32–36] E/e′ greater than 15 is associated with elevated LV filling pressures.[35] In the present study, the

LVEDV in the HD group before colloid infusion was significantly greater than that in the control group despite preceding HD, and E/e′ in the HD group was markedly elevated and significantly greater than that in the control group. These findings suggest that patients with ESRD suffered from LV diastolic dysfunction.

Diastolic heart failure is a confusing concept.[37] This concept has evolved as an attempt to discriminate between "acute vascular" and "acute congestive" heart failure.[37,38] Acute vascular heart failure is caused by diastolic dysfunction, often with preserved EF, acute increases in peripheral resistance, and redistribution (rather than fluid accumulation) of blood from the peripheral to the pulmonary circulation. Moreover, adaptation of the lymph drainage from the lungs occurs in long-term ESRD patients.[39] In contrast to acute vascular heart failure, fluid accumulation is considered as the essential and main mechanism of acute congestive heart failure. In our study, the baseline systolic blood pressure (SBP) in the HD group was significantly higher than that in the control group, indicating that patients with ESRD had a pathologic condition similar to diastolic heart failure, especially acute vascular heart failure. That is to say, they had an enlarged LV with subclinical diastolic dysfunction, normal systolic function, increases in peripheral resistance, and redistribution of blood from the peripheral to the pulmonary circulation. We speculate that the absence of a change in LVEDV after colloid infusion in HD patients is due to diastolic dysfunction and a subsequent redistribution of blood volume.

Our study has some limitations. First, this study was conducted as a pilot study, enrolling minimum number of patients considering a potential risk of colloid infusion in HD group. The potential confounding factors in the patient background were therefore not controlled. Furthermore, the effect of the severity of diastolic dysfunction was not stratified in the study

cohort; therefore, how the severity of diastolic function affects fluid responsiveness was not addressed. Finally, hydroxyethyl starch was used as a study solution because it remains in the intravascular space and is thus more effective for fluid replacement than crystalloid. The European Medicines Agency and Food and Drug Administration of the United States, however, have issued warnings regarding the use of hydroxyethyl starch for volume expansion in critically ill patients. Although the patients in this study were all in a stable condition and there were no complications associated with colloid infusion, careful consideration is necessary in selecting the type of solution for fluid replacement in patients with ESRD.

Conclusion

In conclusion, we investigated changes in SVV and LVEDV associated with colloid infusion in patients with ESRD. In patients with ESRD, colloid infusion was associated with a significant decrease in SVV, but no significant change in LVEDV was observed. Our findings suggest that a change in blood volume can be reflected as a change in SVV, but not in LVEDV, in patients with ESRD due to underlying LV diastolic dysfunction. Diastolic function appears to be an important factor that affects fluid loading-associated changes in LV volume. Further investigation is necessary to elucidate the relationship between fluid responsiveness and LV diastolic function to establish an effective, goal-directed fluid management strategy for patients with ESRD.

Author contributions

Hirotsugu Kanda, Yuji Hirasaki, Megumi Kanao-Kanda, Takafumi Iida, Yuki Toyama, and Takayuki Kunisawa helped design the study, conduct the study, and analyze the data. Hiroshi Iwasaki conducted the study and helped analyze the data. All authors contributed toward drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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