Original Article

Can the global end-diastolic volume index guide fluid management in septic patients? A multicenter randomized controlled trial

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Aim: An index that accurately measures intravascular volume is paramount for the optimal resuscitation of sepsis. Selecting an adequate indicator to substitute for central venous pressure (CVP) has remained an issue. The objective of our study was to compare the usefulness of standard early goal-directed therapy (EGDT) with CVP (EGDT-CVP) and modified EGDT with global end-diastolic volume index (GEDI; EGDT-GEDI) for sepsis.

Methods: This was a multicenter prospective randomized controlled study. All patients with sepsis who were expected to require mechanical ventilator support for a minimum of 48 h were included. The patients were classified into an EGDT-CVP group and an EGDT-GEDI group. All participants underwent the extubation protocol. The primary outcome was the ventilator-free days over a 28-day period.

Results: The ventilator-free days was not significantly different between the two groups ($P = 0.59$). However, the EGDT-GEDI group showed a trend of shorter ventilator support duration (5.1 days [2.0–8.7 days] versus 3.9 days [2.4–5.7 days], $P = 0.27$) and length of stay in the intensive care unit (7.2 days [3.8–10.7 days] versus 5.1 days [3.7–8.8 days], $P = 0.05$) and a smaller 3-day infusion balance than the EGDT-CVP group (4,405 mL [1,092–8,163 mL] versus 3,046 mL [830–6,806 mL], $P = 0.34$), but the differences were not statistically significant.

Conclusion: Although there was no significant efficacy, EGDT guided by GEDI showed a trend of shorter length of stay in the intensive care unit and lower 3-day infusion balance than the EGDT-CVP group in sepsis. The GEDI monitoring did not appear to improve the ventilator-free days over a 28-day period.

Key words: Early goal-directed therapy, global end-diastolic volume index, sepsis, transpulmonary thermodilution, volume resuscitation

INTRODUCTION

SEPSIS IS A severe condition that requires adequate fluid resuscitation and close monitoring of a patient's hemodynamic parameters for effective management. Fluid management in sepsis is a key therapeutic element. However, the most effective method to guide fluid therapy remains controversial because of difficulty in obtaining an accurate volume status assessment in patients with sepsis.

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The Surviving Sepsis Campaign Guideline recommends the use of early goal-directed therapy (EGDT) with central venous pressure (CVP; EGDT-CVP),[1] although a recent trio trial and meta-analysis concluded that EGDT-CVP did not significantly reduce mortality compared with "usual care".[2–5] However, the concept of EGDT that requires adequate volume resuscitation might be appropriate, as inadequate or insufficient fluid delivery could result in increased hypoperfusion of organs and tissues.[6] Thus, one of the reasons that EGDT-CVP failed to show usefulness could be the fact that CVP might not adequately reflect hemodynamic changes.[7–9] An alternative method to measure the correct amount of fluid administration is still needed.

Transpulmonary thermodilution is a technique that is used to evaluate intracardiac blood volume as a volumetric parameter, whereas global end-diastolic volume index (GEDI) assesses the end-diastolic volume of all four chambers of the heart. The degree of change in GEDI was reportedly a more reliable preload parameter than CVP.[10,11] Here we aimed to evaluate and compare standard EGDT-CVP and modified EGDT obtained with GEDI (EGDT-GEDI) in patients with sepsis.

METHODS

THIS PROSPECTIVE RANDOMIZED controlled multi-institutional study was carried out from September 2013 to March 2016. We screened all patients admitted to the intensive care unit (ICU) of 10 separate hospitals in Japan and included all patients with sepsis who were expected to require mechanical ventilator support in the ICU for a minimum of 48 h (Appendix S1: eMethods 1).

The enrolled patients were randomized and categorized into the CVP group resuscitated by EGDT-CVP or the GEDI group resuscitated by EGDT-GEDI (Appendix S1: eMethods 2). The patients in the EGDT-CVP group were monitored with a common CVP measurement, and the EGDT-GEDI group was monitored with a transpulmonary thermodilution system, either an EV1000 (Edwards Lifesciences, Irvine, CA, USA) or a PiCCO (PULSION Medical Systems, Munich, Germany) (Appendix S1: eMethods 3). Following patient admission to the ICU, the CVP and GEDI monitoring devices were promptly readied and the study was immediately initiated. Both groups followed the same EGDT-based protocol for initial hemodynamic resuscitation except the target range of the volume measurement of CVP or GEDI as shown in Figure 1 and Appendix S1: eMethods 4.

All participants underwent a spontaneous breathing trial and the extubation protocol every morning after participating in the study (Appendix S1: eMethods 5).

The primary outcome was defined as the number of ventilator-free days over a 28-day period. The secondary outcomes were mortality of any cause during that same 28-day period, length of ICU stay, and in-and-out fluid balance for the first 72 h (Appendix S1: eMethods 6).

Statistical analyses

We estimated that a sample of 196 patients (98 subjects each in the CVP and GEDI groups) was the minimum required sample population size. All analyses were carried out on an intention-to-treat basis. Continuous values are expressed as median and interquartile range or mean with standard deviation (SD); categorical values are expressed as number (percentage). We used competing risk analysis to compare the effects of the ventilator-free period in the ICU in both groups. We calculated and compared the cumulative incidences of the archived ventilator-free period by using the modified Kaplan–Meier method and the competing risk-adjusted model (the Gray method).[12] To determine whether the GEDI-guided treatment was an independent factor compared with CVP for achieving ventilator-free status, we calculated the hazard ratio (HR) and 95% confidence interval (CI) by using the modified Cox proportional hazard model in the presence of a competing risk event of death.[13] P-values < 0.05 were considered statistically significant (Appendix S1: eMethods 7).

RESULTS

OF THE 372 patients with sepsis who were enrolled during the study period of September 2013 to March 2016, 164 were assessed, of whom 89 (54.3%) were men. The ages were 25–93 years, with a mean (SD) of 67 (13.9) years (Fig. 2, Appendix S1: eResults 1). Table 1 shows the baseline characteristics of the eligible patients. The univariate analysis revealed that the proportion of male patients was significantly higher in the EGDT-GEDI group (53% [42 patients] versus 70% [56 patients]; $P = 0.03$). Otherwise, no other statistically significant differences were found between the EGDT-CVP and EGDT-GEDI groups. The most common cause of sepsis was respiratory disease in both groups (35% in the EGDT-CVP group and 30% in the EGDT-GEDI group; $P = 0.81$).

Outcomes

Table 2 shows the univariate analysis of outcomes. No significant difference in ventilator-free period (days) for 28 days as our primary outcome was found between the EGDT-CVP and EGDT-GEDI groups (22 [19–25] versus

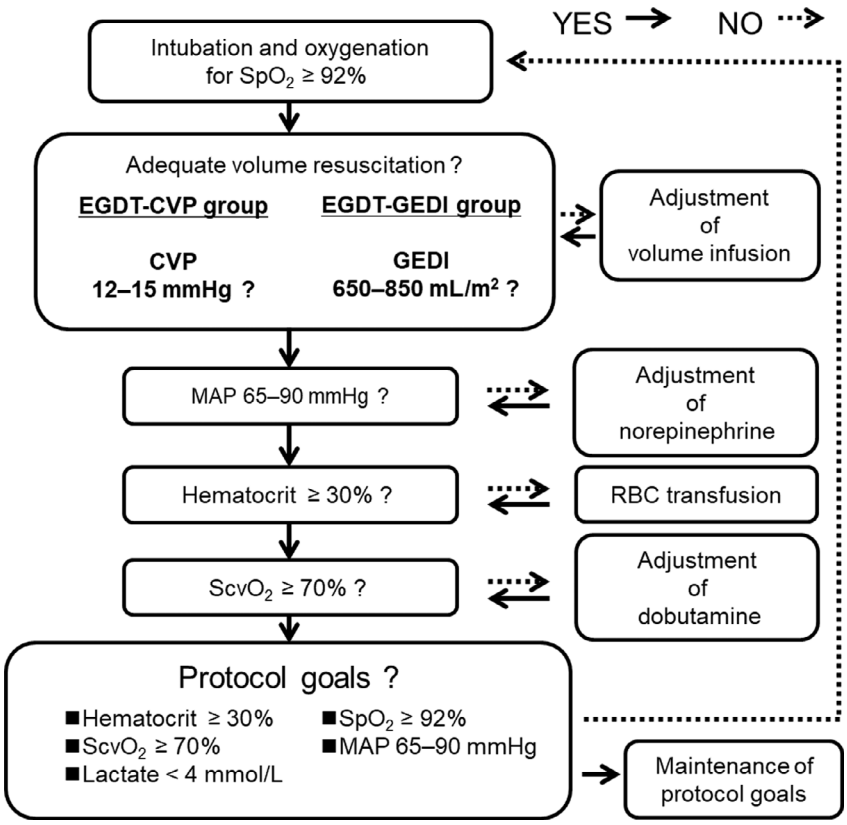

Fig. 1. Protocol for initial hemodynamic resuscitation in patients with sepsis. CVP, central venous pressure; EGDT, early goal-directed therapy; GEDI, global end-diastolic volume index; MAP, mean arterial pressure; RBC, red blood cells; $ScvO_2$, central venous oxygen saturation.

24 [22–25], P = 0.27). A univariate analysis that compared the 28-day outcomes between groups (Table 2) showed no significant differences in protocol withdrawal due to complications. In the analysis of survivors, ventilator duration (5.1 [2.0–8.7] versus 3.9 [2.4–5.7] days, P = 0.27) and length of ICU stay (7.2 [3.8–10.7] versus 5.1 [3.7–8.8] days, P = 0.05) showed no significant differences between the EGDT-CVP and EGDT-GEDI groups, although there were fewer survivors in the EGDT-GEDI group. The proportion of deaths within 48 h after the randomization was higher in the EGDT-GEDI group (2 [2.5%] versus 12 [15.0%] deaths, P = 0.01).

Infusion balance and catecholamine and red blood cell transfusions

The EGDT-GEDI group showed a trend of a lower mean 72-h infusion balance than the EGDT-CVP group (4,405 [1,092–8,163] versus 3,046 [830–6,806] mL, P = 0.34), but the difference was not statistically significant. No significant differences in mean (SD) maximum amounts of 3-day catecholamine and red blood cell transfusions were found between the two groups (Table 2).

Competing risk analysis for ventilator support duration

The competing risk analysis (Fig. 3) indicated that the ventilator support durations (median [interquartile range]) were 6.0 (4.6–8.5) and 5.2 (4.0–7.8) days in the EGDT-CVP and EGDT-GEDI groups, respectively. The cumulative incidence of ventilator-free period adjusted for the competing risk-of-mortality plot was not significantly different between the two groups (modified log-rank, P = 0.59). In the modified Cox proportional hazard models, the HR and 95% CI for the EGDT-GEDI versus EGDT-CVP group was 0.81 (0.57–1.17; P = 0.26).

DISCUSSION

WE INVESTIGATED AND compared the original EGDT-CVP and modified EGDT-GEDI data of

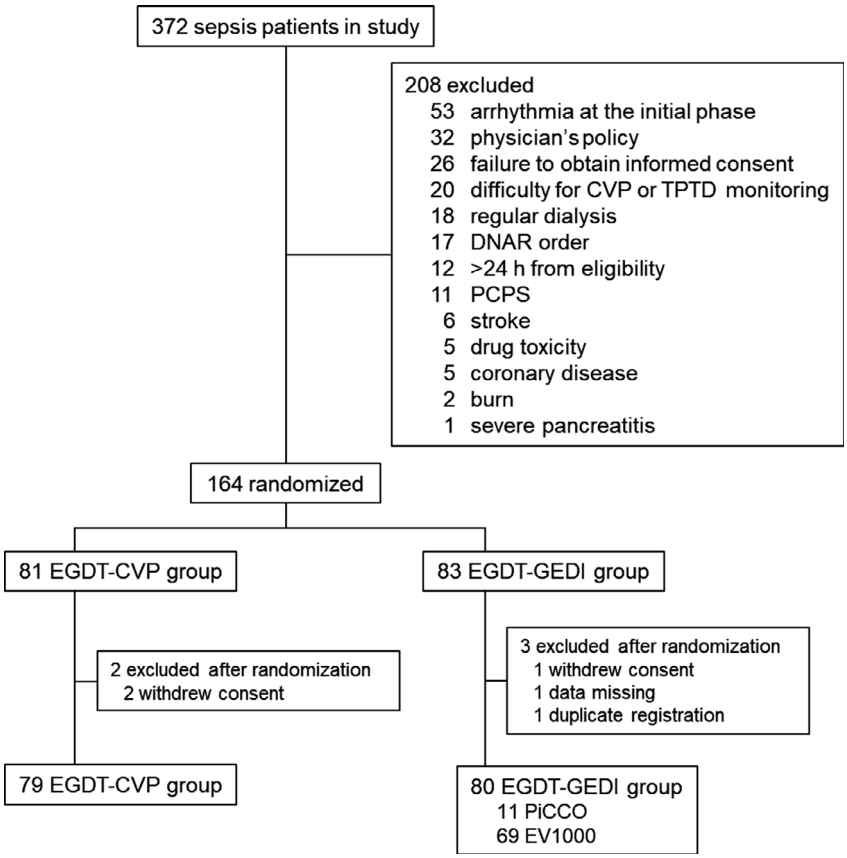

Fig. 2. Diagram of sepsis patients included in this study. CVP, central venous pressure; DNAR, do not attempt resuscitation; EGDT, early goal-directed therapy; GEDI, global end-diastolic volume index; PCPS, percutaneous cardio pulmonary support; TPTD, transpulmonary thermodilution.

patients with sepsis. The cumulative incidence of ventilator support adjusted for the competing risk-of-death plot was not significantly different between the two groups.

The EGDT-GEDI group had more deaths 48 h after the randomization process. Although no statistically significant differences in simplified acute physiology score (SAPS) II, SOFA score, or lactate level were found, more patients died within 48 h after initial measurement in the EGDT-GEDI group (EGDT-CVP group versus EGDT-GEDI group: 2 [2.5%] versus 12 [15%], $P = 0.01$). The lactate concentrations were similar between the EGDT-CVP and EGDT-GEDI groups at 24 h (2.37 [1.35–4.72] versus 2.13 [1.28–4.07], $P = 0.62$), 48 h (1.37 [0.90–2.73] versus 1.40 [0.98–2.05], $P = 0.89$), and 72 h (1.30 [0.84–1.98] versus 1.19 [0.79–1.70], $P = 0.40$). However, in the EGDT-GEDI group, the severity of eight patients with a SAPS II >80 points (maximum, 102 points) were high, and five patients, including one case of strangulated ileus that was not indicated for surgery, died before 4 h. In the EGDT-CVP group, the SAPS II scores of the two patients who died within 48 h after the initial measurement were 50–75 points. Extremely severe cases might be biased toward the EGDT-GEDI group, although central randomization was carried out. We assessed the heterogeneity of source control. There were 24 cases for which source control was not carried out before entering the ICU (16 cases in the EGDT-GEDI group, eight cases in the EGDT-CVP group, $P = 0.07$). Although there was no significant difference, twice as many cases with the possibility of insufficient source control were assigned to the EGDT-GEDI group, which might have caused the proportion of deaths within 48 h was higher in the EGDT-GEDI group. Hence, we evaluated and compared the subjects who survived for more than 48 h under both protocols. Although no significant difference in length of ICU stay was found, the value tended to be lower in the EGDT-GEDI group than in the EGDT-CVP group (5 days [3.7–9.0] versus 7 days [3.8–10.8], $P = 0.06$).

Table 1. Baseline characteristics of eligible patients with sepsis managed with standard early goal-directed therapy (EGDT) with central venous pressure (EGDT-CVP) or modified EGDT with global end-diastolic volume index (EGDT-GEDI)

Baseline	EGDT-CVP group (n = 79)	EGDT-GEDI group (n = 80)	P-value
Characteristic			
Age, years	72 (63–78)	74 (62–82)	0.32
Sex male, *n* (%)	42 (53)	56 (70)	0.03
SAPS II	54 (44–64)	54 (46–69)	0.17
SOFA score			
0 h	10 (8–12)	11 (9–13)	0.09
24 h	10 (7–13)	10 (7–13)	0.82
48 h	9 (5–13)	8 (6–11)	0.63
72 h	8 (5–12)	7 (5–10)	0.48
Lactate, mmol/L	2.37 (1.35–4.72)	2.13 (1.28–4.07)	0.62
Infection focus, *n* (%)			
Respiratory	28 (35)	24 (30)	0.81
Gastrointestinal	21 (27)	26 (32)	
Hepatobiliary	4 (5)	5 (6)	
Urinary tract	8 (10)	11 (14)	
Extremities	7 (9)	7 (9)	
Others	11 (14)	7 (9)	
Comorbidities, *n* (%)			
Chronic respiratory disease	5 (6)	3 (3)	0.70
Heart failure	5 (6)	11 (13)	0.19
Hepatic disease	2 (2)	3 (3)	0.98
Chronic renal disease	5 (6)	5 (6)	0.75
Diabetes	17 (21)	21 (26)	0.61
Cancer	7 (8)	11 (13)	0.46
Hemodynamic variables			
Systolic blood pressure, mmHg	100 (86–120)	99 (80–121)	0.93
Heart rate, b.p.m.	111 (91–126)	103 (89–119)	0.39
$ScvO_2$, %	73 (65–79)	70 (66–78)	0.61

Values are presented as median (interquartile range), unless otherwise indicated.
SAPS, simplified acute physiology score; $ScvO_2$, continuous central venous oxygen saturation; SOFA, sequential organ failure assessment.

Although the final protocol compliance rate was not different between two groups across the entire observation period (53 cases [67%] in the EGDT-CVP group, 53 cases [66%] in the EGDT-GEDI group, P = 0.95), the compliance of protocol regulations in the EGDT-CVP group was lower than that in the EGDT-GEDI group at 48 h in the acute phase (19% versus 43%, P = 0.01). Furthermore, we found the time interval of achievement to protocol goal tended to be longer in the GEDI-CVP group (12.0 [4.1–23.8] hours of the EGDT-CVP group versus 5.5 [2.0–21.7] hours of the EGDT-GEDI group; P = 0.14). These findings might be explained by the greater influence of "usual care" on the EGDT-CVP group than on the EGDT-GEDI group because the uncertainty of CVP and the risk of volume overload were reported in previous studies.[7–9] Studies that reported excessive volume overload appeared to be associated with an increased mortality.[14,15] Malbrain et al.[16] reported that a restrictive fluid management strategy resulted in a less positive cumulative fluid balance and was associated with a lower mortality rate than that in patients treated with an unrestricted fluid management strategy. These reports led ICU physicians to presume that CVP monitoring might be the cause of the excessive infusion.

Furthermore, as our study was not blinded, physicians could adjust the infusion volume and might intentionally change the extubation timing as well. Several studies reported that implementing the EGDT protocol was difficult.[17] Although one report found a high compliance of 52% at the 6-h point, this study did not contain the optimization of central venous oxygen saturation ($ScvO_2$).[18] Including

Table 2. Univariate analysis for comparing outcomes among sepsis patients managed with standard early goal-directed therapy (EGDT) with central venous pressure (EGDT-CVP) or modified EGDT with global end-diastolic volume index (EGDT-GEDI)

Analysis items	EGDT-CVP group (n = 79)	EGDT-GEDI group (n = 80)	P-value
Ventilator-free days for 28 days†	22 (19–25)	24 (22–25)	0.27
Outcomes at 28 days, *n* (%)			
Protocol withdrawal due to complications†	10 (12.7)	4 (5.0)	0.15
Mortality†	11 (13.9)	20 (25.0)	
Ventilator support continuation†	3 (3.8)	2 (2.5)	
Achievement of ventilator-free status†	55 (69.6)	54 (67.5)	
Ventilator duration, days†	5.1 (2.0–8.7)	3.9 (2.4–5.7)	0.27
Length of ICU stay, days†	7.2 (3.8–10.7)	5.1 (3.7–8.8)	0.05
Compliance of protocol regulation within 48 h, *n* (%)	15 (19)	34 (43)	0.01
Died within 48 h after hospitalization, *n* (%)	2 (2.5)	12 (15.0)	0.01
Time to protocol goal from first measurement, h	12.0 (4.1–23.8)	5.5 (2.0–21.7)	0.14
Volume balance, mL†			
Before the first measurement of CVP or GEDI	2,207 (1,064–3,720)	2,425 (1,234–2,988)	0.65
0–24 h	3,358 (1,836–5,478)	2,893 (1,366–4,190)	0.29
24–48 h	722 (−283 to 1,900)	604 (−424 to 1,624)	0.78
48–72 h	−111 (−1,055 to 1,145)	−161 (−1,237 to 936)	0.37
Total in 3 days	4,405 (1,092–8,163)	3,046 (830–6,806)	0.34
RBC transfusion, units‡			
0–24 h	1.46 (3.02)	1.25 (3.01)	0.68
24–48 h	0.23 (0.80)	0.38 (1.01)	0.33
48–72 h	0.17 (0.75)	0.24 (0.76)	0.61
Total in 3 days	1.86 (3.39)	1.79 (3.30)	0.91
Maximum dose of catecholamine, μg/min/kg‡			
Dopamine			
0–24 h	0.91 (2.70)	0.27 (1.25)	0.08
24–48 h	0.18 (0.98)	0.04 (0.30)	0.26
48–72 h	0.09 (0.71)	0.00	0.36
Total in 3 days	0.83 (2.59)	0.23 (1.14)	0.06
Dobutamine			
0–24 h	0.49 (1.77)	0.62 (1.69)	0.65
24–48 h	0.42 (1.78)	0.49 (1.26)	0.81
48–72 h	0.38 (1.59)	0.26 (0.93)	0.61
Total in 3 days	0.51 (1.77)	0.66 (1.70)	0.57
Noradrenaline			
0–24 h	0.30 (0.33)	0.24 (0.16)	0.16
24–48 h	0.18 (0.29)	0.12 (0.15)	0.16
48–72 h	0.07 (0.10)	0.05 (0.10)	0.25
Total in 3 days	0.28 (0.33)	0.22 (0.18)	0.10

Values are given as †median (interquartile range) or ‡mean (standard deviation), unless otherwise indicated.
ICU, intensive care unit; RBC, red blood cells.

$ScvO_2$, the most difficult item to reach in an EGDT protocol, might have led to the low protocol compliance in our study.

A recent trio trial that compared the effect of sepsis management between the EGDT and the commonly practiced "usual care" reported that blood transfusion to maintain the hematocrit level at >30% and dobutamine transfusion to maintain the central venous oxygen saturation at ≥70% were not associated with improved outcomes.[2,4,5] We included the blood and dobutamine transfusions in our protocol because the previous studies, namely ARISE,[2] ProMISe,[4] and ProCESS,[5] had not been reported when our study protocol was established in 2012. In this protocol, the blood and

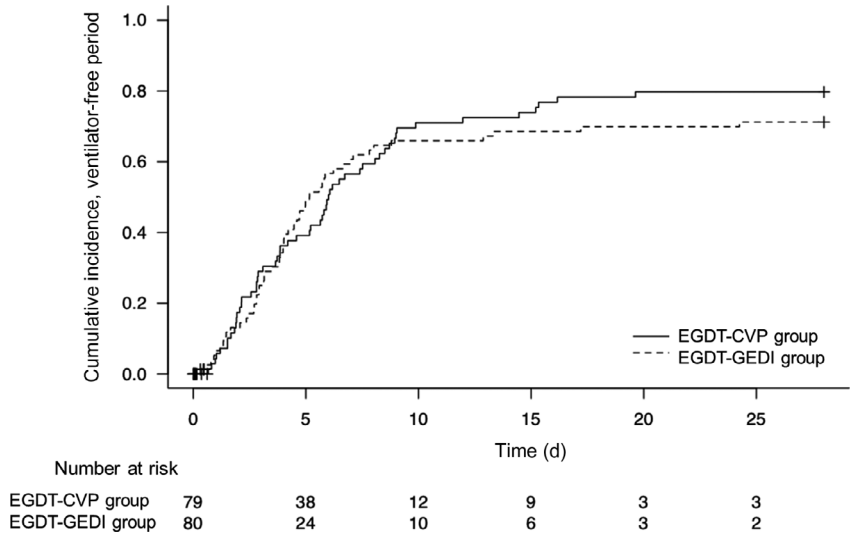

Fig. 3. Cumulative incidence rate of ventilator-free period among sepsis patients managed with standard early goal-directed therapy (EGDT) with central venous pressure (EGDT-CVP) or modified EGDT with global end-diastolic volume index (EGDT-GEDI). The cumulative incidence rate of ventilator-free period adjusted for the competing risk-of-mortality plot was not significantly different between the two groups (modified log-rank, $P = 0.59$). In the modified Cox proportional hazard models, the hazard ratio and 95% confidence interval for the EGDT-GEDI group compared with the EGDT-CVP group was 0.81 (0.57–1.17; $P = 0.26$).

dobutamine transfusions might have influenced our outcomes because we included the amount of transfusion to the amount of volume infusion. However, no significant difference was found in either group in the fluid quantities of the blood and dobutamine transfusions. Thus, we believed that the blood and dobutamine transfusions had less influence on the clinical outcomes.

We found that sufficient volume resuscitation was achieved before the ICU admission. There was no difference in infusion balance before the measurement of CVP or GEDI monitoring (2,207 [1,064–3,720] mL of the EGDT-CVP group versus 2,452 [1,234–2,988] mL of the EGDT-GEDI group, $P = 0.65$). This result might reflect the current standard practice of treatment being initiated in the emergency room and might influence our study comparing the quality of two devices to determine adequate infusion volume in the ICU.

We are cognizant that our study has several limitations. First, we collected only 164 cases despite the minimum of 198 cases being required to undertake a valid statistical evaluation. Thus, we could not rule out the possibility of a β error. In particular, the exclusion rate due to arrhythmia was high (53 cases [14.2%]); one of the reasons for the low recruitment rate of cases could be the high number of arrhythmia complications, defined as exclusion criteria. We judged that it was difficult to reach the target number even if the study period was further extended.

Second, various institutions of different sizes, ranging from university hospitals to community hospitals, participated in this study. The prognosis tended to improve with larger hospitals.[19] We classified facilities into two groups according to the official evaluation for emergency critical care, 3 large hospitals and 7 small hospitals, and reanalyzed these two groups. We found no significant differences in primary and secondary outcomes in the large hospitals. However, the EGDT-GEDI group showed a higher 28-day mortality rate than the EGDT-CVP group (5 cases [15.6%] of the EGDT-CVP group versus 16 cases [51.6%] of the EGDT-GEDI group, $P = 0.003$) among the small hospitals. The GEDI monitoring might not be suitable for use at small hospitals. Thus, the prognosis might fluctuate because our study did not adopt block randomization.

Finally, the EV1000 and PiCCO measure the cardiac output (CO) and the stroke volume variation (SVV) as a basic function and display them on-screen simultaneously with GEDI. Thus, the physicians could not be blinded to CO and SVV values. The clinicians could refer to the CO and SVV for clinical judgements if participants were classified into the EGDT-GEDI group. The participants classified in the EGDT-CVP group might lose the chance to receive the benefit of their clinicians referring to the CO and SVV.

CONCLUSIONS

ALTHOUGH THERE WAS no significant efficacy, EGDT guided by GEDI showed a trend of shorter length of ICU stay and lower 3-day infusion balance than the

EGDT-CVP group in sepsis. The GEDI monitoring did not appear to improve the ventilator-free days over a 28-day period. Global end-diastolic volume index should be monitored as a parameter for EGDT with awareness of these limitations.

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DISCLOSURE

Approval of the research protocol: This study was approved by the institutional research committees of all participating institutions.
Informed consent: Written informed consent to participate was obtained from the patients, their families, or their legally authorized proxies.
Registry and registration no.: The study was registered with the University Medical Information Network Clinical Trial Registry (UMIN-CTR ID000011493).
Animal studies: N/A.
Conflict of interest: YT was a member of the medical advisory board of Pulsion Medical Systems. The other authors declare no competing interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. eMethods 1, Inclusion and exclusion criteria. eMethods 2, Randomization. eMethods 3, Global end-diastolic volume index (GEDI) measurements. eMethods 4, Early goal-directed therapy (EGDT)-based protocols. eMethods 5, Extubation protocol. eMethods 6, Outcome measures. eMethods 7, Statistical analyses. eResults 1, Patients.