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ORIGINAL RESEARCH

A comparison of ventricular systolic function indices provided by VolumeView/EV1000™ and left ventricular ejection fraction by echocardiography among septic shock patients

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Abstract
The aim of this study was to compare the cardiac function index (CFI) and global ejection fraction (GEF) obtained by VolumeView/EV1000™, with the left ventricular ejection fraction (LVEF) by echocardiography in septic shock patients. A prospective observational study was conducted in a medical intensive care unit of a tertiary, teaching university hospital. Thirty-two, mechanical-ventilated septic shock patients were included in this study. We simultaneously measured CFI and GEF with LVEF. The correlation of CFI, GEF along with LVEF and ability of CFI and GEF to predict LVEF ≥ 40, 50 and 60% were evaluated. There were 192 pairs of CFI, GEF and LVEF. CFI was significantly correlated with GEF ($r = 0.82$, $P < 0.0001$). A significant correlation was observed between CFI and LVEF ($r = 0.56$, $P < 0.0001$) and GEF and LVEF ($r = 0.71$, $P < 0.0001$). The CFI and GEF had a good predictive ability for estimating LVEF ≥ 40, 50 and 60%, with an area under receiving operating characteristic (AUC) 0.875–0.934. The CFI ≥ 3/min predicted LVEF ≥ 40% with sensitivity 95.1% and specificity 48.3%. The GEF ≥ 15%, estimated LVEF ≥ 40% with sensitivity 92.6% and specificity 69%. There were 40 thermodilution and LVEF measurements obtained before and after norepinephrine adjustment. Blood pressure as well as the cardiac index were significantly increased, whereas there were no changes in CFI, GEF and LVEF values. Conclusions: Both CFI and GEF obtained by VolumeView/EV1000™, correlated with LVEF, so as to provide a reliable estimation of LV systolic function in septic shock patients.

Keywords Cardiac function index · Global ejection fraction · Hemodynamic monitoring · Transpulmonary thermodilution

1 Introduction

Hemodynamic monitoring is one essential part required for diagnosis and management of critically-ill patients [1, 2]. There are several methods for monitoring patients with acute circulatory failure, and the left ventricular (LV) systolic function is one of these essential parts of hemodynamic assessment for these patients [3, 4]. The left ventricular ejection fraction (LVEF) is a widely as well as easily, available estimate of the LV systolic function. For this estimation echocardiography is considered the gold standard, and is currently used for bedside imaging modality for the estimation of LVEF within the intensive care unit (ICU) [4, 5]. However, the use of echocardiography may be limited as it requires a trained operator [6], is time consuming, does not provide continuous monitoring and has a high interobserver variability [7, 8].

Transpulmonary thermodilution (TPTD) is semi-invasive, advanced monitoring that provides important

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hemodynamic parameters as a guide for managing critically-ill patients [2, 9, 10]. TPTD provides continuous measurements of cardiac output (CO), volumetric preload variables couple with dynamic fluid responsiveness. Moreover, TPTD presents parameters to assess LV systolic function as a cardiac function index (CFI) and global ejection fraction (GEF) [9, 10]. Recently, a new TPTD (VolumeView/EV1000™, Edwards Lifescience, Irvine, CA, USA) has been developed using a novel mathematical algorithm to derive global end-diastolic volume (GEDV) from a thermodilution curve [11]. The GEDV from VolumeView™ relies on the maximum up-slope (S1) and down-slope (S2) of the thermodilution curve and a proprietary function (f) [GEDV = CO × mean transit time (Mtt) × f (S1/S2)] [11, 12]. Previous study in critically-ill patients showed that CO, GEDV calculated by EV1000™ are interchangeable with the PiCCO™ method [12].

Several studies have also reported a good correlation between CFI and GEF measured by PiCCO™ and LV systolic function in different groups of critically-ill patients [13–15]. Furthermore, some studies showed that CFI and GEF could estimate LVEF and also track changes in LVEF induced by inotropic [14, 15]. Interestingly, the validity of systolic function indices obtained by VolumeView/EV1000™ has as of yet, to our knowledge, to be evaluated. Thus, the purpose of this study was to evaluate the accuracy of the CFI and GEF measured by the VolumeView/EV1000™ for estimation of the LVEF in septic shock patients.

2 Methods

A prospective study was conducted in a 10-bed medical ICU of a tertiary, university teaching hospital, at the Prince of Songkla University, Thailand from the 1st of June 2016 to the 30th of June 2017. The study was approved by the Institutional Ethics Committee (REC: 58-366-14-1, on 11 May 2016) and informed written consent was obtained from the next of kin of each patient. Mechanical ventilated septic shock patients with central venous (internal jugular or subclavian) catheters inserted were included in this study. Septic shock was defined by the criteria of Sepsis 3 definition [16]. The exclusion criteria were as follows: (1) Age < 18 years. (2) Poor acoustic window or absence of sufficient echogenicity. (3) Echocardiographic evidence of right ventricular failure (tricuspid annular plane systolic excursion (TAPSE) ≤ 15 mm, ratio of the right over the LV end-diastolic area ≥ 0.6) [14, 15]. (4) Severe valvular disease. (5) Cardiac arrhythmias (atrial fibrillation or frequent premature ventricular contraction).

2.1 Transpulmonary thermodilution and calculation of CFI and GEF

A 5-French 20 cm, thermistor-tipped catheter was placed into the femoral artery. Femoral artery catheter and central venous catheters were then connected to the VolumeView/EV1000™ system. Both cardiac index (CI) and volumetric parameters were measured via the thermodilution technique and obtained after injection of 15–20 mL of cold 0.9% NaCl, via the distal port of the central venous catheter, with subsequent detection by the thermistor embedded in the tip of the femoral catheter. The CI was calculated from the thermodilution curves according to the Stewart-Hamilton algorithm [12]. The mean values of three consecutive injections were recorded.

The VolumeView/EV1000™ system monitor automatically calculated the two cardiac systolic function indices (CFI and GEF).

CFI is the ratio between CO and GEDV (CFI = CO/GEDV, expressed in min^{-1}).

GEF is the ratio of the stroke volume (SV) to the quarter of the GEDV (GEF = SV/(GEDV/4), expressed as a percentage).

2.2 Echocardiography

A transthoracic echocardiography was performed with a Vivid-i (GE Healthcare). The examinations were performed by a single cardiologist (PC) and one critical care fellowship (NK). LVEF was obtained by the biplane Simpson's method. The echo-operators were blinded as to the hemodynamic parameters measurement obtained by the VolumeView/EV1000™.

2.3 Study protocol

The transpulmonary thermodilution parameters along with echocardiography were recorded simultaneously every 8 h, in the period without rate adjustment of norepinephrine or before and 10 min after an increase in the norepinephrine infusion. A total of 6 hemodynamic measurements per patient were evaluated during the study period. The decision to increase norepinephrine was based on the presence of clinical signs of acute circulatory failure (Such as; mean arterial pressure (MAP) < 65 mmHg, oliguria, tachycardia and mottled skin) without parameters of fluid responsiveness (stroke volume variation (SVV) < 10% or negative hemodynamic response to passive leg-raising test). All other treatments other than the norepinephrine dosage were kept unchanged during the study period.

Hemodynamic variables were simultaneously recorded including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, central venous pressure (CVP), CI, stroke volume index (SVI), systemic vascular resistance index (SVRI), SVV, global end-diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI), extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI).

The following data were recorded; age, sex, body weight, height, body surface area, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure assessment (SOFA) score, serum lactate level, ICU length of stay, site of infection, and use of vasoactive agents.

2.4 Statistical analysis

The Shapiro–Wilk test was used for estimating normal distribution, with the variables being expressed as; mean ± standard deviation, median and interquartile range, as appropriate. Categorical variables are expressed as percentages. The correlation between; CFI and GEF, CFI and LVEF, GEF and LVEF were assessed using the Pearson correlation coefficient. A receiver operating characteristics curve was constructed to study the ability of CFI and GEF to predict an LVEF ≥ 40, 50 and 60%. The sensitivity and specificity of CFI and GEF for predicting each level of LVEF were calculated. The best cutoff value was defined by the closet value to the Yoden index [17]. The area under the receiving operating characteristics (AUC) were compared using the Hanley and McNeil method [18]. The comparison of variables between, before and after norepinephrine adjustment was performed with use of pair-T test and Wilcoxon signed-rank test, as deemed appropriate. The correlation between the individual changes in LVEF with the individual changes in CFI and GEF after norepinephrine administration was established using the Pearson correlation coefficient. Inter-observer and intraobserver reliabilities of LVEF measurements were evaluated by intraclass correlations coefficient (ICC). The reproducibility of CFI and GEF was evaluated by calculating the coefficient of variation (standard deviation/mean ratio), within a subgroup of 15 patients. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the Stata version 7.0 (StataCorp, College Station TX, USA).

3 Results

A total of 32 mechanically ventilated septic shock patients were enrolled in our study. The demographic characteristics of the patients within this study are summarized in Table 1. Overall ICU mortality rates were 34.4%. About half of the patients, microrganisms were isolated from hemocultures.

Table 1 Patients clinical characteristic

Men, n (%)	17 (53.1)
Age (years)	58.6 ± 18.9
Body weight (kg)	58.4 ± 12.5
Height (cm)	161.4 ± 7.8
Body surface area (kg/m^2)	1.59 ± 0.18
APACHE II	22.7 ± 8.9
SOFA	10.1 ± 3.4
Lactate (mmol/L)	5.6 ± 5.9
ICU length of stay	6.5 (4–14.5)
Community acquired infection, n (%)	15 (46.9)
Site of infection, n (%)	
Respiratory tract infection	17 (53.1)
Digestive system	7 (21.9)
Urinary tract infection	3 (9.4)
Others*	5 (15.6)
Norepinephrine (ug/kg/min)	0.34 ± 0.25

APACHE acute physiology and chronic health evaluation, *ICU* intensive care unit, *SOFA* sequential organ failure assessment

*Others, skin and soft tissue (2), primary bacteremia (2), surgical site (1)

The most common organisms were *Klebsiella* spp. (25.9%) followed by *Escherichia coli* (18.5%), and *Acinetobacter baumannii* (18.5%). All septic patients required norepinephrine administration, while other vasoactive agents such as; epinephrine (n = 2, 0.2 ± 0.2 µg/kg/min), dopamine (n = 2, 6 ± 2.8 µg/kg/min) and dobutamine (n = 2, 5 µg/kg/min) were administered to some patients.

There were 192 pairs of systolic function indices by VolumeView/EV1000™ and LVEF. The hemodynamic parameters at baseline are shown in Table 2. A significant correlation was observed between CFI and LVEF ($r = 0.56$, $P < 0.0001$) (Fig. 1), as well as GEF and LVEF ($r = 0.71$, $P < 0.0001$) (Fig. 2). The CFI was significantly correlated with GEF ($r = 0.82$, $P < 0.0001$) (Supplement Fig. S1). The CFI and GEF provided a good predictive ability for estimating LVEF. The AUC, sensitivity and specificity of CFI and GEF for predicting at different LVEF (≥ 40, 50 and 60%) are presented in Table 3. The comparison of the ROC curves showed that CFI and GEF predicted LVEF similarly (Fig. 3 and Supplement Fig. S2, S3).

There were 40 thermodilution (24 patients) and LVEF measurements were obtained, both before and after, an increase in norepinephrine infusion. Hemodynamic parameters such as: SBP, DBP, MAP and CI were significantly increased after increasing the norepinephrine dosage, in contrast to SVV being decreased significantly (Table 4 and Supplement Fig. S4, S5). However, the CFI, GEF and LVEF were not different on average after an increase in the norepinephrine level (Table 4 and Supplement Fig. S6–S8). There was neither a correlation between the individual changes in

Table 2 Baseline hemodynamic parameters

HR (/min)	101.4 ± 17.1
SBP (mmHg)	126.1 ± 20.9
DBP (mmHg)	62.8 ± 11.5
MAP (mmHg)	82.8 ± 12.2
CVP (mmHg)	14.0 ± 3.9
SVI (mL/min/m^2)	34.8 ± 10.9
CI (L/min/m^2)	3.3 (2.4–4.2)
SVRI (dyne-s-m^2/cm^5)	1,721.6 ± 620.7
SVV (%)	9 (6–11)
GEDVI (mL/m^2)	702.5 (557–761.5)
ITBVI (mL/m^2)	861.5 (668–941.5)
EVLWI (mL/kg)	9.6 (7.8–12.4)
PVPI	2.3 (1.6–3.1)
LVEF (%)	54.4 ± 16.8
CFI (/min)	5.4 ± 2.3
GEF (%)	21.3 ± 7.3

CFI cardiac function index, *CI* cardiac index, *CVP* central venous pressure, *DBP* diastolic blood pressure, *EVLWI* extravascular lung water index, *GEDVI* global end-diastolic volume index, *GEF* global ejection function, *HR* heart rate, *ITBVI* intrathoracic blood volume index, *LVEF* left ventricular ejection fraction, *MAP* mean arterial pressure, *PVPI* pulmonary vascular permeability index, *SBP* systolic blood pressure, *SVI* stroke volume index, *SVRI* systemic vascular resistance index, *SVV* stroke volume variation

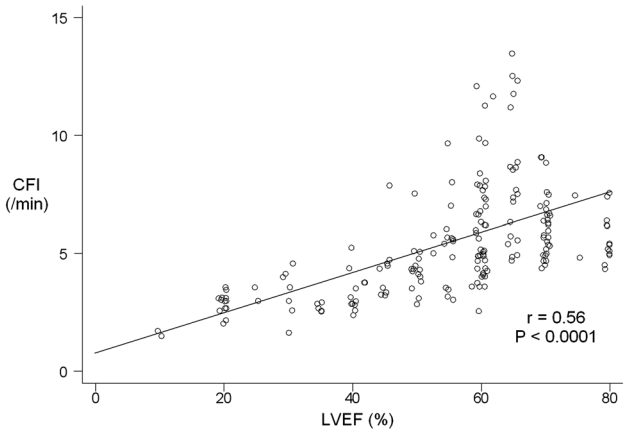

Fig. 1 Correlation between cardiac function index (CFI) and left ventricular ejection fraction (LVEF) (n = 192). Back line: linear regression line

CFI and GEF, nor with the individual changes in LVEF after adjustment of the norepinephrine dosage (r = 0.34, P = 0.08 and r = 0.4 P = 0.06, respectively, Supplement Fig. S9, S10).

We evaluated interobserver couple with intraobserver reliabilties in the measurement of LVEF in 15 cases (82 LVEF data). The ICC for intraobserver reliability of PC and NK were 0.981 (95% CI 0.964–0.998, P < 0.0001) and 0.974 (95% CI 0.955–0.991, P < 0.0001), respectively. The ICC for interobserver reliability among 2 operators was 0.954

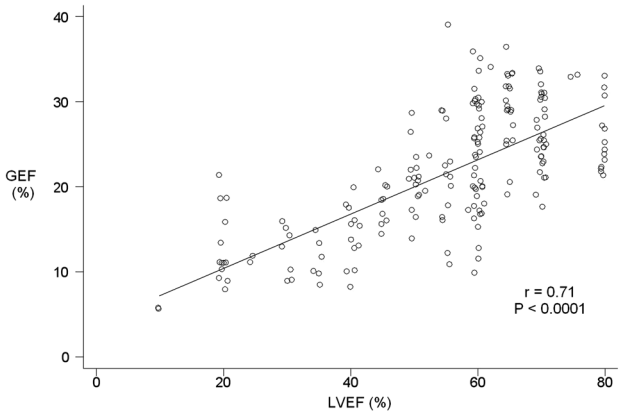

Fig. 2 Correlation between global ejection fraction (GEF) and left ventricular ejection fraction (LVEF) (n = 192). Back line: linear regression line

(95% CI 0.931–0.987, P < 0.0001). The reproducibility for the measurements of CFI and GEF were 1.2 ± 0.2% and 1.3 ± 0.2%, respectively.

4 Discussion

Our study shows that CFI and GEF, obtained by a new TPTD (VolumeView/EV1000™), is a reliable estimation of LVEF. Moreover, we established that both CFI and GEF had a statistical correlation with LVEF, nor was there any alteration with vasopressors infusion in septic shock patients.

Our results are also consistent with previous studies regarding the validity of CFI and GEF measured by TPTD being able to estimate LV systolic function in critically-ill patients. Combes et al. reported that CFI and GEF were correlated with left ventricular fractional area of change (LVFAC) (r = 0.87, P < 0.0001) [13]. Jabot and colleague showed that CFI and GEF correlated with LVEF measurements (r = 0.67, P < 0.001 for both) in ICU patient with acute circulatory failure [14]. In cardiologic shock patients, Perny et al. demonstrated that CFI and GEF were correlated with LVEF as assessed by echocardiography (r = 0.52, P < 0.0001 for both) [15].

The results of our study confirmed that both CFI and GEF could estimate LV systolic function, which coincides with previous study showed that; CFI > 4/min and GEF > 18% predicted LVFAC ≥ 40% [13]. Furthermore, CFI≤3.2 / min and GEF≤12% allowed diagnosing an LVEF < 35%, in patients with acute circulatory failure [14]. Similarly, a low CFI is a good determiner for detecting low LVEF for cardiogenic shock [15] as well as subarachnoid hemorrhage patients [19].

CFI is the ratio between CO and GEDV, however the GEDV refers to the volume of the four chambers within the

Table 3 The area under the receiving operating characteristic (AUC), sensitivity and specificity of CFI and GEF for predicting left ventricular ejection fraction

	n	AUC (95% CI)	Cardiac function index (CFI)			AUC	Global ejection fraction (GEF)			P value
			Cut-point	Sensitivity (%)	Specificity (%)		Cut-point	Sensitivity (%)	Specificity (%)	
≥ 40%	163	0.926 (0.887–0.966)	3.0	95.1	48.3	0.934 (0.895–0.973)	14	92.6	69.0	0.69
≥ 50%	142	0.924 (0.879–0.968)	3.5	94.4	70	0.938 (0.906–0.970)	18	90.2	80	0.43
≥ 60%	107	0.875 (0.824–0.925)	4.5	87.8	71.8	0.887 (0.839–0.935)	22	79.4	85.9	0.45

CI confidence interval, *CFI* cardiac function index, *GEF* global ejection function

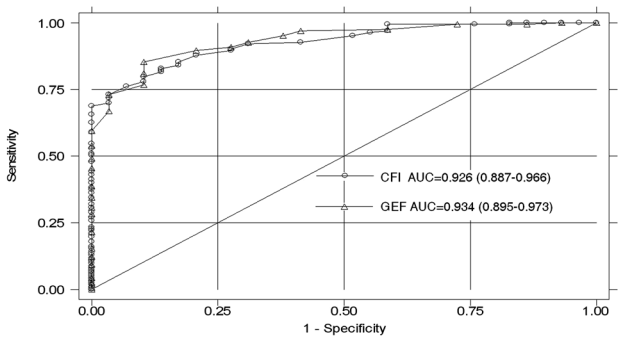

Fig. 3 Receiving operating characteristic curves comparing the ability of CFI and GEF to predict left ventricular ejection fraction ≥ 40%

heart, not only for the left ventricle. In the case of right ventricular dilatation, the GEDV is increased, whereas CFI and GEF are decreased, although the LV contractility is unchanged. Therefore, in this situation it may underestimate CFI, GEF and consequently LVEF. Previous studies demonstrated that a lower correlation of CFI and LVEF has lead to some false-negatives for estimating LV systolic function in patients with right ventricular dilatation [13–15]. GEF is defined as the ratio of the SV to the quarter of the GEDV. Thus, when compared with CFI, the advantage of the calculated GEF, does not take into account the heart rate. However, the present study showed similar results as previous works in that; GEF was not a statistically significant prediction of LVEF, more than that of CFI [13, 14]. Nevertheless, heart rate did not significantly change during our study period, in so saying further studies should be undertaken to evaluate the ability of GEF over CFI when the heart rate is remarkable altered.

Typically, hemodynamic response to sepsis presents with a hyperdynamic state, with an increase in CO and a decrease of SVR. However, sepsis-induced cardiac dysfunction may occur during the early stage of sepsis [20, 21]. Cardiac dysfunction had an impact to worsen the clinical outcome in sepsis patients [22–25]. Previous echocardiographic studies in sepsis-induced cardiac dysfunction patients found a decrease ejection fraction and bi-ventricular dysfunction [21, 26, 27]. LV systolic dysfunction occurs in 27–60% of sepsis patients [21, 27, 28] and is associated with increased mortality [22–25]. Hence, assessment of LV systolic function is important for hemodynamic management in septic shock patients. Cardiac function indices, obtained by VolumeView/EV1000™, provide an alternative to echocardiography in the assessment of LV systolic function. TPTD monitor should not replace echocardiograpahy, however, it is a simple, easily reproducible technique and does provide continuous monitoring. A low CFI or GEF value should be considered as an alarm of a poor global cardiac performance and

Table 4 Hemodynamic parameters before and after norepinephrine adjustment

	Before	After	P value
Heart rate (/min)	97.4 ± 21.9	100.2 ± 18.6	0.24
Systolic blood pressure (mmHg)	108.1 ± 11.4	132.5 ± 22.6	< 0.0001
Diastolic blood pressure (mmHg)	58.4 ± 6.7	69.3 ± 10.8	< 0.0001
MAP (mmHg)	75.1 ± 7.1	92.2 ± 13.3	< 0.0001
CVP (mmHg)	15.5 (12.5–19)	14 (12–16)	0.23
Cardiac index (L/min/m^2)	3.3 ± 1.0	3.7 ± 1.2	< 0.0001
SVI (L/min/m^2)	35.6 ± 11.3	38.6 ± 12.7	0.007
SVRI (dyne-s-m^2/cm^2)	1560.2 ± 564.3	1822.2 ± 701.1	< 0.0001
SVV (%)	11.1 ± 4.7	9.6 ± 4.0	0.01
GEDV (mL)	661.6 ± 135.9	709.9 ± 141.3	0.08
ITBVI (mL/m^2)	802.9 ± 172.8	892.8 ± 200.1	< 0.0001
EVLW (mL/kg)	9 (7.5–12.4)	9.2 (8.0–12.0)	0.87
PVPI	2.1 (1.7–2.9)	1.7 (1.5–2.8)	0.10
CFI (/min)	5.3 ± 2.0	5.4 ± 2.0	0.53
GEF (%)	22.2 ± 6.3	22.2 ± 6.8	0.91
Norepinephrine(ug/kg/min)	0.07 (0.02–0.16)	0.18 (0.11–0.37)	< 0.0001
LVEF (%)	57.3 ± 12.8	57.3 ± 12.8	0.20

CFI cardiac function index, *CI* cardiac index, *CVP* central venous pressure, *DBP* diastolic blood pressure, *EVLWI* extravascular lung water index, *GEDVI* global end-diastolic volume index, *GEF* global ejection function, *HR* heart rate, *ITBVI* intrathoracic blood volume index, *LVEF* left ventricular ejection fraction, *MAP* mean arterial pressure, *PVPI* pulmonary vascular permeability index, *SBP* systolic blood pressure, *SVI* stroke volume index, *SVRI* systemic vascular resistance index, *SVV* stroke volume variation

Indication for norepinephrine dose adjustment: oliguria (n = 16), MAP < 65 mmHg (n = 10), tachycardia (> 110 bpm) (n = 10), and mottled skin (n = 4)

such a value forces one to perform an echocardiography, so to discriminate between right and left ventricular dysfunction. Moreover, CFI and GEF might track changes of LVEF during inotropic administration. Previous studies have revealed that the CFI and GEF were able to track changes in LVEF by dobutamine infusion [14, 15], but not by volume administration [15]. Our study presented that CFI and GEF were not significantly changed after norepinephrine infusion, which is consistent with LVEF. Therefore, CFI and GEF should be used to monitor systolic function during hemodynamic management of critically-ill patients.

There were some limitations of this study. First, we evaluated ventricular systolic function only in septic shock patients, and so accordingly, our results may be limited in the application for other critically-ill patients, suffering from other types of shock. Second, the majority of sepsis patients in our study had preserved LV systolic function, therefore, the validity of CFI and GEF response to inotropic agents should not be evaluated. Third, we used only LVEF to assess LV systolic function. The LVEF is not only dependent on LV contractility, but also LV afterload. Speckle tracking echocardiography identifies systolic dysfunction with more sensitivity than conventional echocardiography [29, 30]. Dalla et al. showed that strain echocardiography may be a useful tool for early detection of myocardial dysfunction in sepsis patients [29]. Further studies should therefore be undertaken for the evaluation of cardiac function indices by TPTD with advance systolic function assessment methods.

5 Conclusion

The Volumeview/EV1000™ derived cardiac function indices (CFI and GEF) gives a reliable estimate of the LVEF in mechanically ventilated septic shock patients. Alteration of CFI or GEF might be considered when performing an echocardiography, so as to evaluate ventricular dysfunction in critically-ill patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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