Hirosaki Med. J. 72 : 6—14, 2022

ORIGINAL ARTICLE

Changes in the Initial Distribution Volume of Glucose in Endotoxin-induced Septic Pig Models

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Abstract

Initial distribution volume of glucose (IDVG) has been demonstrated to reflect central extracellular fluid (ECF) volume and can be used as an indicator of cardiac preload. However, it is unknown whether IDVG reflects the cardiac preload in septic patients. This study aimed to investigate the changes in IDVG in endotoxin (ET)-induced septic pig models.

METHODS: We anesthetized 13pigs and sepsis was induced with intravenous ET. Five pigs were used to investigate changes in IDVG, 3pigs were used as controls and 5pigs underwent fluid resuscitation with Ringer's lactate solutions after ET. IDVG was measured with 2g glucose and calculated with one compartment model. IDVG, CO, intrathoracic blood volume (ITBV), and other parameters were measured after ET. The statistical analysis was performed with RM-ANOVA, followed by Dunnett's test or the Newman-Keuls test. $P<0.05$ was considered significant.

RESULTS: CO and systolic BP significantly decreased and lactate levels significantly increased 4h after ET. IDVG and ITBV significantly decreased but central venous pressure did not change 4h after ET. IDVG and CO were significantly increased with volume loading, but the effects disappeared after 1h.

CONCLUSIONS: IDVG reflected the changes in the central ECF volumes and can be an indicator of cardiac preload in septic states.

Hirosaki Med. J. 72 : 6—14, 2022

Key words: Initial distribution volume of glucose; Cardiac preload; fluid volume monitoring.

Introduction

Sepsis and septic shock are medical emergencies, and immediate resuscitation with fluids is recommended by the 2016 surviving sepsis campaign guidelines[1)]. At least 30 ml/kg of intravenous crystalloid fluid should be given within the first 3 h[1)]. However, excess fluid can have harmful effects on multiple organ systems, particularly in conditions of increased capillary permeability such as sepsis[2)]. Even positive fluid balance has been associated with worse outcomes in patients with sepsis[3,4)] and who underwent surgery[5)]. It has also been demonstrated in a retrospective study that the multimodal restrictive fluid strategy, which aims for a negative fluid balance in patients with acute lung injury, is associated with improved outcomes[6)]. Adequate assessments of the fluid volume status, indicating the cardiac preload, is important in critically ill patients, and it may lead to a decrease in mortality and morbidity in septic patients.

The Initial distribution volume of glucose (IDVG) has been reported to be a useful indicator of the central extracellular fluid (ECF)[7,8)] independent of the effect of insulin[8,9)] and is well correlated with the cardiac output (CO) in animals with fluids volume removal and loading[10,11)] and in critically-ill patients without heart failure[12)]. In esophageal cancer surgery, IDVG showed refilling

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Correspondence: T. Suganuma
Received for publication, June 29, 2021
Accepted for publication, July 27, 2021

of ECF and correlated with CO better than the plasma volume or blood volume[13]. IDVG was also demonstrated to predict hypovolemic hypotension early after abdominal aortic surgery[14]. Moreover, IDVG had an inverse correlation with pulse pressure variation and the Pleth Variability Index[15,16]. We recently demonstrated that IDVG could be measured relatively independent of cardiac function, indicating the usefulness of IDVG even in states of high and low CO[17].

However, glucose is used as an indicator of IDVG measurement, and it distributes not only into intravascular spaces, but also into interstitial spaces. Sepsis induces distributive shock due to the increased vascular permeability and vasodilation. In such a septic state the distributive nature of glucose is considered beneficial to measure central ECF volume, and the ratio of plasma volume to IDVG has been reported to indicate the vascular permeability in burn patients[18] and in septic dog models[19]. However, no study has investigated the effects of septic state on IDVG itself. Therefore, the aim of this study was to investigate the changes in IDVG in response to the endotoxin (ET)-induced septic state in piglets.

Material and Methods

1) Experimental Preparations

This study was conducted after obtaining approval from our institutional animal experiment committee (No. M130111). Thirteen piglets were used in this study. The piglets were anesthetized with intramuscular injection of ketamine (1500 mg) and kept with a continuous infusion of pentobarbital (100-200 mg/hr), remifentanyl (0.1-0.2 μg/kg/min), and vecuronium bromide (2-4 mg/hr). Tracheotomy was performed, and the lung was mechanically ventilated using an intermittent mandatory ventilation mode (fraction of inspiratory oxygen = 0.5, target tidal volume = 8 ml/kg, Respiratory rate = 20~30 b.p.m.) to maintain $PaCO_2$ at approximately 40 mmHg. The right femoral artery was cannulated with a 20G PiCCO indwelling catheter (pulsion Medical Sysytem®, Feldkirchen, Germany) for blood sampling and continuous monitoring of blood pressures, CO, pulse pressure variation (PPV), stroke volume variation (SVV), and intrathoracic blood volume (ITBV). The right external jugular vein was also cannulated with a 6Fr double lumen catheter (Blood access, Nipro, Osaka, Japan) to administer fluids and measure the central venous pressure (CVP). Hemodynamic and the other parameters were measured with transpulmonary themodilutional methods using PiCCO® system (pulsion Medical Sysytem®, Feldkirchen, Germany). Lactic Ringer solution (Hartmann's solution, Nipro, Osaka, Japan) was infused at the rate of 4 ml kg^{-1} hr^{-1} as maintenance fluid infusion. Urine output was measured using a bladder catheterization by a direct puncture method.

2) Experimental protocol

Following the experimental preparations, septic state was induced with an ET (15~50 μg/kg, lipopolysaccharide from E coli, SIGMA ALDORICH, St Louis, USA) infusion over 30~60 min to obtain the 30% decrease in systolic blood pressure and 30% increase in heart rate, compared with the baseline values. The total amount of ET and duration of the administration were changed due to the different degrees of response to the ET. When the systolic blood pressure decreased to less than 80 mmHg, dobutamine (1~3 μg/kg/min) was continuously infused to maintain hemodynamics. Dobutamine was used because it was demonstrated not to affect IDVG measurements in our previous study[17], and noradrenaline was not used because it has been shown to improve venous return in endotoxic conditions[20]. Five pigs weighing

14.5~26.3 kg were allocated to investigate chronological changes in IDVG following ET injection (ET group), and three pigs weighing 11.5~15.3 kg were allocated to the control group (C group), where same amount of saline solution without ET was administered to investigate the stability of the basic fluid volume status. The other five pigs were allocated to the group undergoing fluid resuscitation with 30 ml/kg Ringer's lactate solutions over 60 min, 4 h after ET injection (RL group). The fluid resuscitation timing of 4 h following the ET injection in the RL group was decided after obtaining the result of the sepsis group.

3) Experimental measurements

IDVG was measured with a 2 g glucose injection (4 ml of 50% glucose) through the external jugular vein, based on the one-compartment model as described in a previous report[8]. Blood samples were taken to measure plasma levels of glucose immediately before and at 3, 4, 5, and 7 minutes after the injection. Each blood sample volume was 2 ml, and approximately the same volume of physiological saline was injected through the direct arterial pressure line for the compensation. Plasma glucose levels were measured using the glucose oxidase method (glucose analyzer GA-1151; ARKRAY, Kyoto, Japan). Each blood sample was measured twice and averaged. In the one-compartment model, the distribution volume (Vd) is calculated as follows:

$$Vd = Dose/C_0,$$

where Dose is the amount of drug administered and C_0 is the initial plasma concentration at time zero of instantaneous distribution, but before the start of elimination. Akaike's Information Criterion (AIC) was calculated to evaluate the exponential term of the pharmacokinetic model[21].

$$AIC = -2\log(L1) + 2np,$$

where L1 is the maximum likelihood and np is the number of parameters. Convergence was assumed when AIC was less than -10.

CO, ITBV, and SVV were measured by a bolus injection of 5 ml chilled saline, based on a transpulmonary thermodilution method using PiCCO®. An average of the triplicate measurement values was established.

IDVG and the following parameters were measured before and 1, 2, 4, and 5 h after ET or saline injections for the ET and C groups, respectively, and before and 4, 5, 6, 7, and 8 h after ET injection for the RL group.

The hemodynamic parameters of blood pressure (Bp), heart rate (HR), CO, and one of the cardiac filling pressures of CVP, volumetric parameters of ITBV and IDVG, and dynamic preload indicators of PPV and SVV were measured. Fluid volume loading was performed with 30 ml/kg Ringer's lactate solutions over 60 min between 4 and 5 h after ET injection in the RL group. All blood samples were stored in ice until the glucose measurements were completed.

4) Statistical analysis

Data are expressed as mean ± SD or SEM. Statistical analysis was performed using one-way repeated measures analysis of variance followed by Dunnett's test or the Newman-Keuls multiple comparison test to compare the variables at baseline and for each value. P values less than 0.05 were considered as significant.

Results

Chronological changes in hemodynamics and other parameters in both the sepsis and control groups are shown in table 1. CO and systolic BP

Table 1. Chronological changes in hemodynamic data and other parameters of cardiac preload with or without endotoxin injection

Time (hr)		Baseline	1	2	4	5
CO(L/min)	Control	2.18±0.44	2.24±0.58	2.32±0.48	2.11±0.39	2.06±0.31
	Sepsis	1.67±0.28	1.61±0.31	1.22±0.14＊	0.95±0.39＊	0.84±0.22＊
sBp (mmHg)	Control	125.3±9.8	125.7±7.1	118.0±6.1	110.7±15.4	103.0±10.0
	Sepsis	121.8±12.3	100.0±7.9＊	77.4±21＊	68.8±9.0＊	71.6±9.6＊
HR(bpm)	Control	81.3±4.5	80.0±5.3	87.3±18.1	8.37±10.0	86.3±17.2
	Sepsis	119.6±50.9	157.2±25.5	155.2±39.6	166.4±38.1	159.8±41.1
CVP(mmHg)	Control	7.3±0.6	7.3±1.2	7.0±1.0	6.7±1.5	6.0±1.7
	Sepsis	6.2±0.4	6.6±0.9	6.6±1.5	6.8±2.0	7±2.3
Lactate (mmol/L)	Control	1.1±0.1	1.0±0.1	0.9±0.1	0.8±0.1	0.7±0.2
	Sepsis	0.9±0.3	1.4±0.5	1.7±0.7	1.7±0.8＊	1.9±0.6＊
IDVG/BW(ml/kg)	Control	121.5±32.2	122.0±28.8	123.0±31.7	119.2±35.9	124.1±36.1
	Sepsis	134.9±15.9	119.3±20.1＊	136.4±20.0	120.9±10.6＊	114.2±13.8＊
ITBV (ml)	Control	382.7±103.7	387.0±116.4	384.7±122.4	353.0±93.7	345.7±81.6
	Sepsis	209.2±78.4	201.7±88.4	175.7±20.0＊	158.2±87.9＊	150.1±77.5＊
SVV(%)	Control	7.7±0.6	9.3±1.2	9.0±1.7	7.7±0.6	8.0±2.0
	Sepsis	11.8±4.7	14.0±8.3	18.0±8.8	20.8±10.4＊	21.8±10.1＊
PPV(%)	Control	7.0±0.0	8.0±2.0	8.3±1.2	7.7±0.6	8.0±3.0
	Sepsis	11.5±2.7	14.5±5.8	23.5±13.4＊	28.3±10.7＊＊	27.8±10.4＊＊
Hb(g/dl)	Control	9.7±0.8	9.4±0.5	9.3±0.6	9.5±0.9	9.1±0.7
	Sepsis	9.8±0.8	11.1±1.2＊	10.8±1.0＊	12.0±0.8＊	12.0±1.0＊

IDVG/BW; initial distribution volume of glucose/body weight), ITBV; intrathoracic blood volume), SVV; Stroke volume variation, PPV; pulse pressure variation. Data were expressed as Mean±SD, Sepsis group (n=5, SVV&PPV; n=4 due to the missing data), Control group (n=3).
*P<0.05 vs. Baseline values, ** P<0.01 vs. baseline values.

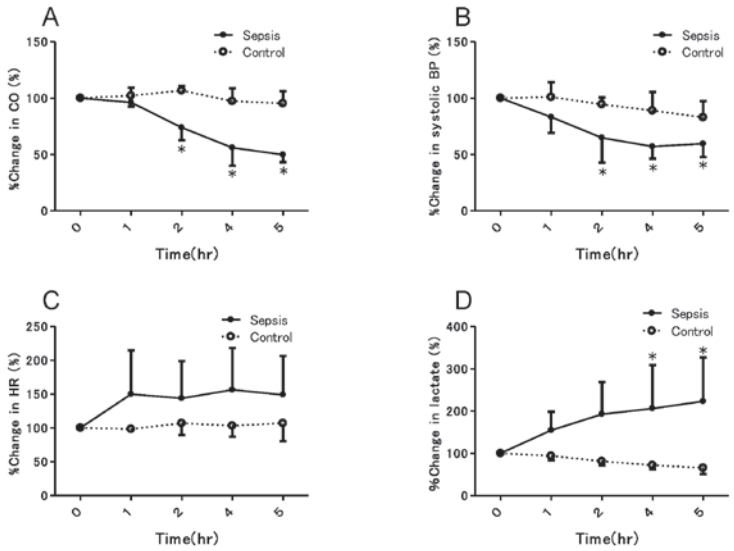

Figure 1 Percentage Changes in Hemodynamic Parameters and Lactate levels in the Endotoxin-induced Septic Model of Piglets

A: Percentage changes in CO (cardiac output), B: Percentage changes in sBp (systolic blood pressure), C: Percentage changes in HR (heart rate), D: Percentage Changes in Lactate. Data are expressed as Mean ± SEM, Sepsis group (n=5), Control group (n=3). *P<0.05 vs. baseline values.

significantly decreased while lactate levels significantly increased 4 h after ET administration as compared with the baseline values. It suggested that septic states in the piglets resulted from ET infusion (Table 1 and Figure 1). A volumetric parameter of cardiac preload, ITBV, significantly decreased and dynamic indicators of cardiac preload, SVV and PPV, significantly increased 4 h after ET administration as compared with the baseline values, but CVP did not show significant changes. IDVG index (IDVG/Kg) significantly decreased immediately after ET administration, then it was recovered at 2 h after ET, and decreased again 4 and 5 h

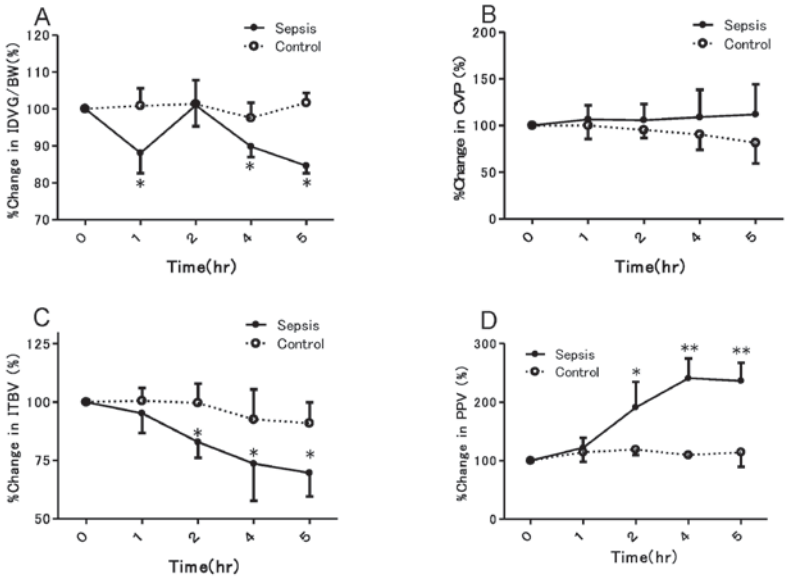

Figure 2 Percentage Changes in the Parameters Related to the Cardiac Preload in Endotoxin-induced Septic Model of Piglets

A: Percentage changes in IDVG/BW (initial distribution volume of glucose/body weight), B: Percentage changes in CVP (central venous pressure), C: Percentage changes in ITBV (intrathoracic blood volume), D: Percentage changes in PPV (pulse pressure variation). Data are expressed as Mean ± SEM, Sepsis group (n=5, PPV; n=4 due to the missing data), Control group (n=3). *P<0.05 vs. baseline values, ** P<0.01 vs. baseline values.

Table 2. Effects of Volume Loading at 4 hours after Endotoxin Injection on The Hemodynamics and Other Parameters Related to Cardiac Preload

Time (hr)	Baseline	4	5	6	7	8
CO(L/min)	2.6±0.3	1.3±0.3**	1.6±0.3**##	1.4±0.3**	1.4±0.3**	1.3±0.3**
sBp (mmHg)	130.8±7.6	79.0±13.0**	91.8±6.1**	90.2±13.0**	86.2±8.8**	82.4±4.3**
HR(bpm)	81.2±5.7	168.0±34.2**	133.6±11.9+**##	120.4±15.1**##	114.2±20.7*##	110.2±22.4*##
CVP(mmHg)	8.0±1.0	8.0±2.9	9.6±2.1	9.4±2.2	9.0±3.0	9.2±3.1
IDVG/BW(ml/kg)	116.9±9.4	107.8±6.8*	118.8±6.5##	100.8±4.9**	96.2±6.3**#	99.4±4.7**
ITBV (ml)	384.4±69.4	257.2±82.0**	302.8±62.8**#	314.8±80.4**##	306.6±72.2**#	279.4±33.9**
SVV(%)	4.8±1.0	11.5±3.7**	8.8±1.5	8.8±2.2	7.5±2.4	8.5±3.1
PPV(%)	5.5±1.7	18.0±7.4**	11.3±3.6#	12.8±4.9*#	9.8±3.6##	10.5±4.8#

Endotoxin was administered just after the baseline measurement. Ringer's lactate solution was transfused between 4 hours and 5 hours. IDVG/BW; initial distribution volume of glucose/body weight), ITBV; intrathoracic blood volume), SVV; Stroke volume variation, PPV; pulse pressure variation. Data were expressed as Mean±SD, Sepsis group (n=5, SVV&PPV; n=4 due to the missing data). *P<0.05 vs. Baseline values, ** P<0.01 vs. baseline values. #P<0.05 vs. Data at 4 hour after endotoxin injection. ##P<0.01 vs. Data at 4 hour after endotoxin injection.

after ET, compared with the baseline value (Table 1 and Figure 2).

The effects of volume resuscitation with Ringer's lactate solutions on the hemodynamics and other parameters related to cardiac preload are shown in table 2. CO, IDVG index, and ITBV significantly increased, while HR and PPV significantly decreased, after volume loading as compared with the values 4 h after ET injection (Table 2 and Figure 3). The effects of volume loading on CO and IDVG index disappeared 1 h after volume loading as compared with the values 4 h after ET injection, but the effects for ITBV, HR, and PPV continued for several hours (Table 2 and Figure 3) after volume loading. CVP did not show any significant changes in response to volume loading (Table 2).

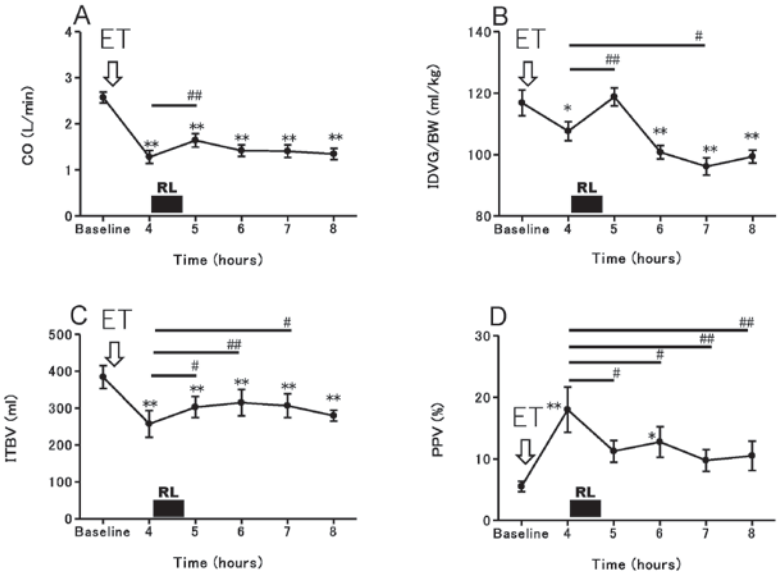

Figure 3 Effects of Volume Loading on CO and Other Parameters of Cardiac Preload in the Endotoxin-induced Septic Model of Piglets

A: Changes in CO (Cardiac Output), B: Changes in IDVG/BW (initial distribution volume of glucose/body weight), C: Changes in ITBV (intrathoracic blood volume), D: Changes in PPV (pulse pressure variation). ET: endotoxin infusion, RL: volume loading of Ringer's lactate solution (30 ml/kg). Data are expressed as Mean ± SEM, *P<0.05 vs. baseline, **P<0.01 vs. baseline, # P<0.05 vs. the values at 4 h, ## P<0.01 vs. the values at 4 h.

Discussion

It was found that IDVG index significantly decreased immediately and 4 h after the administration of ET in piglets without fluid volume loading. The ET injection induced a septic shock state by 4 h following the injection in this animal model because CO and systolic BP significantly decreased and the plasma levels of lactate significantly increased by that time (Fig.1). Brigham et al. demonstrated that ET increased vascular permeability 4 h after its injection and induced hypovolemia[22]. Previously, our group reported that IDVG could detect histamine-induced capillary protein leakage and hypovolemia, investigated through the simultaneous measurements of the plasma volume using indocyanine green (PV-ICG) in dogs[23]. In that report, it was also demonstrated that the PV-ICG/IDVG ratio increased in a dose-dependent manner after histamine administration because PV-ICG was overestimated due to the binding of ICG to plasma albumin, some of which leaked from the intravascular space to the extravascular space. Sakai et al. also demonstrated capillary protein leakage following ET injection by the measurement of the PV-ICG/IDVG ratio in dogs[19], where IDVG decreased 4 h after the ET injection. The present results of our study in pigs were in line with the results of those studies about capillary leakage in dogs.

IDVG has been shown to indicate the central ECF volume, which consists of the plasma volume and highly perfused interstitial fluid volume[7]. Matsui et al. demonstrated that IDVG reflected central ECF volumes even when redistribution of fluid from the central to the peripheral compartment was induced with phentolamine, which was an α-adrenergic antagonist, and increased blood pooling in the absence of fluid gain or loss[24]. Therefore, it was also considered that the decrease in IDVG immediately and 4 h after ET administrations was related to the vasodilatation, which resulted in redistribution of blood. Particularly, the

decrease in IDVG immediately after ET was recovered without fluid volume loading 2 h after ET administration in this study, which could be because of the compensation due to the increase in sympathetic nervous system activity against vasodilation.

IDVG and CO significantly increased in response to the volume resuscitation with 30 ml/kg Ringer's lactate solution over 60 min, as compared with the values 4 h after ET injection (Table 2 and figure 3). However, the effects of volume loading for CO and IDVG disappeared by the next 1 h. Sevensen et al. demonstrated that rapidly-infused crystalloid was eliminated from the central to the peripheral fluid space within 60 min in sheep and the effects of increased cardiac preload on CO also disappeared within 60 min [25]. Although the glucose administered for IDVG measurement is rapidly distributed from the intravascular to the extravascular compartments, the results of our volume resuscitation experiment in the septic shock state suggested again that IDVG reflects the central ECF volume, which could be related to cardiac preload.

Regarding the other parameters of cardiac preload, ITBV significantly decreased and SVV and PPV significantly increased 4 h after ET administration as compared with the baseline values, suggesting the decreased cardiac preload due to the vasodilation and increased vascular permeability. In addition, ITBV significantly increased and HR and PPV significantly decreased after volume loading as compared with the values 4 h after ET injection. Nakamura et al. reported that IDVG had a linear correlation with ITBV in animal models of hemorrhage and volume loading[26]. However, in our ET-induced septic models, IDVG did not show parallel changes with CO, but the trend of ITBV was similar to that of CO (Fig 1 and 2). Septic insults also affect cardiac function[27], and we used dobutamine to maintain the BP. This was one of the reasons why IDVG did not show parallel changes with CO. However, as ITBV is basically calculated as a product of cardiac output and the mean transit time of a tracer between the site of injection and the site of the detection, it is known that "mathematical coupling" between ITBV and CO is generally observed[28]. Therefore, we thought that IDVG reflected the state of cardiac preload in sepsis more than ITBV.

He et al. reported that IDVG had an inverse correlation with PPV[15]. However, it is well known that there are several clinical limitations for the usage of SVV and PPV, such as the need for mechanical ventilation (tidal volume >8 ml/kg) in the absence of spontaneous breathing and/or cardiac arrhythmias[29]. Actually, in the present study, we could not obtain some data of SVV and PPV due to the arrhythmia. As IDVG has been demonstrated to be measured relatively independent of cardiac function and arrhythmias[17, 30], IDVG could be used for wider type of critically-ill patients in the ICU than the dynamic indicators.

In clinical practice, we used IDVG as the one of the indicator to make decisions on body fluid management for not only septic patients but also the patients after long highly invasive surgery, because patients after invasive surgery needs volume resuscitation in acute phase and needs diuretic in refilling phase.

Conclusion

It was found that IDVG decreased in the ET-induced septic state and increased with volume resuscitation. IDVG indicated the changes in the central ECF volumes and can be an indicator of cardiac preload in the septic state.

Conflicts of interest

All authors have no conflicts of interest directly relevant to the content of this article.

Funding

This study was supported by a Research grant (C) of the Japan Society for the Promotion of Science (No.15K10529).

Acknowledgments

The authors thank Dr. H Ishihara in Kuroishi Kosei Hospital for his useful suggestions and corrections of the manuscript. We would also like to thank Editage (www.editage.com) for English language editing.

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