Non-Invasive Estimated Continuous Cardiac Output (escCO) during Severe Sepsis and Septic Shock Resuscitation

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Background: *Cardiac output (CO) is an important hemodynamic parameter during sepsis and septic shock resuscitation. Conventionally, this value is obtained at bedside by the thermodilution technique, which requires a pulmonary artery catheter (PAC). Estimated Continuous Cardiac Output (esCCO, Nihon Kohden®, Japan) calculated from pulse-wave transit time (PWTT) was examined here as an alternative.*

Material and Method: *A prospective study was performed in a 14-bed ICU facility. Patients with severe sepsis and septic shock who had PAC placed were included. Serial thermodilution cardiac outputs (CO_{IBT}) and esCCO (CO_{esCCO}) were obtained at the beginning of resuscitation (t_0), at 48 hours (t_{48}), and at 72 hours (t_{72}). Other parameters from the tested device; namely, estimated continuous cardiac index (esCCI), estimated stroke volume (esSV), and estimated stroke volume index (esSVI), were also achieved.*

Results: *A total of 90-paired readings from ten ICU patients were collected. The overall correlation coefficient (R) between CO_{esCCO} and CO_{IBT} was 0.76. When focusing on the correlation from each time point, we found R at t_0 = 0.65, t_{48} = 0.74, and t_{72} = 0.84 (all p<0.001). Bland and Altman analysis corrected for repeated measures showed a bias of 1.2 liter/min and limits of agreement from -2.8 to +5.2 liter/min. Results also showed fair to poor correlation with other parameters that derived from this device (esCCI, esSV, esSVI).*

Conclusion: *The estimated continuous cardiac output (esCCO) correlated well with the cardiac output obtained by thermodilution techniques, especially when patients were out of shock.*

Keywords: *Cardiac output, esCCO, Intermittent bolus thermodilution method, Sepsis, Septic shock*

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Severe sepsis and septic shock are the major causes of ICU mortality. The data from our institution revealed a mortality rate of 34.3% and 52.6%, respectively[1]. The management principle includes adequate fluid therapy, proper vasopressors, prompt antibiotics together with adequate source control[2]. Monitoring during shock resuscitation is crucial; among the parameters used, cardiac output is frequently utilized. This value is generally obtained by intermittent bolus thermodilution technique (IBT) via a pulmonary artery catheter (PAC). This procedure is becoming less popular due to its invasiveness and the need for experienced physicians to administer it.

Instead, cardiac output monitoring by various non-invasive techniques is increasingly used[3]. Examples include pulse contour analysis, esophageal Doppler, thoracic electrical bioimpedance, partial CO_2 rebreathing, etc. The estimated continuous cardiac output (esCCO) from Nihon Cohden Co., Ltd. Japan has also been launched[4,5]. A study in preoperative patients revealed that esCCO and the standard IBT correlated well (R 0.82, p-value <0.001)[6]. Recently, a large multicenter study in intensive care units and perioperative areas disclosed a good correlation of both values with R = 0.79 and p<0.001[7]. Bataille B et al[8] compared esCCO with CO from transthoracic echocardiography in patients with severe sepsis and septic shock and found a fair correlation (R = 0.63 and p<0.001). The authors report here a comparison study between esCCO and CO from IBT in patients with severe

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sepsis and septic shock in our institution.

Material and Method

A prospective, observational study was performed in a 14-bed university hospital, medical intensive care unit. The study protocol was approved by the Hospital Ethics Committee. Each patient or relative provided written informed consent.

Patients

Patients were eligible for inclusion if they were older than 18 years old, had severe sepsis or septic shock defined according to the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference[9]. Those who required pulmonary catheterization for cardiac output measurement were enrolled. Patients with cardiac arrhythmia, stenotic valvular heart disease, temporary or permanent pacemaker, intra-aortic pulse-contour assisted device, and patients with PAC or IBT complications were excluded. After obtains informed consent, the patients serially received IBT cardiac output measurement simultaneously with esCCO. These measurements were obtained at the beginning of resuscitation (t_0), at 48 hours (t_{48}), and at 72 hours (t_{72}) thereafter. The investigators and the attending physicians performed measurements independently but at the same time. Patients' baseline characteristics including age, sex, height, weight and body mass index (BMI) were recorded. Clinical information, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, site of infection, ventilator uses, vasopressor uses (dosages and types) and renal replacement therapy were noted.

The estimated continuous cardiac output (esCCO)

The estimated continuous cardiac output (esCCO) was obtained from the device supported by E For L International CO., Ltd. This parameter is determined by using Pulse Wave Transit Time (PWTT), which is obtained by the pulse oxymetry and ECG-signals from each cycle of the ECG. Theoretically, cardiac output is the product of stroke volume and heart rate. The possibility to derive the stroke volume (SV) from pulse pressure (PP) information allows creation of this the equation: $CO = SV \times HR = K \times (\alpha \times PWTT + \beta) \times HR = escCO$ (K = constant value and α, β: experimental constants). The scientific details are described in the work presented by Ishihara[5].

Statistical analysis

The statistical analysis was divided into descriptive and inferential analysis. Baseline characteristics of patients were presented as mean ($\pm$ standard deviation, SD) and percent. The relationship between CO_{esCCO} and CO_{IBT} was calculated by using Pearson's correlation with a two-sided significant of 0.05 and a power of 80%. Bland and Altman's plot was used to evaluate the agreement between both techniques.

Ethical considerations

The study was reviewed and approved by the Siriraj Ethic Committee, using the Declaration of Helsinki.

Results

Ten patients were included in the study. The mean age of was 76.3$\pm$7.4 years and the male to female ratio was 5:5. The average BMI was 26.1$\pm$5.3 kg/m^2 and the mean APACHE II score was 21.4$\pm$2.8. The majority (60%) of the patients had pneumonia, followed by intrabdominal infection (20%), necrotizing fasciitis (10%) and acute respiratory distress syndrome (10%). All patients received mechanical ventilator and vasopressors. The baseline characteristics were summarized in Table 1.

Ninety-paired samples were analyzed from all participants. As presented in Fig. 1, Pearson correlation analysis demonstrated a significant correlation between CO_{esCCO} and CO_{IBT} with R = 0.76, ($p<0.001$). Bland and Altman plot in Fig. 2 disclosed a good agreement between both parameters with a bias of +1.2 liter/min and limits of agreement from -2.8 to +5.2 liter/min. In addition, as shown in Table 2, when focusing on the correlation at each time of assessment, we found that the correlation coefficient (R) at t_0 was 0.65, at t_{48} 0.74,

Table 1. Patients' baseline characteristics (n = 10)

Patients' characteristics	
Age (years)	76.3 ($\pm$7.4)
Sex (male: female)	5: 5
BMI (kg/m^2)	26.1 ($\pm$5.3)
APACHE II score (points)	21.4 ($\pm$2.8)
Diagnosis	
Pneumonia	6 (60%)
Intra-abdominal infection	2 (20%)
Necrotizing fasciitis	1 (10%)
Acute respiratory distress syndrome (ARDS)	1 (10%)
Mechanical ventilator	100%
Use of vasopressor (s)	100%

and at t_{72} 0.84. All correlations were significant with p value less than 0.001.

The other parameters received from device were also analyzed. The estimated continuous cardiac index (esCCI), the estimated stroke volume (esSV), and the estimated stroke volume index (esSVI) were compared with those from IBT (Table 3). The correlations coefficients (R) were 0.54, 0.48, and 0.44, respectively.

Discussion

This report finds that cardiac output values from the Estimated Continuous Cardiac Output (CO_{esCCO}) correlated with those obtained by intermittent bolus thermodilution technique (CO_{IBT}). The correlation was better when patients were out of shock. Other parameters of the tested instrument, namely continuous cardiac index, stroke volume and stroke volume indexes, also correlate, though not to the same extent, with the values derived from pulmonary catheter.

In general, the steps of shock resuscitation, apart from source control, begin with prompt fluid replacement to correct intravascular volume deficit. If the patient is still hypotensive after adequate fluid replacement, vasopressors or inotropes are used according to underlying pathophysiology. The process is aimed to restore tissue perfusion and must be performed in rapid fashion in order to prevent organ damage[2]. Monitoring of adequate preload is necessary. At the moment, two types of monitoring are available. First, there are static parameters, which consist of central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP). These parameters have long been used despite the fact that accumulated evidence has disclosed their poor correlation with intravascular volume[10]. Second, there are volume responsive tests and various non-invasive types of cardiac output monitoring. Monitoring changes of cardiac output in response to volume loading is the most direct way to determine fluid responsiveness. By far, CO_{IBT} is considered a standard method to determine cardiac output but this system requires certain equipment, expertise and complex set up. Hence, different non-invasive tests have been developed by utilizing various techniques. Examples include pulse contour analysis, esophageal Doppler, thoracic bioimpedance and bioreactance[3]. Abundant reports disclosed different correlations between the values from these tests with those from TDCO.

The non-invasive Estimated Continuous Cardiac Output (esCCO) shares a similar concept with

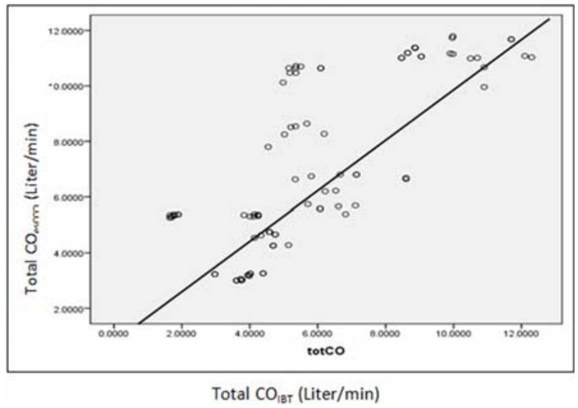

Fig. 1 Significant correlation between CO_{esCCO} and CO_{IBT} with R = 0.76, p<0.001, n = 90 paired samples.

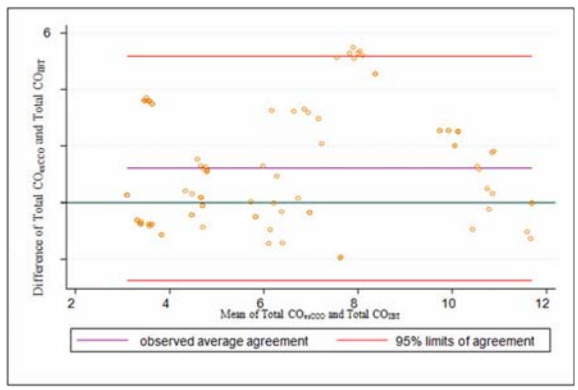

Fig. 2 Bland and Altman Plot between CO_{esCCO} and CO_{IBT} demonstrated reasonable agreement between CO_{IBT} and CO_{esCCO}.

Table 2. Significant correlation coefficient (R) when focused on each time point

Time points	Correlation coefficient (R)	p-value
At 0 hour	0.65	<0.001
At 48 hour	0.74	<0.001
At 72 hour	0.84	<0.001

Table 3. Significant correlation coefficient (R) of other parameters from device compared with standard results from intermittent bolus thermodilution method (IBT)

Comparators	Correlation coefficient (R)	p-value
esCCI	0.54	<0.001
esSV	0.48	0.008
esSVI	0.44	0.03

the above tests while employing some different inputs. By calculating three hemodynamic variables, namely, pulse oximeter wave, pulse wave transit time and noninvasive blood pressures, cardiac output or esCCO is derived. The advantage of this approach includes its noninvasiveness and simplicity. Recent multicenter studies from surgical ICUs and operating rooms disclose a good correlation between esCCO and CO_{IBT} (correlation coefficient 0.79, $p<0.0001$)[7] with small bias. However, a study comparing esCCO with CO obtained by tranthoracic echocardiography in critically ill patients (68% had a diagnosis of septic shock) revealed a correlation coefficient of 61% ($p<0.0001$) with a wide limit of agreement and a poor concordance rate (73%)[8]. Our results paralleled these studies. There was good correlation ($r = 0.76$, $p<0.001$) and fair agreement between the esCCO and CO_{IBT}. The main differences from previous studies are these: 1) type of patients and 2) number of patients. Our study included only patients with septic shock while others included mixed, critically ill patients. The small number of our patients was a matter of concern despite the fact that 90-paired measurements were methodologically sufficient. A study on a larger scale of patients may better verify esCCO validity, especially during fluid challenge.

The improvement of correlation coefficients on late follow-up might be clarified by the alterations in vasomotor tone during shock, both from disease and from treatment. When the patients' condition improved with decreased vasopressor dosages, these changes subsided. Information from the work of Bataille[8] supported this idea. There was a significant log-linear relationship between the bias and the estimation of systemic vascular resistance, SVR ($R = 0.45$, $p<0.0001$). This indicated that systemic vascular resistance significantly interfered with esCCO measurement.

Besides cardiac output, information obtained from the tested instrument including cardiac index (esCCI), stroke volume (esSV) and stroke volume index (esSVI) correlated with the values obtained from PAC, but to a lesser extent. This could be explained by the nature of these parameters, starting with esCCO, which was calculated from certain equations derived from many variables. The surrogate values needed more calculation and are therefore less correlated.

In conclusion, during septic shock resuscitation, esCCO correlated with cardiac output obtained from pulmonary catheter. This method may be used as an alternative for cardiac output monitoring during fluid challenges, especially in early stages when vasopressors are not being used.

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Potential conflicts of interest

None.

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*การตรวจวัดปริมาณเลือดที่ออกจากหัวใจโดยใช้วิธี **Estimated Continuous Cardiac Output** (esCCO) ในผู้ป่วยช็อกจากการติดเชื้อ*

ไชยรัตน์ เพิ่มพิกุล, ธงชัย ลีลายุทธชัย

วัตถุประสงค์: *ภาวะช็อกจากการติดเชื้อมีอัตราตายสูง แพทย์ต้องรักษาให้ผู้ป่วยพ้นจากภาวะช็อกอย่างรวดเร็วและถูกต้อง การติดตามเฝ้าระวังปริมาณเลือดที่ออกจากหัวใจมีความสำคัญ แต่การตรวจมาตรฐานโดยวิธี thermodilution technique (intermittent thermodilution technique, CO_{IBT}) ต้องอาศัยการใส่สายสวน pulmonary ซึ่งแพทย์ต้องทำหัตถการและอาจมีความเสี่ยง ระยะหลังนี้มีผู้นำการตรวจวัดปริมาณเลือดที่ออกจากหัวใจชนิด non invasive มาใช้ การศึกษานี้ได้ตรวจสอบความแม่นยำของการตรวจการตรวจวัดปริมาณเลือดที่ออกจากหัวใจโดยใช้วิธี Estimated Continuous Cardiac Output (esCCO)*

วัสดุและวิธีการ: *เป็นการศึกษาไปข้างหน้า เปรียบเทียบการตรวจ esCCO กับการตรวจ COIBT ในผู้ป่วยช็อกจากการติดเชื้อ โดยเปรียบเทียบการตรวจทั้ง 2 วิธีในขณะให้เริ่มการรักษา (t_0), เมื่อ 48 ชั่วโมงและ 72 ชั่วโมง หลังเริ่มรักษา (t_{48} และ t_{72}) ค่าอื่นๆ ที่ได้วัดได้จากเครื่องมือนี้และได้ตรวจสอบด้วยคือ estimated continuous cardiac index (esCCI), estimated stroke volume (esSV) และ estimated stroke volume index (esSVI)*

ผลการศึกษา: *จากข้อมูลเปรียบเทียบค่า CO_{esCCO} และCO_{IBT} 90 คู่ที่ได้จากผู้ป่วย 10 ราย พบว่ามีความสัมพันธ์ (correlation coefficient, R) 0.76 เมื่อแยกคำนวณความสัมพันธ์ระหว่างค่าทั้งสองในช่วง t_0, t_{48} และ t_{72} พบว่าได้ = 0.65 = 0.74, and = 0.84 (all p<0.001) การทดสอบความไปด้วยกันโดยใช้วิธี Bland and Altman พบค่า bias 1.2 ลิตร/นาที และค่าความแตกต่างจากการวัดกระจายอยู่ใน limit of agreement ช่วง -2.8 ถึง +5.2 ลิตร/นาที ความสัมพันธ์ระหว่างค่า CI, SV และ SVI ที่ได้จากการตรวจโดยวิธีมาตรฐานและจากเครื่องมือที่ทดสอบมีค่าเท่ากับ 0.54, 0.48 และ 0.44 ตามลำดับ*

สรุป: *การตรวจการตรวจวัดปริมาณเลือดที่ออกจากหัวใจโดยใช้วิธี Estimated Continuous Cardiac Output (esCCO) มีความสัมพันธ์กับการตรวจโดยวิธีมาตรฐาน (intermittent thermodilution technique, CO_{IBT}) โดยเฉพาะอย่างยิ่งเมื่อผู้ป่วยพ้นจากภาวะช็อก*