Clinical Validation of Pulse Contour and Pulse Wave Transit Time-Based Continuous Cardiac Output Analyses in Thai Patients Undergoing Cardiac Surgery

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Objective: *To evaluate the performance of arterial pressure-based cardiac output (APCO) and pulse wave transit time-based cardiac output (esCCO) monitors in Thai patients undergoing cardiac surgery with cardiopulmonary bypass.*
Material and Method: *The authors studied fifty Thai surgical patients undergoing coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass and requiring pulmonary artery catheters and radial artery catheter placement as a standard of clinical care. All patients were measured for APCO using the Vigileo/FloTrac™ and esCCO using the esCCO™ monitoring system. The data were compared to thermodilution cardiac output (TDCO) monitoring as a reference method, simultaneously at pre-induction of anesthesia, post-induction, and every 30 minutes thereafter until the completion of the surgery. The bias and precision were assessed using Bland-Altman analysis.*
Results: *310 pairs of simultaneous measurements of APCO vs. TDCO and 303 pairs of esCCO vs. TDCO were obtained from fifty patients. Both APCO (R = 0.53, p<0.0001) and esCCO values (R = 0.56, p<0.0001) were correlated with TDCO values. Either of the changes in APCO (R = 0.63, p<0.0001) or any changes in esCCO (R = 0.60, p<0.0001) were correlated with changes in TDCO. For APCO relative to TDCO, the bias, precision, and the limits of agreement were 0.70, ±1.63, and -2.5 to 3.9 L/min while of esCCO were 1.20, ±1.59, and -1.9 to 4.3 L/min, respectively. Comparisons of the bias of APCO and esCCO revealed a level of significance of p<0.001.*
Conclusion: *Despite the overestimation of CO measurements, APCO and esCCO calibrated with patient information has shown an acceptable trend as compared to TDCO in Thai patients undergoing CABG with cardiopulmonary bypass. Compared to esCCO, APCO demonstrated no significant differences of precision however; a lower mean bias was exhibited.*

Keywords: *Pulse wave transit time, Pulse contour, Cardiac output*

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Inadequate tissue perfusion related to acute circulatory failure is the most common cause of organ failure in critically ill patients. Perioperative hemodynamic optimization is a cornerstone and is essential in maintaining adequate tissue perfusion especially in high risk surgery. Cardiac output (CO) is a main factor in the regulation of oxygen delivery. Although determination of CO by the classic thermodilution method (TDCO) is widely considered the gold standard, its reproducibility is not impressive(1) as well as it is not a risk-free procedure due to the requirement of an invasive pulmonary artery catheter (PAC)(2). To avoid the risks associated with the placement of the PAC, alternative techniques such as, minimally invasive or truly non-invasive cardiac output measurement technologies have been developed. They are available with either; standard radial artery catheter placement using arterial pulse contour-based analysis or using pulse wave transit time (PWTT; the interval between the ECG R wave and the pulse plethysmograph upstroke) analysis. This requires only the placement of three, non-invasive devices; 3 leads of an ECG monitor, pulse oximetry measurements, and non-invasive blood pressure (NIBP) measurements(3). However, their accuracies are still not clearly established in the Thai population. Also, some studies have revealed the effects of racial differences in endothelial function at the level of the finger's arteries(4-7). This raises the question as to whether the arterial pulse-based cardiac output (APCO) and estimated continuous cardiac output (esCCO) derived from PWTT analysis may be influenced and could

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possibly differ from that in Caucasians.

In the present study, we conducted a prospective observational study in Thai patients undergoing coronary artery bypass graft surgery (CABG) to help determine whether; 1) APCO and esCCO correlates with TDCO values; 2) changes in APCO and esCCO correlates with changes in TDCO, and 3) esCCO is comparable to APCO in terms of bias and precision.

Material and Method

The present study was approved by the Institutional Review Boards and Ethics Committees, The Royal Thai Army Medical Department, and informed consents were obtained from all subjects. We conducted a single-center, prospective, observational study in fifty adult Thai patients who underwent elective primary CABG surgery with cardiopulmonary bypass (CPB) that required PACs and radial artery catheters as part of their standard clinical care, during the period of October 1, 2012 to April 30, 2013 at Phramongkutklao Hospital. Patients with evidence of pre-operative valvular regurgitation, cardiac arrhythmias, intra-aortic balloon pumps, severe left ventricular systolic dysfunction (defined by left ventricular ejection fraction less than 30%), or symptomatic peripheral vascular diseases were excluded.

Study protocol

Before the induction of anesthesia, hemodynamic measurements were obtained for all patients. Invasive hemodynamic monitoring consisted of cannulation of the right or left radial artery with a standard arterial catheter and a PAC inserted via the right internal jugular vein (PAC-TD, 7F, Edwards Lifescience, Irvine, CA, USA). Hemodynamic measurements (central venous pressure, pulmonary capillary wedge pressure, mean arterial pressure, mean pulmonary artery pressure, stroke volume, TDCO, systemic vascular resistance, and core blood temperature) were collected using PACs, while APCOs were collected using the Vigileo/FloTrac^{TM} (Edwards Lifesciences, USA) and esCCO were collected using esCCO^{TM} (Nihon-Kohden, Japan) monitoring systems. All of these hemodynamic variables were collected at the pre-induction of anesthesia, post-induction, and every 30 minutes, thereafter, until completion of the surgery. Following induction, all patients were mechanically ventilated with a tidal volume 8-10 mL/kg (volume-controlled ventilation) with a positive end-expiratory pressure of 5 cmH_2O, and a respiratory rate set to 12-20/min with a target of a partial pressure of carbon dioxide ($PaCO_2$) of 35-40 mmHg.

Intermittent thermodilution cardiac output (TDCO)

TDCO values were obtained from an injection of 10 mL cold isotonic saline (<8°C) through the injection port of the PAC. Measurements were performed in triplicate then averaged.

Arterial pressure-based cardiac output (APCO)

To validate the arterial pressure-based cardiac output device, a radial artery catheter was placed and attached to the pulse contour cardiac output system (Vigileo/FloTrac^{TM}; Edwards Lifesciences, Irvine, CA, USA) in all patients to allow determination of stroke volume based on standard arterial wave form characteristics and individual patient demographics (age, height, weight, and gender), without calibration. The third generation Vigileo/FloTrac^{TM} software (version 3.06) was used in the present study.

Truly non-invasive cardiac output (esCCO)

The esCCO^{TM} measurement system (Nihon-Kohden, Tokyo, Japan) using PWTT obtained as the interval between the R wave of electrocardiogram (ECG) and the arrival of the pulse wave obtained with pulse oximetry, allows determination of esCCO. All patients were monitored for esCCO during the intra-operative period as previously mentioned. Oxygen saturation finger probes were placed on the right index finger of the patients, the NIBP cuff was placed on the left forearm, and three electrodes for ECG measurements were placed in all patients. The esCCO was calibrated first with the patients' NIBP beginning at pre-induction of anesthesia in all patients.

Statistical analysis

The sample size (at least 290 measurements) was calculated for an equivalence trial[8]. The normality of the quantitative data was verified using a Kolmogorov-Smirnov test, and expressed as a means and standard deviation (SD). Baseline demographics and comorbidities were recorded in a data set. Correlations between APCO vs. TDCO, esCCO vs. TDCO, performance for tracking changes in CO of APCO (ΔAPCO) and esCCO (ΔesCCO) were analyzed using linear regression analysis. To investigate whether esCCO is comparable to APCO, the bias (mean difference between tested CO and TDCO), precision (SD of bias), and limits of agreement (bias $\pm$ 1.96 SD of bias) were assessed as recommended by Bland and

Altman[9]. Comparisons of the biases of APCO and esCCO were analyzed using an unpaired t-test. The statistical analysis was performed using SPSS software, version 17.0.

Results

A total of fifty patients were selected for analysis. The patients' demographics and surgical data are listed in Table 1. The average patient age was 62 years of age. A higher proportion of patients that were observed were males (78%). ASA classification was III and the surgeries were without complications for all subjects. A total of 310 pairs of simultaneous cardiac output measurements from the APCO vs. TDCO methods and 303 pairs of esCCO vs. TDCO methods were recorded. During the surgery, both APCO and esCCO measures were overestimations as compared to the TDCO values (Fig. 1).

Correlations between APCO and esCCO versus TDCO values

Using linear regression analysis, both APCO ($p<0.0001$) and esCCO values ($p<0.0001$) were significant in their correlation with TDCO values with moderate correlation coefficients of 0.53 and 0.56, respectively (Fig. 2).

Tracking change in cardiac output (ΔCO)

The authors found that either ΔAPCO ($p<0.0001$) or ΔesCCO ($p<0.0001$) were correlated with ΔTDCO with the moderate correlation coefficient of 0.63 and 0.60, respectively (Fig. 3).

Validity of pulse contour and PWTT analysis devices

Compared to TDCO method, the bias and precision of APCO was 0.70 and 1.63 L/min while the bias and precision of esCCO was 1.20 and 1.59 L/min. The limits of agreement for APCO versus TDCO were -2.5 to 3.9 L/min, and those for esCCO versus TDCO were -1.9 to 4.3 L/min (Fig. 4). In comparison to APCO, esCCO reveals a significantly higher mean bias ($p<0.001$), whereas there were no differences of the precision between the two techniques ($p = 0.15$).

Discussion

CO is a global index of circulatory status. Measurement of CO and its response to therapeutic interventions are commonly employed therapeutic protocols in critically ill patients. While TDCO using PACs is generally considered the gold standard, studies comparing it with the Fick method have not shown

Table 1. Patient demographic data

Patient characteristics (n = 50)	Mean (SD)
Age-yr	62 (12)
Sex: male-n (%)	39 (78)
Height-cm	164.10 (8.3)
Weight-kg	68.70 (14.7)
BSA-m^2	1.74 (0.21)
Left ventricular ejection fraction-%	58 (11.6)
Co-existing disease-n (%)	
Chronic pulmonary disease	2 (4)
Hypertension	49 (98)
Diabetes	23 (46)
Renal insufficiency	13 (26)
Surgical data	
Operation time-min	326 (77)
Cardiopulmonary bypass time-min	131 (47)

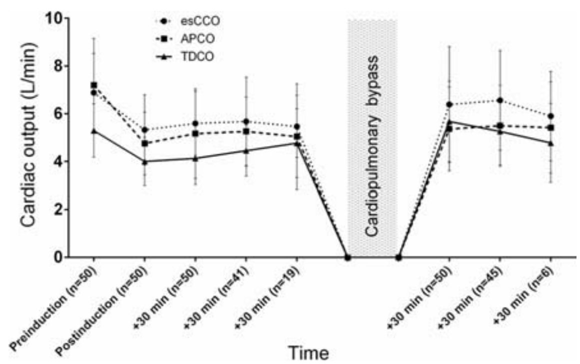

Fig. 1 Cardiac output changes by the time during CABG surgery (esCCO = estimated continuous cardiac output derived from truly non-invasive method, APCO = cardiac output derived from arterial pulse-based analysis method, TDCO = thermodilution cardiac output). Data are means, error bars represent SD.

agreement[10]. APCO and esCCO monitoring devices have been validated in a variety of races including the Europeans, Americans, and the Japanese[11,12]. In the present study, Thai patients underwent CABGs with CPB. The most important finding is that APCO and esCCO are clinically acceptable and correlate with TDCO (Fig. 2). Although APCO and esCCO show moderate to high bias (0.7 and 1.2 L/min, respectively), in clinical purposes, the absolute CO might be less important than changes in CO[13]. In the present study, the authors found that both APCO and esCCO devices demonstrate acceptable performances for tracking changes in cardiac output (Fig. 3). Therefore, regardless of the causes of changes in cardiac output, our findings provide evidence that APCO and esCCO has potential implications for use in monitoring trends of CO during cardiac surgery in Thai patients.

Vigileo/FloTrac^{TM} system has been developed and validated studies of their updated software have been verified[14]. In the present study, the latest software of Vigileo/FloTrac^{TM}, the third generation, was used and our results align with a study by Biancofiore et al, which had been studied in cirrhotic patients undergoing liver transplant surgery. It had been found that the correlation between the cardiac index as measured from the thermodilution technique and cardiac index as derived from Vigileo/FloTrac^{TM} are moderate (R = 0.67). However, when compared to the second generation software, the third generation software shows an improved trending ability[14].

To estimate CO by esCCO^{TM} devices, adequate digital perfusion is necessary. In our study, we confirm that good peripheral perfusion to the fingers in all patients when using the perfusion index suggested by Lima et al, the perfusion index of <1.4% is a very sensitive cutoff point for determining abnormal

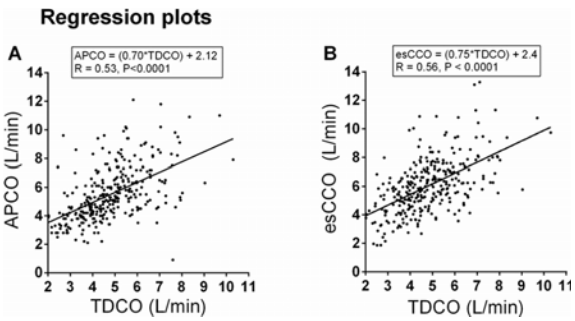

Fig. 2 Regression analysis of A) APCO vs. TDCO, and B) esCCO vs. TDCO. The equation of the regression line and the correlation coefficient (R) are displayed.

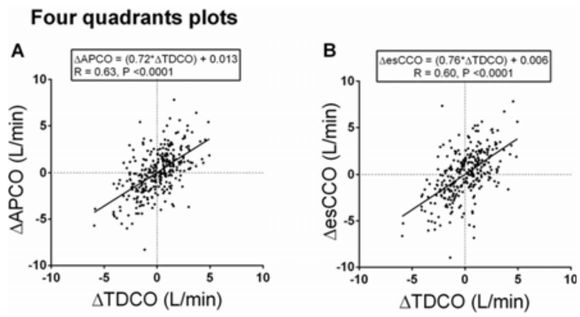

Fig. 3 The changes in cardiac output as measured by intermittent thermodilution cardiac output (ΔTDCO) versus; A) arterial pressure-based cardiac output (ΔAPCO) and B) estimated continuous cardiac output (ΔesCCO). ΔCO is the difference in two measurements (by one method) of cardiac output and was expressed as L/min. The equation of the regression line and the correlation coefficient (R) are displayed.

Table 2. Global hemodynamic variables and peripheral circulation parameters in patients undergoing CABG surgery at each time points

	Preinduction	Postinduction	Pre CPB	Post CPB
Heart rate (min)	76 (16)	68 (15)	71 (14)	89 (14)
Mean ABP (mmHg)	109 (15)	79 (13)	81 (14)	77 (12)
Mean NIBP (mmHg)*	106 (12)	82 (16)	79 (12)	80 (15)
Mean PAP (mmHg)$^{+}$	24 (8)	21 (6)	24 (7)	24 (7)
CVP (mmHg)$^{+}$	8 (4)	11 (5)	12 (5)	13 (5)
Pcwp (mmHg)$^{+}$	16 (6)	15 (5)	17 (6)	18 (6)
SVR (dyn.s/cm^{5})$^{+}$	1,666 (573)	1,517 (491)	1,377 (448)	1,037 (389)
SVR (dyn.s/cm^{5})$^{++}$	1,203 (399)	1,185 (318)	1,099 (319)	987 (338)
PPV (%)	8.5 (6.5)	8.6 (4.2)	7.2 (6.5)	9.1 (6.9)
SVV (%)$^{++}$	7.8 (4.5)	9.0 (4.0)	6.9 (4.2)	8.0 (4.9)
Perfusion index (%)*	1.6 (1.35)	3.96 (3.03)	3.42 (2.81)	2.16 (1.96)
PWTT (ms)*	218.93 (50.07)	249.71 (30.39)	258.28 (35.77)	237.90 (45.14)
Blood temperature (°C)$^{+}$	36.5 (0.5)	35.8 (0.6)	35.1 (2.9)	36.3 (0.3)

CPB = cardiopulmonary bypass; ABP = arterial blood pressure; NIBP = non-invasive blood pressure; PAP = pulmonary artery pressure; CVP = central venous pressure; Pcwp = pulmonary capillary wedge pressure; SVR = systemic vascular resistant; PPV = pulse pressure variation; SVV = stroke volume variation; PWTT = pulse wave transit time

Data are expressed as mean (SD) and data derived from pulmonary artery catheter^{+}, Vigileo/FloTrac^{++}, and esCCO* devices

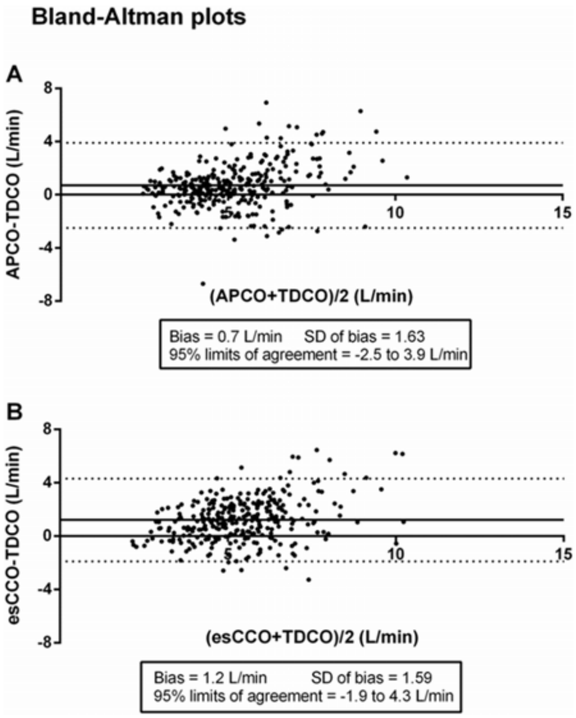

Fig. 4 Bland-Altman plots comparing intermittent thermodilution cardiac output (TDCO) with A) arterial pulse-based continuous cardiac output (APCO) and B) estimated continuous cardiac output (esCCO) for all measurements (n = 50 patients; 310 pairs of APCO vs. TDCO and 303 pairs of esCCO vs. TDCO). The differences in cardiac output as determined by the two methods are plotted against the mean cardiac output. Central solid lines mark the mean of the differences (bias) whereas dashed lines represent limits of agreement (95% confidence intervals).

peripheral perfusion(15). The average perfusion index in our study is at the least, 1.6%.

In conclusion, the results of the present study show that APCO and PWTT methods provide acceptable performance in tracking changes of TDCO in Thai undergoing cardiac surgery. However, esCCO demonstrates a higher mean bias than APCO.

Potential conflicts of interest

None.

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การศึกษาผลการตรวจวัดปริมาตรเลือดที่ออกจากหัวใจต่อนาทีโดยการใส่สายสวนหลอดเลือดแดงและการวิเคราะห์ความต่างของระยะเวลาระหว่างคลื่นไฟฟ้าหัวใจกับคลื่นความอิ่มตัวของออกซิเจนในเลือดแดงบริเวณปลายนิ้วมือในผู้ป่วยไทยที่เข้ารับการผ่าตัดหัวใจ

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วัตถุประสงค์: *เพื่อศึกษาถึงประสิทธิภาพของอุปกรณ์สองชนิดที่ใช้ตรวจวัดปริมาตรเลือดที่ออกจากหัวใจต่อนาที (cardiac output; CO) โดยชนิดแรกใช้เทคนิคการใส่สายสวนหลอดเลือดแดงบริเวณข้อมือเพียงอย่างเดียว (APCO) และชนิดที่ 2 ใช้เทคนิควิเคราะห์ความต่างของระยะเวลาระหว่างคลื่นไฟฟ้าหัวใจกับคลื่นความอิ่มตัวของออกซิเจนในเลือดแดงบริเวณปลายนิ้วมือ (esCCO) ในผู้ป่วยไทยที่เข้ารับการผ่าตัดหัวใจ*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยไทยที่เข้ารับการผ่าตัดทำทางเบี่ยงหลอดเลือดหัวใจและใช้เครื่องปอดหัวใจเทียม จำนวน 50 ราย โดยศึกษาเปรียบเทียบค่า APCO (จากอุปกรณ์ Vigileo/FloTrac™) และ esCCO (จากอุปกรณ์ esCCO™) เทียบกับค่า CO ที่ได้จากวิธีมาตรฐานโดยการใส่สายสวนหัวใจด้านขวา (TDCO) และเก็บข้อมูล ณ จุดเวลาต่างๆ ตั้งแต่ก่อนเริ่มดมยาสลบ หลังดมยาสลบ และต่อไปทุกๆ 30 นาที จนเสร็จสิ้นการผ่าตัด การวิจัยใช้สถิติ Bland-Altman analysis*

ผลการศึกษา: *จากจำนวนผู้ป่วยทั้งหมด 50 ราย พบว่าค่า APCO ($R = 0.53$, $p<0.0001$) และ esCCO ($R = 0.56$, $p<0.0001$) มีความสัมพันธ์กับค่า TDCO อย่างมีนัยสำคัญ และพบว่าการเปลี่ยนแปลงของค่า APCO ($R = 0.63$, $p<0.0001$) และ esCCO ($R = 0.60$, $p<0.0001$) สัมพันธ์กับการเปลี่ยนแปลงของค่า TDCO อย่างมีนัยสำคัญ ค่า APCO มีความโน้มเอียงทางสถิติ (bias) 0.7 ลิตรต่อนาที ซึ่งน้อยกว่าความโน้มเอียงทางสถิติของ esCCO (1.2 ลิตรต่อนาที) อย่างมีนัยสำคัญ ($p<0.001$)*

สรุป: *ในผู้ป่วยไทยที่เข้ารับการผ่าตัดทำทางเบี่ยงหลอดเลือดหัวใจที่ต้องใช้เครื่องปอดหัวใจเทียม ค่า APCO และ esCCO มีค่าสูงกว่าค่า TDCO อย่างไรก็ตามการเปลี่ยนแปลงของค่า APCO และค่า esCCO มีความสัมพันธ์ไปในทิศทางเดียวกันกับการเปลี่ยนแปลงของค่า TDCO อย่างมีนัยสำคัญ หากเปรียบเทียบกับค่า TDCO พบว่าค่า APCO มีความโน้มเอียงทางสถิติน้อยกว่าค่า esCCO*
