Uncalibrated Continuous Cardiac Output Measurement in Liver Transplant Patients: LiDCO*rapid*™ System versus Pulmonary Artery Catheter

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Objective: **The aim of the study was to assess the level of agreement between continuous cardiac output estimated by uncalibrated pulse-power analysis ($PulseCO_{LiR}$) and intermittent (ICO) and continuous cardiac output (CCO) obtained using a pulmonary artery catheter (PAC).**

Design: **Prospective cohort study.**

Setting: **University hospital intensive care unit.**

Participants: **Twenty patients after liver transplantation.**

Intervention: **Pulmonary artery catheters were placed in all patients, and ICO and CCO were determined using thermodilution. $PulseCO_{LiR}$ measurements were made using a LiDCO*rapid*™ (LiDCO Ltd, Cambridge, UK).**

Measurements and Main Results: **ICO data were determined after intensive care unit admission and every 8 hours until the 48th postoperative hour. CCO and $PulseCO_{LiR}$ measurements were recorded simultaneously at these same time intervals as well as hourly. For the 8-hour data set (140 data pairs), the mean bias and percentage errors (PE) were, respectively, −0.10 L/min and 39.2% for ICO versus $PulseCO_{LiR}$ and 0.79 L/min and 34.6% for CCO versus $PulseCO_{LiR}$. For the hourly comparison of CCO versus $PulseCO_{LiR}$ (980 data pairs), the bias was 0.75 L/min and the PE 37%. To assess the ability to measure change, a 4-quadrant plot was produced for each pair of methods. The performance of $PulseCO_{LiR}$ was moderate in detecting changes in ICO.**

Conclusions: **In conclusion, the uncalibrated $PulseCO_{Lir}$ method should not be used as a substitute for the thermodilution technique for the monitoring of cardiac output in liver transplant patients.**

KEY WORDS: *cardiac output, measurement techniques, thermodilution, monitoring, intensive care, liver transplantation*

PERIOPERATIVE MONITORING of cardiac output (CO) is used in both the intraoperative and postoperative periods[1] in the hemodynamic management of patients affected by end-stage liver disease (ESLD) undergoing liver transplantation. In clinical practice it has been measured since 1970 based on thermodilution technique with a pulmonary artery catheter (PAC), which still is considered the gold standard for cardiac output monitoring.[2] It commonly was measured intermittently with a PAC (ICO), even though continuous measurement is preferable.[3] In the 1980s a modified PAC that allows semi-continuous cardiac output (CCO) monitoring was introduced into clinical practice, showing clinically acceptable accuracy compared with the intermittent bolus technique in liver transplant patients.[4,5] However, questions have been raised about its invasiveness and risk for severe complications, and its use is now declining in favor of less invasive techniques.[6]

Over the last 10 years, various studies have shown that cardiac output can be assessed continuously with less invasive devices based on pulse-wave analysis.[7–9] These devices can be classified as either calibrated or uncalibrated. The calibrated devices show a good level of accuracy and precision compared with a PAC in liver transplant patients.[10–12] However, uncalibrated devices show conflicting results that depend on the different software versions used, and the level of accuracy and precision was found to be poor in patients with hyperdynamic cardiovascular conditions.[13–16] In this regard, in the field of cardiac output monitoring, Bland-Altman analysis is used to study 2 measurements in terms of bias and limits of agreement.[17] This is difficult to interpret, and it can lead clinicians to use a cutoff of 30% in the percentage error to decide whether a new technique may be considered as an alternative. This percentage error of ±30% derives from the concept that the reference technique, bolus thermodilution, has a precision of ±20% or less. The combination of two levels of precision of ±20% equates to a total error rate of ±28.3%, which commonly is rounded up to ±30%.

More recently, a new uncalibrated device, the LiDCO*rapid* (LiDCO Ltd, Cambridge, UK), has been introduced into clinical practice.[18,19] The LiDCO*rapid* uses a nomogram to estimate the calibration factor for scaling and transforming the nominal maximum aortic volume for cardiac output measurement. The LiDCO*rapid* nomogram was derived by the manufacturer from a multivariate analysis of the relationship among aortic volume, age, height, weight, and body surface area.

The aim of this study was to assess the accuracy, precision, and trending ability of this minimally invasive, uncalibrated pulse-power analysis system by comparing its results with both the intermittent and continuous cardiac output values obtained with a PAC in liver transplant patients over the course of the immediate postoperative period.

METHODS

Approval by the Ethics Committee was obtained along with written informed consent from 20 patients before orthotopic liver transplantation (Ltx). Liver transplant candidates were evaluated for the study's suitability during preoperative clinical assessment; patients with pre-existing pulmonary or cardiac diseases other than the common end-stage liver dysfunction symptoms,[20] fulminant hepatic failure, hepatopulmonary syndrome, or pulmonary hypertension, were excluded from the study. After liver transplant surgery, all patients were admitted to the intensive care unit (ICU) for routine postoperative care. They were

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all extubated in the operating room after surgery. Patients underwent central and peripheral intravenous and arterial catheterization before liver transplantation, and these catheters were used postoperatively. Arterial pressure was measured invasively in all patients using a 20-gauge arterial catheter (radial artery) connected to pressure tubing and a pressure transducer (Edwards Lifesciences, Irvine, CA).

An 8.0-Fr pulmonary artery catheter (CCOmbo CCO/SvO_2/CEDV/VIP catheter 777HF8; Edwards Lifesciences, Irvine, CA) was introduced into the right internal jugular vein via an 8.5-Fr introducer (AVA 3Xi 8.5-Fr Edwards Lifesciences, Irvine, CA) and connected to a Vigilance monitor (Edwards Lifesciences, Irvine, CA) for intermittent cardiac output (ICO), stroke volume (SV) and continuous cardiac output (CCO) measurements. ICO measurements were assessed by injecting 10 mL of cold ($<10^{\circ}C$) saline into the superior vena cava through the atrial port. Three consecutive injections were made randomly during the respiratory cycle over a 2-minute period for each interval of the predefined time series. In the case of a discrepancy in CO value greater than 10%, the measurement was repeated 2 more times (5 times in total) and the lowest and the highest results were discarded. To avoid operator variability, the same investigator always performed the injection. The plot of the washout curve was analyzed for stable baseline temperature, undisturbed rapid upstroke, and exponential decay without signs of early recirculation. All data were obtained with patients spontaneously breathing. All patients were supine and the zero reference was taken as the midaxillary line.

$PulseCO_{Lir}$-derived continuous cardiac output data were recorded using the commercially available LiDCO*rapid* monitor (LiDCO System, London, UK). With this device, the stroke volume is estimated by the PulseCO algorithm.[21,22] The accuracy and the trending ability of the PulseCO algorithm (LiDCOPlus, LiDCO System, London, UK) after transpulmonary indicator dilution calibration previously has been investigated in different clinical settings.[11,23,24] In the LiDCO*rapid*, bias reduction is not achieved by indicator dilution but via a nomogram derived from a previous patient population. In the LiDCO*rapid* setup, the user only needs to enter the patient details (weight and age) into the monitor and the scaling factor is automatically estimated.

The study was carried out in the ICU starting approximately 2 hours after the end of surgery, (T0). The cardiac output then was measured using each technique at least every 8 hours (T8, T16, T24, T32, T40, T48). CCO and $PulseCO_{LiR}$ data also were collected every hour from admission until the 48th postoperative hour. $PulseCO_{LiR}$ values were obtained as the mean of 3 values read from the LiDCO*rapid* monitor before each injection performed to obtain ICO. At each time point, CCO measurements were recorded immediately before and after ICO measurements and the mean of these CCO data pairs was recorded. The mean CCO was compared with the corresponding mean $PulseCO_{LiR}$ value collected every hour, and ICO was compared with $PulseCO_{LiR}$ collected at the predefined time points (T0-T48).

All measurements were collected when patients were hemodynamically stable, considered as presenting values of mean arterial pressure, cardiac output, and heart rate that were $\leq 10\%$ different from those assessed at the time of admission. Before each measurement, the arterial pressure catheter and transducer were checked by performing a 5-mL blood aspiration and a 5-mL saline injection test; investigators also visually evaluated the quality of the arterial waveform contour. All catheters were flushed and aspirated easily, and the arterial pressure waveform was optimized, if necessary, by wrist extension or catheter manipulation. The arterial pressure monitoring system then was assessed objectively using a "flush" test. If arrhythmias occurred during the measurements, the results were discarded and measurements repeated.

The study plan was for the enrollment of 20 subjects, CO being assessed in each subject using 3 different methods at 7 time points. This design achieves 90% power to test the factor "time," 97% power to test the factor "method of measurement," and 80% power to test the method "time interaction," each with a 5% significance level and an effect size of 1. Power analysis was performed using the routine "Advanced Repeated Measures ANOVA Power Analysis" in Pass 11 software. Pass 11 software (NCSS, LLC, Kaysville, UT).

Descriptive statistics were produced for the demographic, clinical, and laboratory characteristics of the study population. Mean values and standard deviations (SD) are presented for normally distributed variables, whereas median values and interquartile ranges (IQR) are presented for non–normally distributed variables, and number and percentages are provided for categoric variables.

Hemodynamic measurements and mean CO values derived from ICO and CCO versus $PulseCO_{LiR}$ were analyzed by analysis of variance for repeated measurements. Three methods were compared: ICO, $PulseCO_{LiR}$, and CCO; concordance between CO measurements among the 3 methods was assessed by means of multilevel linear models for analysis of variance. To account for repeated measurements in the same subject over time and over 3 methods, the authors used the xtmixed command in STATA 12 (STATA Statistical Software Version 12, StataCorp, College Station, TX) as a tool for variance components.[25] The authors included "method" and "time" as the fixed effect (the coefficient for method is the bias of one method over the other; while the coefficient for time allows for postoperative changes); and allowed random slopes (ie, it was taken into account that each patient can have different baseline CO, different trends over time, and different trends by method) for method-patient interaction, for patient-time interaction, and (within the random intercept for the method-patient-time interaction) for method. The model with the smallest variance was taken as the reference for the calculation of residual variance attributable to each method (specifically, ICO $<$ $PulseCO_{LiR}$ $<$ CCO). Method-specific variance was used to calculate the 95% limits of agreement (LOA) modified for repeated measures, as follows:

$$\alpha 1 - \alpha 2 \pm 1.96 \sqrt{2\,\tau 2 + \sigma 21 + \sigma 22}$$

where $\alpha 1 - \alpha 2$ is the mean difference, $\tau 2$ is the between-methods variance, and $\sigma 21 + \sigma 22$ are the residual variances for each of the 2 methods being compared once the variance due to replicates has been subtracted.

In additional models, the authors also adjusted for the baseline measurement of cardiac output assessed by each of the 3 methods and for the hyperdynamic status of the patient (defined as CO >8 L/min as assessed with the ICO method); although these adjustments produced a slight further reduction in the residual variance attributable to the methods, they did not significantly improve the models or change the LOA. The fit of each model was assessed using the Akaike information criterion.[26,27]

For each pair of methods (in accordance with Critchley et al, 2010) the authors calculated the percentage error as the limit of agreement (2SD) of the bias divided by the mean CO obtained using the 2 methods—for example, 100 * (2SD of bias) / [(ICO + $PulseCO_{LiR}$)/2].[28] A PE $\leq$ 30% has been suggested as the cutoff value for accepting a new technique.[28]

For each patient and method, percentage changes (%Δ) in CO were calculated for all successive readings. To assess ability to measure change, 4 quadrant plots were produced for each pair of methods, the regression line fitted, and R^2 calculated. Furthermore, %ΔCO was categorized as zero change (%ΔCO: within $\pm$ 20%) or as a decrease or increase, and the Cohen kappa statistic was calculated as the measure of inter-rater agreement.

STATA 12 for Windows was used for statistical analyses, and GraphPad Version 2.0 for MAC (GraphPad^{TM} Software, San Diego, CA) was used for the creation of Bland-Altman plots.