Performance of a new pulse contour method for continuous cardiac output monitoring: validation in critically ill patients

BENDJELID, Karim, et al.

Abstract

BACKGROUND: A new calibrated pulse wave analysis method (VolumeView™/EV1000™, Edwards Lifesciences, Irvine, CA, USA) has been developed to continuously monitor cardiac output (CO). The aim of this study was to compare the performance of the VolumeView method, and of the PiCCO2™ pulse contour method (Pulsion Medical Systems, Munich, Germany), with reference transpulmonary thermodilution (TPTD) CO measurements. METHODS: This was a prospective, multicentre observational study performed in the surgical and interdisciplinary intensive care units of four tertiary hospitals. Seventy-two critically ill patients were monitored with a central venous catheter, and a thermistor-tipped femoral arterial VolumeView™ catheter connected to the EV1000™ monitor. After initial calibration by TPTD CO was continuously assessed using the VolumeView-CCO software (CCOVolumeView) during a 72 h period. TPTD was performed in order to obtain reference CO values (COREF). TPTD and arterial wave signals were transmitted to a PiCCO2™ monitor in order to obtain CCOPiCCO values. CCOVolumeView and CCOPiCCO were recorded over a 5 min [...]
Performance of a new pulse contour method for continuous cardiac output monitoring: validation in critically ill patients

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Editor’s key points

- Previously, continuous cardiac output (CO) measurement techniques required the insertion of a pulmonary artery catheter.
- The PiCCO and VolumeView systems use arterial pulse contour analysis for continuous CO measurement.
- Both require calibration with transpulmonary thermodilution (TPTD) measurements using a central venous catheter.
- The current study compared the performance of PiCCO, VolumeView, and TPTD measurements.

Background. A new calibrated pulse wave analysis method (VolumeView™/EV1000™, Edwards Lifesciences, Irvine, CA, USA) has been developed to continuously monitor cardiac output (CO). The aim of this study was to compare the performance of the VolumeView method, and of the PiCCO™ pulse contour method (Pulsion Medical Systems, Munich, Germany), with reference transpulmonary thermodilution (TPTD) CO measurements.

Methods. This was a prospective, multicentre observational study performed in the surgical and interdisciplinary intensive care units of four tertiary hospitals. Seventy-two critically ill patients were monitored with a central venous catheter, and a thermistor-tipped femoral VolumeView™ catheter connected to the EV1000™ monitor. After initial calibration by TPTD CO was continuously assessed using the VolumeView-CCO software (CCOVolumeView) during a 72 h period. TPTD was performed in order to obtain reference CO values (COREF). TPTD and arterial wave signals were transmitted to a PiCCO™ monitor in order to obtain CCO PiCCO values. CCO VolumeView and CCO PiCCO were recorded over a 5 min interval before assessment of CO TPTD. Bland–Altman analysis, % errors, and concordance (trend analysis) were calculated.

Results. A total of 338 matched sets of data were available for comparison. Bias for CCO VolumeView–COREF was −0.07 litre min⁻¹ and for CCO PiCCO–COREF +0.03 litre min⁻¹. Corresponding limits of agreement were 2.00 and 2.48 litre min⁻¹ (P<0.01), %errors 29 and 37%, respectively. Trending capabilities were comparable for both techniques.

Conclusions. The performance of the new VolumeView™-CCO method is as reliable as the PiCCO™-CCO pulse wave analysis in critically ill patients. However, an improved precision was observed with the VolumeView™ technique.

Clinical trials.gov identifier. NCT01405040.

Keywords: continuous cardiac output; pulse wave analysis; transpulmonary thermodilution

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Cardiac output (CO) assessment is a cornerstone in advanced haemodynamic management, especially in critically ill patients. Pulmonary artery thermodilution (PATD) has been used as a standard method for this purpose for >20 years and is progressively being replaced in many patients by less invasive monitoring techniques. One of these techniques is continuous analysis of the arterial pressure waveform. Today, different companies provide a variety of devices based on this method using different algorithms for the estimation of CO. In general, pulse wave analysis devices can be divided into un-calibrated and calibrated monitoring systems; both can be adequately used in dedicated settings and patient groups according to their limitations and technical properties. Based on the fact that there is no ‘perfect’ monitoring device, ongoing development is required that may lead to improved measurements and hence improved patient management.

Recently, a new pulse wave analysis system has been developed and introduced into clinical practice that consists of a specific thermistor-tipped arterial catheter (the VolumeView™ catheter) and the EV1000™ monitoring platform (Edwards Lifesciences, Irvine, CA, USA). The system uses a novel proprietary algorithm to continuously assess CO based on the femoral arterial pressure curve signal and
it uses TPTD for calibration. The modified TPTD algorithm has been successfully evaluated recently in an animal model and in critically ill patients. However, this system has not yet been validated for continuous CO determination against a reference method.

The aim of the present multi-centre clinical study was to compare the new EV1000™-VolumeView™ and the PiCCO2™ pulse contour methods (Pulsion Medical Systems, Munich, Germany) with the reference TPTD technique in a mixed population of critically ill patients.

Materials and methods

Patients

This prospective observational study was conducted in four hospital centres in Germany and Switzerland (Aachen, Bonn, Geneva and Zurich). The trial was registered at a public registry (clinicaltrials.gov identifier: NCT01405040). Approval from local institutional review boards at all participating institutions was obtained: (EthikKommission an der Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen, Aachen, Germany; Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, Bonn, Germany; Commission Centrale d’Ethique de la recherche sur l’être humain, Hôpitaux Universitaires de Genève, Genève, Switzerland; Ethikkommission der beiden Stadtspitäler Triemli und Waid, Kantonale Ethikkommission des Kantons Zürich, Zürich, Switzerland).

All patients or their legal representatives gave written informed consent. Patients who had been admitted to an intensive care unit (ICU) and who the treating clinician thought required advanced haemodynamic monitoring, were enrolled. Patients <18 years or patients with a body weight <40 kg were not eligible for the study. Other exclusion criteria comprised significant aortic regurgitation, use of intra-aortic balloon pump and participation in an investigational drug or device study interfering with endpoints of this study and a known or potential pregnancy. All patients were treated at the discretion of the ICU staff in charge; there was no specific protocol for any intervention.

Devices and measurements

CO assessment was performed during a 72 h observation period in all patients. A VolumeView™ catheter (diameter: 5 Fr, length 20 cm; Edwards Lifesciences) was introduced into the left or right femoral artery and connected to the EV1000™ system which includes a panel interface and data box (Edwards Lifesciences, software version 1.0). No complications related to the femoral line during the study period were observed.

Continuous CO was determined by pulse wave analysis using the new VolumeView-CCO software (CCOVolumeView). TPTD measurements were performed as sets of at least three consecutive injections of 20 ml cold saline via a central venous line, randomly distributed over the respiratory cycle. A bolus was rejected and deleted by the observer, usually the attending physician, when visual inspection of the TPTD curve revealed artifacts, or a measurement error occurred. Boluses were repeated until three valid thermodilution curves were obtained with a reproducibility ≤15%. There was no regular time interval between two successive measurements. All measurements were randomly spread according to the attending physicians. Measurements were performed during the regular ICU treatment of the patients under different ventilator modalities (i.e. completely mechanically ventilated patients, spontaneously breathing patients with and without ventilator support).

The mean CO value of the TPTD measurements was used as the reference method (COREF). These data were electronically recorded at 500 Hz on the EV1000™ system and downloaded for analysis via a universal serial bus connection. Later, arterial pressure data were delivered electronically as real-time procedure into a PICCO™ monitor (Pulsion Medical Systems, Munich, Germany) in order to obtain continuous PiCCO™ pulse wave analysis CO values (CCOPiCCO) and these data were also electronically recorded. This procedure is now used on a regular basis for the comparison of different measurement techniques. Both pulse contour methods were re-calibrated each time TPTD measurements were done. CCOVolumeView and CCOPiCCO data for statistical analysis were recorded during a 5 min interval before assessment of COREF (i.e. just before the re-calibration of CCOVolumeView and CCPiCCO). These data, and measurements recorded during a 5 min interval post assessment of COREF, were also used to assess the corresponding changes of CCOVolumeView CO PiCCO and COREF; initial calibration data at baseline were excluded from the analysis.

Pulse wave analysis algorithms

The pulse wave analysis algorithm for CCOVolumeView (i.e. the EV1000™ monitoring platform), uses a proprietary ‘combination’ CCO algorithm:

\[ \text{CCOVolumeView} = \text{CO} \left( \frac{\text{TPTD}}{f(\Delta \text{conventional pulse-wave parameters}, \Delta \text{advanced wave shape parameters})} \right) \]

‘Conventional’ pulse-wave parameters are determined considering the fundamental work of Wesseling assuming that the area under the systolic part of the pressure waveform is related to stroke volume by aortic impedance. Further development based on a three-element ‘Windkessel’ model involved the assessment of the aortic impedance as quotient of an un-calibrated pulse wave stroke volume and a stroke volume derived by TPTD. Because only the systolic portion of the pressure waveform is analysed, a detection of the ‘notch’, the transition point after the systolic peak as a result of the aortic valve closure is required. ‘Advanced’ arterial pressure wave shape parameters, on the other hand, are derived from analysis of the pressure waveform of the entire heart cycle. An in-depth description of this method can be found in a recent publication. In summary, the advanced analysis relies primarily on the assessment of
Cardiac output using a new pulse contour method

aortic compliance according to Langewouters and colleagues and dedicated waveform assessment, including skewness calculations, where symmetry characteristics on arterial pressure indicates a change in vascular tone and resistance, and kurtosis calculations, where the measurement of the divergence from a normally distributed wave is associated with large vessel compliance.

The pulse wave analysis algorithm for CCO PiCCO, on the other hand, is an algorithm based on the ‘conventional’ pulse-wave parameters described above. Details have been previously described. The principles of TPTD calibration measurements have also been described in detail elsewhere.

Statistics

Statistical calculation was performed using the R software (Version 2.11.1, a free software environment for statistical computing; http://www.r-project.org). Linear regression, Bland–Altman analysis including % error calculation were done in order to compare absolute CCO VolumeView and CCO PiCCO with CO REF values. Concordance analysis was performed as trend analysis for changes of CCO VolumeView and CCO PiCCO when compared with changes of CO REF; an exclusion zone of 15% was applied as recommended recently. Statistical significance was set at a -value of <0.05. Results are expressed as mean [standard deviation (sd)].

Results

The study was mainly performed in patients who had undergone cardiac surgery. Biometric and socio-demographic data of the 72 patients enrolled in this study are presented in Table 1. Sixty-one patients were undergoing mechanical ventilation. For these patients a total of 338 matched sets of data during a time window of 72 h were collected and analysed. The study period was 34.5 (20.9) h [mean (sd)], range 5.4–72 h. Regarding the number of boluses, 3.6 (1.1) [mean (sd)], range 1–6, were used per CO measurement, with only 3.7% of the thermodilution sets rejected because of a reproducibility >15%.

CO data are summarized in Table 2. A broad range of CO values for all measurement techniques (i.e. CCO VolumeView, CCO PiCCO, and CO REF) was observed with a comparable mean CO for all measurement techniques. Mean changes of CO and the corresponding range were 5.2 (3.8) litre min\(^{-1}\) (0–14.3) for CCO VolumeView, 5.3 (3.8) litre min\(^{-1}\) (0–14.9) for CCO PiCCO, and 6.4 (4) litre min\(^{-1}\) (0–15) for CO REF. Mean arterial pressure during the study period was 10.1 (0.13) kPa (range: 43–114) and a mean systemic vascular resistance was 839 (286) dyn s cm\(^{-5}\) ranging from 273 to 1940 dyn s cm\(^{-5}\).

Comparing CCO VolumeView and CCO PiCCO with CO REF revealed a low mean bias in the Bland–Altman analysis (Table 2, Fig. 1) that was comparable for both continuous measurement techniques. The precision, defined as sd of the mean bias, was better when comparing CCO VolumeView with CO REF than when comparing CCO PiCCO with CO REF (P<0.01). A high coefficient of correlation (Table 2) for both techniques was found when compared with the reference technique, no statistical difference could be detected between correlation coefficients. Trend analysis for both techniques was comparable considering concordance analysis (Table 2, Fig. 2).

Discussion

This prospective, multi-centric clinical study demonstrates that the assessment of continuous CO in a critically ill patient population using a new pulse wave analysis algorithm implemented in the VolumeView™-EV1000™ monitoring platform can be characterized as being as accurate as the established calibrated pulse wave analysis device, the PiCCO™ method. Moreover, based on the presented data, the new technique showed an improved precision when compared with the established method.

The CCO VolumeView™ algorithm can be characterized as ‘improvement’ of the classic algorithm established and modified by Wesseling that is also being used of the PiCCO™ system. The ‘improvement’ process consisted of the addition consideration of an advanced pressure waveform analysis. This creates potential advantages for the new combination algorithm. The classic Wesseling algorithm requires ‘only’ the systolic interval of the pressure curve for CO assessment assuming constant aortic properties. This algorithm proved to be susceptible for changes in the vascular system with a limited accuracy of CO assessment. Taking a dynamic interaction between cardiac function and aortic compliance (i.e. aortic impedance) into account resulted in an improved performance. However, for accurate measurements a reliable detection of the end of the systole—the ‘notch’—is required, which is not always given in daily practice and in these situations an assumption has to be made when the systole ends. It can be argued that the advanced waveform analysis implemented in the new ‘hybrid’ algorithm may overcome this problem in part as

**Table 1** Patient characteristics and indications for ICU admission.

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>Years (range)</th>
<th>66 (25–81)</th>
</tr>
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<tbody>
<tr>
<td>F/M ratio</td>
<td>n/n</td>
<td>21/51</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 (20)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (8)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>28 (1.3)</td>
<td></td>
</tr>
<tr>
<td>ICU admissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery (n, %)</td>
<td>40 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Non-cardiac surgery (n, %)</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Sepsis (n, %)</td>
<td>7 (9.7)</td>
<td></td>
</tr>
<tr>
<td>ARDS (n, %)</td>
<td>3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Other (n, %)</td>
<td>18 (25)</td>
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both the systolic and the diastolic waveform portion are assessed. This may better reflect the actual conditions of the cardiovascular system that includes diastolic issues of the aortic Windkessel function, diastolic wave reflection and the aortic-femoral pulse coupling. In this regard, it is important to note that all pulse contour methods should be affected by this physiological phenomenon. Considering the results of the actual study (i.e. the improved precision) it can be argued that the combination of two methods resulted in a more robust algorithm able to capture acute changes in vascular tone. However, previous studies have already demonstrated that CO measurements using advanced waveform computation are less precise and less accurate in patients presenting vasoplegic states. And even if, in the present study, patients SVR ranged from 273 to 1940 dyn s cm$^{-2}$, further study should be performed to evaluate the present CCO-VolumeView$^\text{TM}$ algorithm in vasoplegic patients.

In contrast to the PICCO$^\text{TM}$ algorithm the CCO—VolumeView$^\text{TM}$ algorithm met the so-called Critchley criteria of an acceptable $\%$ error of $<30\%$, but it should be emphasized that this widely used $\%$ error threshold has been questioned recently by Peyton and colleagues. In their large meta-analysis they demonstrated that no group of the minimally invasive haemodynamic monitoring systems (i.e. pulse wave analysis, Doppler, Bioimpedance, and applied Fick principle) met the set $\%$ error threshold and therefore it has been argued that for clinical purposes a higher $\%$ error should be accepted based on the technical limitations of all CO measurement techniques. On the other hand, it is often assumed that the ability to reliably track CO changes is more important than the assessment of absolute CO values and in the present study both algorithms showed comparable trending capabilities but failed to meet the goals of an acceptable concordance as proposed by Critchley and colleagues. The concordance analysis for CO trend assessment is clearly an improvement in the evaluation of CO monitoring devices, but a major problem is the lack of ability of the adjustment for repeated measurements and the potential bias that may limit the informative value of this test. Pulse wave

**Table 2** CO measurements and comparative analyses. CCO$^\text{VolumeView}$, continuous cardiac output assessed by the new VolumeView$^\text{TM}$/EV1000$^\text{TM}$ monitoring platform; CO$^\text{REF}$, cardiac output determined by TPTD; CCO$^\text{PICCO}$, continuous cardiac output assessed by the PICCO$^\text{TM}$ system. NA, not available; SD, standard deviation; LoA, limits of agreement ($=\pm 2 \times \text{SD}$)

<table>
<thead>
<tr>
<th></th>
<th>Mean (so) (litre min$^{-1}$)</th>
<th>Mean bias (LoA) (litre min$^{-1}$)</th>
<th>Error (%)</th>
<th>Correlation, $r^2$</th>
<th>Concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCO$^\text{VolumeView}$</td>
<td>$6.7 (2.3)$ (2.5–15.3)</td>
<td>CCO$^\text{VolumeView}$−CO$^\text{REF}$</td>
<td>$-0.1 (2.0)$</td>
<td>29</td>
<td>0.83</td>
</tr>
<tr>
<td>CCO$^\text{PICCO}$</td>
<td>$6.8 (2.5)$ (2.5–16.2)</td>
<td>CCO$^\text{PICCO}$−CO$^\text{REF}$</td>
<td>$+0.1 (2.5)$</td>
<td>37</td>
<td>0.76</td>
</tr>
<tr>
<td>CO$^\text{REF}$</td>
<td>$6.8 (2.4)$ (2.7–18.6)</td>
<td>CCO$^\text{VolumeView}$−CCO$^\text{PICCO}$</td>
<td>$-0.1 (2.1)$</td>
<td>31</td>
<td>0.82</td>
</tr>
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</table>

**Fig 1** Bland–Altman analysis for CCO$^\text{VolumeView}$ vs CO$^\text{REF}$ (a) and CCO$^\text{PICCO}$ vs CO$^\text{REF}$ (a). VolumeView, continuous CO assessed by the new VolumeView$^\text{TM}$/EV1000$^\text{TM}$ monitoring platform; TPTD=CO$^\text{REF}$, cardiac output determined by transpulmonary thermodilution; PICCO, continuous cardiac output assessed by the PICCO$^\text{TM}$ system. Dashed lines represent mean bias, upper and lower limits of agreement.
analysis devices in general have gained greater interest for continuous CO measurement recently and are increasingly being applied in different patient settings today (e.g. un-calibrated systems based on radial arterial signal primarily for the management of perioperative goal-directed therapy) and systems based on a femoral signal that are calibrated by TPTD for the haemodynamic management of ICU patients. This can be attributed to the fact, that most of these devices can be easily handled, adequately used without major operator interference and that they provide ‘real time’ continuous CO and functional haemodynamic parameters such as stroke volume variation. However, despite the importance of further improvements of the algorithms optimal signal quality is a major prerequisite for reliable CO assessment and major limitations need to be taken into account that include use of intra-aortic balloon pump and major arrhythmias. Clearly, modern algorithms may detect single ventricular extrasystoles and may exclude them for CO assessment. However, the performance of pulse wave analysis during absolute arrhythmia may limit their use. In recent years research and development has focused on non-calibrated pulse wave analysis devices and subsequent validation identified appropriate areas of application, but it also revealed the limits of the devices. A major issue is definitely the fact that limited accuracy may occur in situations of major changes and extremes of individual vascular tone. It has to be emphasized that these vascular tone effects may influence the performance of all pulse wave devices, if they have to be calibrated or not, to a various degree as this was observed in different studies. These effects may largely depend on the robustness of the algorithms and for the un-calibrated devices on their underlying electronic databases that comprise nomograms and information of the different vascular conditions. In contrast, calibrated pulse wave analysis techniques such as the VolumeView™/EV1000™ and the PICCO2™ system permit an individual initial assessment of the cardiovascular condition by the calibration via TPTD, and when major haemodynamic instability (i.e. considerable changes in vascular tone) occurs, re-calibration allows for a situational adjustment, a ‘re-setting’ of continuous CO assessment. Moreover, when general limitations for the use of pulse wave analysis devices are present, intermittent TPTD can still be used for reliable CO determination and thirdly, TPTD provides additional haemodynamic parameters such as global end-diastolic volume (GEDV) and extravascular lung water (EVLW). GEDV has shown in recent years to be a superior indicator of cardiac preload than standard pressure parameters and EVLW can be useful in the treatment of a pulmonary oedema or acute respiratory distress syndrome and as a prognostic marker in critically ill patients.

The following limitations need to be considered when interpreting the data of the actual study: TPTD was used as a reference technique and not as an independent CO measurement technique such as an aorta Doppler probe or PATD. However, given the fact that there is no gold standard for CO measurements it seems to be reasonable to use TPTD, which has been shown to provide CO measurements as accurate as the PATD. Moreover, CCO was not simultaneously assessed by two different devices connected to two different femoral arterial lines but directly to only one device, the VolumeView™/EV1000™ and the data were then transmitted to the PICCO2™ monitor. However, this approach can be considered acceptable for technical and ethical reasons and is frequently used. Furthermore, this study was not designed to specifically assess the CCO performance during massive haemodynamic instability and major changes of vascular tone in a mixed ICU patient population with a predominant set of patients after cardiac surgery. Thus, our results must be interpreted within the context of the

Fig 2 Concordance plot for % changes of CCOVolumeView vs COREF (a) and CCOPICCO vs COREF (a). VolumeView, continuous CO assessed by the new VolumeView™/EV1000™ monitoring platform; TPTD=COREF, cardiac output determined by transpulmonary thermodilution; PICCO, continuous cardiac output assessed by the PICCO2™ system. Data points within the 15% exclusion zone (white points) are excluded from analysis.
chosen setting as it is very difficult to make clear the expected results in patients with highly variable vascular tone, sudden changes in CO and needing vasoactive drugs.

Conclusions

In conclusion, in a mixed ICU population and a wide range of clinical situations the new VolumeView™-CCO method performed as accurately as the PiCCO™-CCO pulse wave analysis. Furthermore, an improved precision was observed for the VolumeView™ technique.

Authors’ contributions

A.H., C.K.H., G.M., and K.B. conceived the study. N.K., C.K.H., M.G., T.P.S., and N.S. collected the data. K.B. and C.K.H. carried out the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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Declaration of interest

K.B. has received consultant fees from Edwards Lifesciences and Novartis. G.M. has received speakers’ honoraria, consultant fees and a research grant from Edwards Lifesciences. N.K. has received speakers’ honoraria from Edwards Lifesciences and support for congress fees. C.K.H. has received speakers’ honoraria and research grants from Edwards Lifesciences, Pulsion Medical Systems, and CSL Behring, Berne, Switzerland. A.H. has received speakers’ honoraria from Edwards Lifesciences. M.G., T.P.S., and N.S. have no potential conflicts of interest to declare.

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