Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability

Oliver Gödje, MD, PhD; Kerstin Höke, MD; Alwin E. Goetz, MD, PhD; Thomas W. Felbinger, MD; Daniel A. Reuter, MD; Bruno Reichart, MD, PhD; Reinhard Friedl, MD; Andreas Hannekum, MD, PhD; Ulrich J. Pfeiffer, MD, PhD

The concept of arterial pulse-contour analysis for the determination of continuous cardiac output (CO) has been the subject of investigation for a number of years (1–5). Although the technology that was first developed was based on relatively simple principles, satisfying results were demonstrated in comparisons with standard pulmonary artery thermodilution (PATD) CO (6–8). Nevertheless, the method has not been widely accepted by clinicians, not least because the original pulse-contour approach required calibration with PATD CO, therefore making it a highly invasive technique.

Recently, a new device for pulse-contour analysis was developed (PiCCO, Pulsion Medical Systems, Munich, Germany) that does not require PATD for calibration. This new approach uses transpulmonary thermodilution (TPTD) for calibration, building on previous work that validated TPTD as comparable with standard PATD for CO measurement (9–16). The TP method requires the placement of central venous and arterial catheters only, and because this type of vascular access is used routinely for the majority of critically ill patients, the TP method is convenient and much less invasive. Good results have been demonstrated in both peri- and postoperative intensive care (17–20), and the technology is gaining increasing clinical acceptance as a result.

Another argument against the clinical use of pulse-contour analysis for continuous CO monitoring was the belief of some investigators that during profound changes in hemodynamic status, pulse-contour analysis might become unreliable (8, 21, 22). Interestingly, several other authors have been unable to confirm this problem (6, 18, 19, 23). Nevertheless, for any system of CO monitoring to be valid in clinical practice, it is exactly in situations of hemodynamic instability that precise measurement of CO is essential and continuous monitoring is most important. The intention of this study, therefore, was to address directly the question of whether continuous CO measurement determined by pulse-contour analysis is reliable during episodes of hemodynamic instability. A further purpose was to compare the performance of the original approach to pulse-contour analysis developed by Wesseling and co-workers in 1974 (3) with the new, more sophisticated algorithm implemented within the current PiCCO device.

MATERIALS AND METHODS

Patients. With institutional review board approval, 24 patients at a cardiac surgical intensive care unit were enrolled in this study after major surgery. They were from a larger group in whom data were being collected as part of the development and clinical validation of the PiCCO system. The key entry criteria for this study were the clinical requirement for hemodynamic monitoring and that the patient should demonstrate changes in CO of \( > \pm 20\% \) during the study period when compared with the initial measurement, this having been defined prospectively. All hemodynamic changes occurred as the result of the spontaneous postoperative course or clinically driven postoperative treatment with vasoactive drugs. The postoperative course of CO was calculated by both pulse-contour algorithms and compared with simultaneous measurements of CO by TPTD in all the patients investigated. The study was conducted according to the Declaration of Helsinki in its revised version of Tokyo (1975), Venice (1983), Hong Kong (1989), and Somerset West (1996), and the Guidelines of Good Clinical Practice devised by the International Conference for Harmonization (1997). Informed consent was obtained from all patients before their participation in the investigation.

Devices and Measurements. The PiCCO system for hemodynamic monitoring consists of a bedside computer, an inline injectate temperature sensor connected to a central venous catheter, and a 4-French thermistor-tipped arterial catheter (PV204L16, Pulsion Medical Systems). In addition to providing intermittent CO measurement by bolus arterial thermodilution, the arterial catheter is also connected to a disposable high-fidelity pressure transducer. This allows determination of the arterial pressure waveform and heart rate and, hence, continuous CO by pulse-contour analysis. The pressure wave from each cardiac cycle is digitized and analyzed according to the pulse-contour algorithm. The thermodilution measurement of CO is used to calibrate the pulse-contour measurement, according to the principles outlined below.

The 4-French femoral arterial pulse-contour catheter was inserted into each study patient preoperatively or immediately postoperatively and connected to the PiCCO system. The pulse-contour computer was then calibrated by triplicate TPTD measurements, and no further calibrations were performed during the study period. The indica-
PiCCO digitizes the arterial pulse wave for CO computing, it was possible to record the pulse curves of each patient during the thermodilution measurements with a portable computer and specially programmed software linked with the serial interface of the PiCCO device. Having recorded the pulse curves during the thermodilution measurements, CO measured by both pulse-contour algorithms was then computed. Direct comparisons between both the two pulse-contour algorithms and the TPTD bolus thermodilution measurements were then made at identical time points.

**Algorithms.** The basic algorithm for the determination of CO from pulse-contour was developed by Wesseling and co-workers in 1974 (3–5). According to this algorithm, left ventricular stroke volume is computed by measuring the area under the systolic portion of the arterial pressure waveform and dividing this area by the aortic impedance. A subsequent multiplication by the heart rate yields pulse-contour CO. To adjust for aortic impedance, which differs from patient to patient, a thermodilution measurement of CO for the calibration of the system is required and is calculated as follows: CO = heart rate × Asys/Zao, where Zao = SVpc/SVtd (Asys = area under systolic pressure waveform, Zao = aortic impedance, SVpc = uncalibrated stroke volume based on pulse-contour, and SVtd = stroke volume by thermodilution). This original Wesseling algorithm was implemented in the previous PiCCO software version 1.0.14. More detailed information is available in the literature (3–5).

The second software version used for comparison in the investigation was version 4.1, as currently implemented within the PiCCO device. This new pulse-contour algorithm is a more sophisticated formula that analyzes the actual shape of the pressure waveform in addition to the area under the systolic portion of the pressure waveform. Furthermore, the software takes into account the individual aortic compliance and systemic vascular resistance based on the following considerations. During systole, more blood is ejected from the left ventricle than actually leaves the aorta. During the subsequent diastole, the volume remaining in the aorta flows into the arterial network at a rate dictated by the aortic compliance, the systemic vascular resistance, and the blood pressure (Windkessel effect), and the shape of the arterial pressure curve after the diastolic notch is representative of this passive emptying of the aorta. The individual compliance is determined by using TPTD CO as a reference method to obtain the blood flow while simultaneously measuring the blood pressure. As with the original Wesseling algorithm, there is still the need for a patient-

![Graphical and mathematical display of the new pulse-contour algorithm for determination of cardiac output.](image)

**Figure 1.** Graphical and mathematical display of the new pulse-contour algorithm for determination of cardiac output. **PiCCO**, cardiac output determined by arterial pulse-contour analysis.

**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, Yrs</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Vasoactive Drugs</th>
<th>Measurements, no.</th>
<th>Range of SVR, Dyn/sec</th>
<th>Range of CO, L/min</th>
<th>Maximum CO Deviation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>M</td>
<td>CABG</td>
<td>—</td>
<td>9</td>
<td>910–1140</td>
<td>5.8–7.6</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>MVR</td>
<td>Epi, Enx</td>
<td>23</td>
<td>450–940</td>
<td>7.2–11.3</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>CABG</td>
<td>Dop, Nit</td>
<td>23</td>
<td>1140–1210</td>
<td>3.8–5.1</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>MVR</td>
<td>Epi, Enx</td>
<td>21</td>
<td>1250–1480</td>
<td>4.0–6.1</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>CABG</td>
<td>—</td>
<td>23</td>
<td>620–1010</td>
<td>5.3–8.2</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>CABG</td>
<td>Epi, Nit, Enx</td>
<td>24</td>
<td>1320–2160</td>
<td>3.3–6.8</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>M</td>
<td>MVR</td>
<td>Epi</td>
<td>28</td>
<td>450–770</td>
<td>7.3–13.1</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>M</td>
<td>CABG, MOF</td>
<td>Dop, Epi, Nor</td>
<td>26</td>
<td>950–1350</td>
<td>5.1–14.8</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>AVR, SHHCK</td>
<td>Dop, Epi, Nor, Nit</td>
<td>19</td>
<td>460–770</td>
<td>8.6–11.9</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>MVR, ARDS, MOF</td>
<td>Dop, Epi, Nor</td>
<td>23</td>
<td>660–1060</td>
<td>7.5–9.9</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>M</td>
<td>LHI + LE</td>
<td>Dop, Dob</td>
<td>19</td>
<td>470–870</td>
<td>10.9–14.1</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>61</td>
<td>M</td>
<td>CABG</td>
<td>—</td>
<td>19</td>
<td>620–940</td>
<td>8.1–11.2</td>
<td>22</td>
</tr>
<tr>
<td>13</td>
<td>72</td>
<td>M</td>
<td>AVR + CABG</td>
<td>Epi, Enx</td>
<td>17</td>
<td>610–1490</td>
<td>2.8–6.7</td>
<td>136</td>
</tr>
<tr>
<td>14</td>
<td>76</td>
<td>F</td>
<td>CABG</td>
<td>—</td>
<td>17</td>
<td>790–1200</td>
<td>4.3–6.3</td>
<td>46</td>
</tr>
<tr>
<td>15</td>
<td>70</td>
<td>M</td>
<td>CABG</td>
<td>Epi</td>
<td>44</td>
<td>750–1260</td>
<td>2.7–6.3</td>
<td>70</td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>M</td>
<td>CABG</td>
<td>—</td>
<td>29</td>
<td>750–1920</td>
<td>4.0–10.0</td>
<td>54</td>
</tr>
<tr>
<td>17</td>
<td>74</td>
<td>M</td>
<td>AVR + CABG</td>
<td>Enx</td>
<td>27</td>
<td>1070–2360</td>
<td>2.9–4.4</td>
<td>26</td>
</tr>
<tr>
<td>18</td>
<td>71</td>
<td>F</td>
<td>CABG</td>
<td>Nit</td>
<td>16</td>
<td>710–920</td>
<td>6.5–8.6</td>
<td>25</td>
</tr>
<tr>
<td>19</td>
<td>88</td>
<td>F</td>
<td>AVR + CABG</td>
<td>Epi, Nor</td>
<td>17</td>
<td>970–1250</td>
<td>4.7–7.0</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>55</td>
<td>F</td>
<td>CABG</td>
<td>—</td>
<td>17</td>
<td>840–1050</td>
<td>6.0–7.3</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>56</td>
<td>M</td>
<td>CABG</td>
<td>Nit</td>
<td>17</td>
<td>620–810</td>
<td>6.6–8.2</td>
<td>25</td>
</tr>
<tr>
<td>22</td>
<td>76</td>
<td>M</td>
<td>CABG</td>
<td>Dob</td>
<td>15</td>
<td>550–750</td>
<td>8.0–10.1</td>
<td>21</td>
</tr>
<tr>
<td>23</td>
<td>77</td>
<td>M</td>
<td>AVR + CABG</td>
<td>—</td>
<td>15</td>
<td>790–980</td>
<td>6.4–9.5</td>
<td>33</td>
</tr>
<tr>
<td>24</td>
<td>74</td>
<td>M</td>
<td>CABG</td>
<td>Epi, Nit</td>
<td>17</td>
<td>780–1040</td>
<td>7.0–9.4</td>
<td>26</td>
</tr>
</tbody>
</table>

**Sum** M/F; 17/7

<table>
<thead>
<tr>
<th>Mean</th>
<th>66.5</th>
<th>22</th>
<th>772–1197</th>
<th>5.7–8.6</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>so</td>
<td>9.4</td>
<td>7</td>
<td>242–417</td>
<td>2.0–2.5</td>
<td>27</td>
</tr>
</tbody>
</table>

SVR, systemic vascular resistance; CO, cardiac output; M, male; F, female; CABG, coronary artery bypass grafting; MVR, mitral valve replacement; Epi, epinephrine; Enx, enoximone; Dop, dopamine; Nit, norepinephrine; MOF, multiorgan failure; Nor, norepinephrine; AVR, aortic valve replacement; SHHCK, septic shock; ARDS, acute respiratory distress syndrome; LHI, left heart insufficiency; LE, lung emboli; Dob, dobutamine.
specific calibration, which is also determined by the TPTD CO measurement. The new algorithm is shown in detail in Figure 1.

Statistics. CO was computed by pulse-contour analysis based on software version 1.0.14 (COpc-old) and software version 4.1. (COpc-new) and compared with CO based on triplicate TPTD by means of multiple regression and Bland-Altman analyses. To avoid the possibility that the pulse-contour-derived values could have been influenced by the thermodilution measurements, the average of the values recorded immediately before and after each set of bolus measurements were used for the statistical analysis. At each time point for which measurements from at least 10 patients were available, the stability of the initial calibration was evaluated by analyzing change in bias over time using Friedman’s two-way analysis of variance, followed by Wilcoxon’s matched-pair test, making allowances for multiple testing. Multiple regression was performed to assess the influence of heart rate and mean arterial pressure on the difference in CO derived from pulse-contour analysis vs. TPTD. All statistical analyses were computed by SPSS for Windows (version 10.0, SPSS, Chicago, IL).

RESULTS

Twenty-four patients were identified in whom there was a change of CO measured by TPTD of $ \pm 20\%$ compared with the initial value. A total of 517 CO measurements were made in these patients during study periods ranging from 8 to 44 hrs, with a mean of 22 measurements per patient. The mean change of CO was 40% ± 27% for the group overall; however, in four patients, changes in CO were $>50\%$, and in one patient, a change in CO of $>100\%$ was observed. Mean systemic vascular resistance (SVR) as calculated from TPTD ranged from between 772 ± 242 and 1197 ± 417 dyne-sec/cm5. The lowest SVR recorded was 450 dyne-sec/cm5, and the highest was 2360 dyne-sec/cm5, with changes $>500$ dyne-sec/cm5 identified in five patients. As described previously, all hemodynamic changes occurred either spontaneously or as a result of clinically driven postoperative treatment with vasoactive or positive inotropic drugs. Detailed descriptions of the patients, their underlying diseases, vasoactive or inotropic drug use, and hemodynamic variances are shown in Table 1.

The comparison of COpc-old to COtd resulted in a correlation coefficient of 0.76 with a $p$ value of 0.027. In the Bland-Altman analysis, the bias was 0.08 L/min with a single SD of 1.81 L/min (Fig. 2, top and bottom). The results of the comparison of COpc-new to COtd are presented in Figure 3, top and bottom. The regression analysis resulted in a correlation coefficient of 0.88 at a significance level of $p = .0001$. In the corresponding Bland-Altman analysis, the bias was $-0.2$ L/min, with a single SD of 1.2 L/min.

The change in mean CO by different methods over time is shown in Figure 4. At three time points, the bias of COpc-old vs. COtd was significantly higher than the bias of COpc-new vs. COtd. Although at all other times differences in bias were not statistically significant, visual inspection shows that the curve for COpc-new is closer to the curve of COtd than is the curve of COpc-old at most measurement points. This is also evident when the values for CO obtained by the different methods are plotted against time in individual patients. Figure 5, top and bottom, shows the patients with the highest percentage changes in CO (139% in patient 13 and 94% in patient 6). The mean differences of COtd vs. COpc are 0.14 L/min and 0.54 L/min for the new algorithm and 1.1 L/min and 1.14 L/min for the old algorithm, respectively. Figure 6, top and bottom, shows the two patients with the greatest variation in SVR during the measurement period (1290 dyne-sec/cm5 in patient 16 and 1170 dyne-sec/cm5 in patient 6). The mean difference of COtd vs. COpc is
lower for the new algorithm with values of 0.10 L/min and 0.19 L/min, in comparison with the old algorithm with mean differences of 1.17 L/min and 0.25 L/min, respectively.

Multiple regression analysis did not show any influence of heart rate or arterial systemic pressure on the differences between COpc and COtd for either of the old or the new algorithm.

**DISCUSSION**

Measurement of CO by thermodilution using a pulmonary artery (PA) catheter (24, 25) is well established, and generally performs well. Even so, the PA catheter has been criticized due to the invasiveness and inherent complications of the procedure, and the misleading nature of cardiac filling pressures as clinical preload parameters (26, 27). These disadvantages of the PA catheter have fuelled the search for new methods of hemodynamic monitoring, and the pulse-contour technology contained within the PiCCO system provides such an alternative. However, to establish that the method is clinically acceptable it must be demonstrated that the accuracy of CO measurement by pulse-contour analysis is comparable to that of PATD.

Several investigators have already shown that this is the case in different clinical settings and under varying circumstances (7, 17, 19, 23). Nevertheless, although the results of these studies are encouraging, the evidence to counteract concerns that pulse-contour analysis may not be reliable during profound changes of CO has previously been lacking. The focus on this study was therefore tailored specifically to address this question. Analysis of the pulse-contour signal using the original Wesseling algorithm shows that this approach may be unreliable under rapidly changing hemodynamic conditions. On the other hand, our results show that pulse-contour analysis is reliable during profound CO changes when the new algorithm implemented within the PiCCO system is used. We investigated a broad range of COs (2.7–14.1 L/min) and peripheral resistance changes (450–2360 dyne·sec/cm²) and found reproducible results and satisfying accuracy in the comparison with thermodilution CO. This confirms the reliability of the new approach to pulse-contour analysis in clinical use even in hemodynamically unstable patients.

As not all of the patients enrolled in the study had PA catheters in place, we used the TPTD technique implemented in the PiCCO system as the reference method for CO measurement. TPTD has been shown to be identical to PATD in the past (9–16), and a comparison of TPTD to CO measurement by the reference Fick method also showed good results (28). In fact, in studies in which both thermodilution methods were compared with pulse-contour analysis, the agreement and correlation between PATD and TPTD was good (17, 18, 20). Using TPTD instead of PATD to evaluate and calibrate the pulse-contour method is therefore justified for the purpose of this study. This approach also makes clinical sense, inasmuch as it means that only a central venous catheter and an arterial catheter are required for the method to be used.

Because the major focus of this study was the performance of the pulse-contour device in daily clinical practice, we chose not to induce any changes in hemodynamics in the study patients through artificial therapeutic interventions, but instead observed the "natural clinical course" in a predefined group demonstrating substantial hemodynamic changes. This provided the necessary test conditions without subjecting the patients to the potential risks of
The pulse waveforms were digitally recorded immediately before, during, and after the thermodilution measurements to control for any corruption of the results by the thermodilution measurement interventions themselves. This also allowed CO to be computed with the two different pulse-contour algorithms at exactly the same time points using the identical pulse waves from each individual patient. Therefore, under these circumstances, any influence of patient-specific variables can be excluded. This would have not have been possible had we investigated two separate patients groups. For example, matching cases for the identical presence or type of arrhythmias would clearly have been impossible.

The presence of arrhythmias is an important issue in the measurement of CO by pulse-contour analysis and may have a distinct influence on the comparison of the two measurement techniques. According to the basic principle, pulse-contour analysis computes CO by multiplying separately measured stroke volumes with the heart rate at those time points. Thermodilution measures CO independent of single-stroke volumes by computing flow per time. During arrhythmias, stroke volume and heart frequency change constantly, and so the resulting CO will also change constantly. This will be dampened during the time frame of a thermodilution measurement, especially during the relatively longer (as compared with PATD) TPTD period, but this is not the case for the beat-to-beat pulse-contour analysis. This means that during one thermodilution period pulse-contour CO may differ from the thermodilution value without it being clear which CO is the true CO at that exact moment. Indeed, the pulse-contour method may actually be more accurate at this time than thermodilution, but, to answer this question, a specific study such as comparison of pulse-contour analysis with electromagnetic or ultrasonic flow measurement would be required. Being aware of this issue, we did not differentiate according to presence or type of arrhythmia in our patients. Although we cannot exclude any influences of arrhythmias on the accuracy of the pulse-contour analyses themselves, the identical conditions and timings at
which both algorithms were tested mean that we can exclude the influence of arrhythmias on the results of our comparison between the methods.

Another area of potential concern is the possible requirement to recalibrate the pulse-contour analysis with further bolus measurements after the initial calibration has been carried out. Figures 3–5 address this point and demonstrate that the elapsed time between initial calibration and subsequent measurements had no influence on the bias between the pulse-contour and the thermodilution methods. With the newly developed algorithm, we found no significant differences between mean COpc-new and mean COtd at all, while with the original Wesseling algorithm there were significant differences between COpc-old and COtd at three time points, but these differences did not increase toward the end of the measurement period. This suggests that the time between calibration and measurement is not important as regards the accuracy of the approach, especially with the new algorithm, under the study conditions. It should be noted that care was taken to flush, check, and, if necessary, re-zero the pressure transducers on a regular basis, and this is a prerequisite for the successful use of the technique. Although during our study recalibration was not performed during a time frame that ranged from between 8 and 44 hrs, we do not suggest that recalibration should be neglected for longer periods of time in clinical practice. An acceptable accuracy vs. effort ratio is obtained with recalibration at every 8 hrs or if substantial changes 

in the condition of the patient occur. This provides the extra information that is available from the bolus TPTD measurements (extravascular lung water and intrathoracic blood volume), as well as providing a routine for controlling the quality of the performance of the device.

At the moment, the use of pulse-contour analysis is limited to femoral, brachial, or axillary arterial access. As radial artery pressure measurement is known to be unreliable under certain conditions (29), especially in severely ill patients requiring high-dose catecholamine or vasoconstrictor support (30), the use of the radial artery approach for pulse-contour analysis cannot be recommended at present. This phenomenon is increasingly well recognized and, as in this study population, many physicians prefer to utilize a more central arterial access site to improve the accuracy and precision of their monitoring. Nevertheless, the conventional method of arterial catheterization is still to use the radial artery where possible for standard blood pressure and arterial blood gas analysis. The radial artery is technically straightforward to cannulate and normally has a good collateral circulation, so developing the technique further to allow the radial approach to be used for pulse-contour measurements would be an important refinement of the technique.

We have demonstrated that, even in hemodynamically unstable patients, the continuous pulse-contour analysis is a valid alternative to PA catheterization, as it is as accurate but far less invasive as a method for monitoring CO. In addition, the new pulse-contour algorithm is a significant improvement upon the older Wesseling approach, and concerns about the requirement for fre-
quent recalibration do not appear to be justified.

When compared with continuous CO measuring PA thermol dilution systems, the PiCCO is not only a less invasive, but also a less expensive alternative. The PiCCO arterial catheter and pressure transducer, a central venous catheter with standard pressure transducer and an in-line sensor, are disposable. According to the manufacturer, the price for this material in the United States is currently around $150. To set up a continuous PA catheter system, disposable products costing approximately $180 are required (PA catheter with two standard pressure transducers, in-line sensor, introducer kit, central venous and arterial catheter with standard pressure transducers).

Personnel time exposure is also less for the PiCCO system. In our department, the medium set-up time is 29 mins for the PiCCO and 54 mins for a continuous PA catheter system (data based on the mean of 10 set-ups of each system). This, however, depends not only on the system itself, but also on individual experience, especially in placing of PA catheters.

The worries regarding PA catheter measurements as surrogates of preload have only briefly been alluded to in our discussion, but here also there are less invasive parameters currently available that provide higher predictive value (11, 31, 32), and we agree with other authors (15) that, today, the use of PA catheters should be limited to patients in whom knowledge of right ventricular afterload or mixed venous oxygen saturation is essential. In conclusion, pulse contour analysis is an easy and reliable method for the continuous monitoring of CO in critically ill patients.

REFERENCES


