Reproducibility of Double Indicator Dilution Measurements of Intrathoracic Blood Volume Compartments, Extravascular Lung Water, and Liver Function*

Oliver Godje, MD; Marcus Peyerl, MS; Tobias Seebauer, MS; Oliver Dewald, MS; and Bruno Reichart, MD

Study objective: Arterial thermal dye dilution (TDDart) with the COLD system (Munich, Germany) allows measurement of cardiac index (CI), partial blood volumes, lung water, and liver function. The aim of the study was to determine agreement of TDDart measurements with pulmonary artery thermal dilution measurements (TDpa) and to assess the reproducibility of TDDart parameters.

Design: Prospective study.
Setting: ICU of a university hospital department of cardiac surgery.
Patients: Thirty consecutive patients after coronary artery bypass grafting.

Measurements and results: Triplicate measurements of TDDart parameters were performed 1, 3, 6, 12, and 24 h postoperatively and coefficients of variation (CVs) were computed. At the 3-h point, additional fivefold TDDart measurements were done and compared with TDpa measurements. The coefficient of correlation for CI from TDDart vs TDpa was 0.96 (p < 0.001), and the mean difference was 0.16 L/min/m² (2.4%). The CVs of the TDDart and TDpa CI measurement were 7.2% and 5.9%; the CVs of other TDDart parameters were 4.6% (cardiac function index), 8.3% (global end-diastolic volume), 7.0% (intrathoracic blood volume), 7.6% (total blood volume), 7.4% (right ventricular end-diastolic volume), 7.4% (right heart end-diastolic volume), 11.3% (left heart end-diastolic volume [LHEDV]), 12.0% (right to left heart volume proportion [R/LHV]), 8.8% (pulmonary blood volume), 10.8% (extravascular lung water), 16.4% (plasma disappearance rate of dye), and 19.8% (dye clearance). The CV did not depend on Glasgow coma scale or on body temperature.

Conclusion: The CVs of LHEDV and R/LHV are influenced by asynchronous TDDart and TDpa variation. The CVs of plasma disappearance and dye clearance are increased as the half-life of the dye is longer than the measurement sequence. All other parameters derived from TDDart and TDpa show a clinically sufficient reproducibility.

CHEST 1998; 113:1070-77

Key words: cardiac output measurement; extravascular lung water; indocyanine green dye; intrathoracic blood volume; thermal dye dilution

Abbreviations: CB Tig = blood clearance rate of indocyanine green; CI = cardiac index; CIArt = cardiac index measured in femoral artery; CIAp = cardiac index measured in pulmonary artery; CO = cardiac output; CV = coefficient of variation; DSt = downslope time; EVLW = extravascular lung water; GCS = Glasgow coma scale; GEDV = global end-diastolic blood volume; ICC = indocyanine green; ITBV = intrathoracic blood volume; LHEDV = left heart end-diastolic volume; MTt = mean transit time; PA = pulmonary artery; PDR = plasma disappearance rate; R/LHV = right to left heart volume proportion; RHEDV = right heart end-diastolic volume; TBV = total blood volume; TDDart = arterial thermal dye dilution; TDpa = pulmonary arterial thermal dilution

Hemodynamic monitoring and treatment of deviation from normovolemia belong to the fundamental and most difficult tasks in intensive care.1-3

*From the Department of Cardiac Surgery, University Hospital Großhadern, Ludwig-Maximilians-Universität München, Munich, Germany. Manuscript received May 30, 1997; revision accepted September 10, 1997. Reprint requests: Oliver Godje, MD, Dept of Cardiac Surgery, University of Munich, Klinikum Grosshadern, 81377 Munich, Germany

Usually, monitoring is performed with a pulmonary artery (PA) catheter that allows determination of cardiac output (CO) and measurement of central venous pressure and pulmonary capillary wedge pressure, both of which are assumed to reflect central blood volume and hence to be reliable guides to volume therapy. These pressures, however, are indirect volume indicators at best, and increase with intrathoracic pressure, most pronounced in ventilated patients.2,4 Moreover, because of its inherent
risks and invasiveness, the PA catheter is met with criticism.\textsuperscript{6-7} A recent study\textsuperscript{8} reports a higher patient mortality caused by the mere use of this catheter. As a consequence, a reevaluation of the use of this catheter was recommended.\textsuperscript{9-13}

However, determination of intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV) with the COLD system (COLD Medical Systems; Munich, Germany) gains more and more clinical acceptance to guide volume therapy in ICU patients.\textsuperscript{3,14-16} These direct parameters of volume are obtained by arterial thermal dye dilution (TDDart), which requires a thermistor-equipped arterial fiberoptic catheter to be placed in the femoral artery and a central venous injection of the double indicator. As a PA catheter is not required, the system can be titled “less invasive.” With the same technique, extravascular lung water (EVLW), liver function (by plasma disappearance rate [PDR] and blood clearance rate [CBbig] of the dye), and total blood volume can be determined. Only if subcompartments of ITBV like right heart end-diastolic volume (RHEDV), left heart end-diastolic volume (LHEDV), or right heart outflow are to be determined separately is a PA catheter necessary.

Experimental data and clinical experiences of this method are encouraging,\textsuperscript{3,15,16} concerning reproducibility, however, only few data exist in the literature. In a selected group of cardiac surgery patients, we investigated reproducibility and precision of all TDDart measurements with the COLD system and compared it with conventional pulmonary arterial thermal dilution (TDPa).

**Materials and Methods**

**Patients**

Thirty consecutive patients (26 male) were studied after uncomplicated coronary bypass grafting. Mean age was 66.9±10.2 years (range, 44 to 87 years). Patients with extensive peripheral arterial occlusive disease and patients with a known allergy against indocyanine green (ICG) dye were not considered for this investigation, and only those patients in whom a PA catheter (Ohmeda; Erlangen, Germany) had already been inserted upon induction of anesthesia were included. Written informed consent was obtained from all patients prior to the operation; the study protocol was approved by the ethics committee.

**Measurement Protocol**

The femoral artery catheter already in place was replaced by a 4F introducing sheath (Arrow; Reading, Pa) by the Seldinger technique. A 3F thermistor-tipped fiberoptic catheter for thermal dye dilution (PV 2024; Pulsion Medical Systems; Munich, Germany) was inserted into the descending aorta via the femoral artery sheath and connected to the COLD system. As this catheter also serves for pressure monitoring and blood withdrawal, no additional arterial access was required.

The double indicator consisted of 1 mg/kg of body weight ICG dye mixed in 10 mL iced dextrose 5% solution, and was injected as a bolus into the superior vena cava via the proximal port of the PA catheter, which was also connected to the COLD system. To maintain a constant indicator temperature and to exclude variations of manual injection, an automatic thermodilution injector (ZI-03; Pulsion Medical Systems) was used, which kept the indicator temperature at 4°C and injected it at a constant rate of 10 mL/s.

At the ICU, 1, 3, 6, 12, and 24 h postoperatively, triplicate thermal dye dilution measurements with the COLD system (measurement interval, 5 min) were performed. To compare the different thermal dilution techniques, at 3 h postoperatively, five additional measurements were performed, which included arterial thermal dilution with the COLD system and conventional PA thermal dilution started by the same indicator injection. For this purpose, the PA catheter was disconnected from the COLD system and connected to the CO module of the patient monitor (Streccus 125Si; Siemens; Erlangen, Germany).

To take into account effects of restlessness or movement, the degree of alertness at the measurement times was assessed using the Glasgow coma scale (GCS).

**Method of Double Indicator Measurements**

The dilution curves for dye and temperature were recorded simultaneously in the descending aorta, using the signals from the thermistor-tipped fiberoptic catheter. This catheter was connected to the COLD system, which calculated flow and volumes from the dilution curves. Detecting the thermal curve in the PA allows right heart CO measurement and is required for calculation of the ITBV subcompartments.

Estimation of flow and volumes by thermal dye dilution is based on simultaneous application of substances that distribute either to the intravascular space of the cardiopulmonary system or to the intravascular and extravascular space. The thermal indicator distributes to the intravascular and extravascular space, thereby marking the intrathoracic thermal volume. ICG, which even with severe lung injuries stays intravascularly,\textsuperscript{17,18} after injection immediately binds to plasma proteins, thereby marking the intrathoracic blood volume exclusively.

After injection of the cold/dye bolus into the superior vena cava, pulmonary arterial CO and arterial CO are derived from thermal indicator dilution, based on the Stewart-Hamilton formula.\textsuperscript{19-21} To determine intrathoracic volumes, dye and thermal dilution curves are analyzed yielding the mean transit time of the indicator and its exponential downslope time (DST) (Fig 1). Multiplication of arterial and pulmonary arterial CO, respectively, with the mean transit times (MTt), yields the “needle to needle volume,” which means the volume between the point of injection and the point of detection. Multiplication of COs with the DST yields the volume of the largest mixing chamber between the point of injection and the point of detection. Combining these volumes, additional parameters like EVLW, LHEDV, and GEDV can be computed. All volumes derived from this method are end-diastolic volumes, as these correspond to the largest mixing chambers of the heart. Together with its corresponding algorithms, all volumetric intrathoracic parameters derived from the COLD system are schematically presented in Figure 2.

ICG is eliminated from the blood selectively by the liver.\textsuperscript{17} The PDR reflects the amount of dye which, after complete mixing, is eliminated in percent of the initial value and hence is a monitor of the excretory liver function.\textsuperscript{22}

If the decay of the ICG concentration is mathematically extrapolated backwards to the time of injection, the initial concentration (instantaneous mixing assumed) can be estimated. Knowing now the initial dye concentration in the blood and the...
amount of dye injected, calculation of total blood volume (TBV) is possible according to the Fick principle.\textsuperscript{19,23} Formulas of CO, PDR, TBV, and CBlig are presented and explained in Figure 3.

As in the present study, we focused on reproducibility; the clinical relevance and use of these parameters as well as their course during the 24-h period will not be discussed in detail.

\textbf{Statistics}

For statistical analysis, all values have been indexed to body surface area. Concerning precision, the corresponding parameters derived from TDDart and TDa were compared using a regression analysis. Due to the lack of the true value of CO, an additional analysis according to Bland and Altman\textsuperscript{24} was also performed. Reproducibility was assessed in terms of the coefficient of variation (CV) for three successive measurements. Mean results at different measurement times were compared with the \textit{t} test for unpaired samples. Significance was considered at \(p<0.05\); values were expressed as mean \(\pm SD\). All statistical analyses were computed by software (SPSS for Windows, version 7.0; 1995; SPSS Inc; Chicago).

\textbf{RESULTS}

The results for simultaneous measurements of cardiac index (CI) in the artery (Clart) with the \textit{COLD} system and in the PA (Clpa) with the Sirecust system are given in Table 1. CVs for either measurement were below 10\% without a significant difference between both methods. Regression analysis in Figure 4 shows the correlation between Clart (\textit{COLD}) and Clpa (Sirecust); the correlation coefficient (CV) is 0.96 (\(p<0.001\)). Mean difference between Clart and Clpa (bias) was 0.16 L/min/m\(^2\) corresponding to 2.4\%, as shown in the Bland-Altman plot (Fig 5). Limits of agreement were +0.79 L/min/m\(^2\) and -0.44 L/min/m\(^2\). The mean difference did not depend on the level of CI.

CVs (Table 2) were below 10\% at all measurement times for Clart, Clpa, cardiac function index, GEDV index, ITBV index, TBV index, and right ventricular end-diastolic volume index, respectively. For LVEDV index, right to left heart volume proportion (R/LHV), EVLV index, CBlig, and PDR at several measurement times, CVs were higher than 10\%, with 17\% for CBlig at 12 h maximally. CV did not vary with level of alertness or with baseline body temperature, as significant changes of GCS or body temperature did not result in significant changes of CV.

Concerning the results of each of the three repetitive measurements at each time, for PDR and CBlig a clear dependence on the interval time was found. At every measurement time, the result of the second and third single measurement was significantly higher than that of the preceding one. Figure 6 depicts the constant increase of PDR results within

\textbf{Conclusions}

Different systems and principles were used for CO measurement. The results of the \textit{COLD} system with Clart were different from those achieved with the Sirecust. Differences between CI values measured with the Sirecust and \textit{COLD} were higher at baseline than at other times. Between CI values of Clart and Clpa there was a high correlation at different measurement times. Due to the high reproducibility of CI, CO, and PDR, there is a great potential for the use of the \textit{COLD} system as a monitoring device in critical care medicine.
\[
CO(l/\text{min}) = \frac{(Tb - Ti) + Vi \times K}{\int Tb \times dt}
\]

- \(CO\): cardiac output
- \(Tb\): blood temperature before injection (°C)
- \(Ti\): temperature of injected solution (°C)
- \(Vi\): volume of injected solution (ml)
- \(K\): specific correction factor
- \(\int Tb \times dt\): area under thermal dilution curve

\[
PDR(\%) = 100 \times \frac{\ln 2}{t1/2}
\]

- \(PDR\): plasma disappearance rate
- \(\ln 2\): logarithm 2
- \(t1/2\): ICG halftime (min)

\[
TBV(ml) = \frac{n(t = 0)}{c(t = 0)}
\]

- \(TBV\): total blood volume
- \(n(t=0)\): amount of injected dye (mg)
- \(c(t=0)\): computed dye concentration at time of injection (mg/ml)

\[
CBlig(\%/\text{min}) = TBV \times PDR
\]

- \(CBlig\): blood clearance index of indocyanine green dye
- \(TBV\): total blood volume (ml)
- \(PDR\): plasma disappearance rate (%)

**Figure 3. Formulas for calculation of CO, liver function, and total TBV.**

The triplicate injections. PDR derived from the second measurement was 4.3±1.1%, and from the third measurement it was 7.9±1.3% higher than from the first measurement. The same effect was seen in CBlig but in no other parameter.

**Discussion**

CO derived from TDDart was higher than CO from TDpa, which supports results from other authors. Two divergent explanations are suggested to account for this discrepancy. The indicator is possibly lost on transcardiopulmonary passage with a resulting overestimation of CIart as compared with CIpa. Other workers could not confirm the loss of indicator. They argue that a slowing of the heart rate caused by a reaction of the sinus node to the injected cold influences the estimation of CIpa. Slowing of the heart rate, however, would underestimate the true CI, as the major impact of a slow heart rate is during the short passage between vena cava and PA. During the longer passage to the descending aorta, this influence would tend to level out. Which CI is the true CI, therefore, cannot be decided. In any case, both values were tightly correlated as judged from the correlation coefficient of 0.96 and the Bland-Altman analysis with a mean difference CIart/CIpa of 2.4% only (Fig 4-5). As CVs show an equal reproducibility and there are only minor differences between both methods, CIpa can be replaced by CIart without restrictions.

The majority of CVs of the volumes derived from TDDart were also below 10%, which makes them applicable in daily clinical routine. Catheter position and prevailing body temperature might influence the detection of the TDDart signal; however, significant

**Table 1—Comparison of CIpa and CIart Measurements 3 h Postoperatively**

<table>
<thead>
<tr>
<th></th>
<th>Mean CI, L/min/m²</th>
<th>Mean SD L/min/m²</th>
<th>Mean CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIpa (Siemens 1281)</td>
<td>3.17</td>
<td>0.20</td>
<td>6.31</td>
</tr>
<tr>
<td>CIart (COLD Z 021)</td>
<td>3.31</td>
<td>0.23</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*N=150. Five consecutive measurements in each patient.*

**Figure 4. Regression analysis for CO measurement (by the COLD system and the Siemens Sirecust 1281).**

**Figure 5. Bland-Altman plot for CO measurement (by the COLD system and the Siemens Sirecust 1281).**
Table 2—Mean Results, Standard Deviation, and Variation Coefficients of COLD Measurements During the 24 h Postoperative Course*

<table>
<thead>
<tr>
<th>Time Measurement</th>
<th>1 h</th>
<th>3 h</th>
<th>6 h</th>
<th>12 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>CV, %</td>
<td>Mean±SD</td>
<td>CV, %</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>CIpa (L/min/m²)</td>
<td>3.1±0.2</td>
<td>5.9</td>
<td>3.0±0.2</td>
<td>5.1</td>
<td>3.3±0.2</td>
</tr>
<tr>
<td>CIart (L/min/m²)</td>
<td>3.5±0.2</td>
<td>6.0</td>
<td>3.3±0.2</td>
<td>7.2</td>
<td>3.7±0.2</td>
</tr>
<tr>
<td>CFI (L/min)</td>
<td>5.0±0.2</td>
<td>4.6</td>
<td>5.0±0.2</td>
<td>3.2</td>
<td>5.1±0.1</td>
</tr>
<tr>
<td>GEDV index (mL/m²)</td>
<td>748±62</td>
<td>8.3</td>
<td>696±53</td>
<td>7.6</td>
<td>720±37</td>
</tr>
<tr>
<td>ITBV index (mL/m²)</td>
<td>903±58</td>
<td>6.4</td>
<td>865±61</td>
<td>7.0</td>
<td>902±42</td>
</tr>
<tr>
<td>TBV index (mL/m²)</td>
<td>2496±188</td>
<td>7.5</td>
<td>2621±199</td>
<td>7.6</td>
<td>2802±161</td>
</tr>
<tr>
<td>RVEDV index (mL/m²)</td>
<td>107±8</td>
<td>7.5</td>
<td>111±7</td>
<td>6.1</td>
<td>118±7</td>
</tr>
<tr>
<td>RHEDV index (mL/m²)</td>
<td>242±18</td>
<td>7.4</td>
<td>252±10</td>
<td>4.0</td>
<td>270±10</td>
</tr>
<tr>
<td>LHEDV (mL/m²)</td>
<td>506±57</td>
<td>11.3</td>
<td>444±49</td>
<td>11.2</td>
<td>459±39</td>
</tr>
<tr>
<td>R/LHV (−/−)</td>
<td>0.6±0.1</td>
<td>12.0</td>
<td>0.6±0.1</td>
<td>11.5</td>
<td>0.7±0.1</td>
</tr>
<tr>
<td>PBV index (mL/m²)</td>
<td>167±15</td>
<td>8.8</td>
<td>169±14</td>
<td>8.1</td>
<td>172±12</td>
</tr>
<tr>
<td>EVLW index (mL/kg)</td>
<td>7.2±0.8</td>
<td>10.8</td>
<td>6.6±0.5</td>
<td>7.0</td>
<td>6.3±0.5</td>
</tr>
<tr>
<td>CHf (mL/min/m²)</td>
<td>660±106</td>
<td>16.1</td>
<td>670±122</td>
<td>18.2</td>
<td>753±126</td>
</tr>
<tr>
<td>PDRig (%/min)</td>
<td>26.1±3.8</td>
<td>14.6</td>
<td>25.3±4.1</td>
<td>16.4</td>
<td>26.8±4.1</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>35.9</td>
<td>36.4</td>
<td>36.7</td>
<td>37.6</td>
<td>37.2</td>
</tr>
<tr>
<td>GCS</td>
<td>3.9</td>
<td>5.2</td>
<td>7.6</td>
<td>12.1</td>
<td>14.5</td>
</tr>
</tbody>
</table>

*p<0.05 compared to preceding value.

*CI=cardiac index; RVEDV=right ventricular end-diastolic volume; PBV=pulmonary blood volume; PDRig=plasma disappearance rate of indocyanine green.
changes in baseline body temperature or alertness according to the GCS only occasionally came along with changes of CVs. The height of body temperature or changes in position of the catheter caused by patient movement therefore were not critical for the reproducibility of the double indicator measurements in our study group.

Several workers previously evaluated and confirmed the precision of the estimation of EVLW in humans, as well as in dogs, sheep, and pigs. The CV for EVLW determinations in humans is reported to be 8 to 9%, which is supported by the data presented herein. The highest CV of EVLW measurement was 10.8% and was found 1 h postoperatively. This higher value might be due to the thermal instability of the patients at this time. Although the absolute height of body temperature is uncritical as discussed above, a stable baseline temperature without major drift is essential for reliable EVLW determinations. Short-term variations in body temperature as caused by massive volume supply or rapid external warming or cooling of the patients (as it sometimes is necessary at arrival in the ICU or during and at departure from cardiopulmonary bypass) can result in higher CVs. CVs may also be influenced by the height of the EVLW results, because all EVLW values we measured were within the normal range and no values were measured in the pathologic range. However, even a small variation of 1 mL/kg in the low absolute EVLW range will result in a high CV. The same variation of 1 mL/kg in the pathologic high range of EVLW, which in absolute figures may amount to the fourfold of the normal level, now yields in lower CV. In fact, in high EVLW ranges, other authors working with the same technique found CVs of around 4%.

High CV for LHEDV and R/LHV is caused by their nature as derivatives from three and four parameters, respectively: LHEDV is calculated from ITBV, pulmonary blood volume, and RHEDV measurements. Although each of them has a CV of <10%, the combination of these parameters can increase the CV, because the underlying measurements may vary in different directions: ie, ITBV may vary to a higher value (within its own CV), whereas pulmonary blood volume or RHEDV may vary to a lower value. Combining these measurements to a new parameter, this asynchronous variation leads to a higher CV. The same is true for R/LHV, which includes a fourth parameter. This effect is a basic problem in mathematically combining multiple measurements to a new parameter.

The CVs of PDR and CBlig measurements are influenced by the relatively rapid measurement sequence (5-min interval between each of three measurements). The second and third measurement always yielded a higher result than the previous one, resulting in an increased CV on average. However, in order to have a near identical hemodynamic situation, the triplicate measurements were to follow each other as fast as possible, the 5-min interval being probably within the range of the ICG half-life which is 3 to 4 min with normal liver function. Despite ongoing elimination, the next dye bolus was always added to a still measurable dye concentration. However, to attain the maximum elimination capacity of the liver, 5 to 10 mg/kg of body weight ICG must be injected, as percentage elimination increases when ICG concentration approaches maximum elimination capacity. Despite the small amount injected, dye accumulated, and higher elimination capacity was reached. As a consequence, rapid sequential determinations led to accumulating dye concentrations and thus will always produce increasing plasma disappearance and clearance rates of the dye. Monitoring of liver function by means of measuring maximum ICG elimination rate therefore requires a higher ICG dose and a single dye injection. An amount between 0.5 and 1.0 mg/kg as reported in the literature is, according to the present results, equally appropriate to assess liver function, but a constant dosage of dye and a measurement interval of 30 min (to allow for complete elimination) must be provided. This is of particular importance in patients with reduced liver function, as halftime of the dye is longer and maximum elimination capacity is reached by lower ICG doses. The amount of increase of plasma disappearance rate within injections in rapid sequence.
could conceptually also be used to assess liver function. However, this remains to be investigated.

To conclude, we could show that arterial thermal dilution for CO measurement is as precise as PA thermal dilution and double indicator measurements performed by the COLD system have a clinically satisfactory reproducibility of below 10%, except the measurements of LHEDV, R/LHV, and liver parameters PDR and CBIIg. As the results of the latter ones are wrongly influenced by our measurement protocol, only LHEDV and R/LHV determinations remain to be improved by the manufacturer.

Regarding the ongoing discussion on the use of PA catheters, this method seems to be an interesting alternative and shows considerable potential as a monitoring tool for volume status and hemodynamics. This is of special interest, because most of its parameters are available without PA catheterization.

REFERENCES
19. Stewart GN. Researches on the circulation time in organs and on the influences which affect it. Am J Physiol 1897; 22:159-83
20. Stewart GN. The pulmonary circulation time, the quantity of blood in the lungs and the output of the heart. Am J Physiol 1921; 58:20-44
40 Levey CM, Bender J. Physiology of dye extraction by the liver: comparative studies of sulfobromophthalein and indocyanin green. Ann NY Acad Sci 1963; 111:161-68