Continuous Cardiac Output in Septic Shock by Simulating a Model of the Aortic Input Impedance

A Comparison with Bolus Injection Thermodilution

Wilbert T. Jellema, M.D.,* Karel H. Wesseling, M.Sc.,† A. B. Johan Groeneveld, M.D., Ph.D.,‡ Chris P. Stoutenbeek, M.D., Ph.D.,§ Lambertus G. Thijis, M.D., Ph.D.,|| Johannes J. van Lieshout, M.D., Ph.D.#

Background: To compare continuous cardiac output obtained by simulation of an aortic input impedance model to bolus injection thermodilution (TDCO) in critically ill patients with septic shock.

Methods: In an open study, mechanically ventilated patients with septic shock were monitored for 1 (32 patients), 2 (15 patients), or 3 (5 patients) days. The hemodynamic state was altered by varying the dosages of dopamine, norepinephrine, or dobutamine. TDCO was estimated 189 times as the series average of four automated phase-controlled injections of iced 5% glucose, spread equally over the ventilatory cycle. Continuous model-simulated cardiac output (MCO) was computed from radial or femoral artery pressure. On each day, the first TDCO value was used to calibrate the model.

Results: TDCO ranged from 4.1 to 18.2 l/min. The bias (mean difference between MCO and TDCO) on the first day before calibration was −1.92 ± 2.3 l/min (mean ± SD; n = 52; 95% limits of agreement, −6.5 to 2.6 l/min). The bias increased at higher levels of cardiac output (P < 0.05). In 15 patients studied on two consecutive days, the precalibration ratio TDCO:MCO on day 1 was 1.39 ± 0.28 (mean ± SD) and did not change on day 2 (1.39 ± 0.34). After calibration, the bias was −0.1 ± 0.8 l/min with 82% of the comparisons (n = 112) < 1 l/min and 58% (n = 79) < 0.5 l/min, and independent of the level of cardiac output.

Conclusions: In mechanically ventilated patients with septic shock, changes in bolus TDCO are reflected by calibrated MCO over a range of cardiac output values. A single calibration of the model appears sufficient to monitor continuous cardiac output over a 2-day period with a bias of −0.1 ± 0.8 l/min. (Key words: Afterload; arctangent aortic pressure–area relationship; nonlinear model.)

In critically ill patients, cardiac output is a parameter often used to assess the hemodynamic status and the efficacy of therapy. The most accepted method to estimate cardiac output in the intensive care unit is the intermittent bolus injection thermodilution technique.1,2

Because the hemodynamic status of critically ill patients may change rapidly and unpredictably, the usefulness of intermittent cardiac output determinations is limited. Continuous monitoring of cardiac output could facilitate a more thorough and adequate assessment.3 As a result, the interest in continuous cardiac output has increased over the years.3-5 Impedance cardiography, Doppler ultrasound echocardiography, and pulse-wave analysis are the beat-to-beat techniques presently available. Cardiac output from impedance cardiography correlates moderately with thermodilution in the intensive care setting,5,7 and multiple assumptions about chest dimensions and composition have to be made. Doppler ultrasound echocardiography has limitations with respect to maintenance of the original location of the appropriate systolic velocity profile in the aortic root and of the insolation angle.8 Pulse-wave analysis is also used in beat-to-beat cardiac output monitoring9 and is based on a variety of models of the arterial system.10

Recently a new method of pulse-wave analysis was introduced that estimates beat-to-beat cardiac output from the arterial pressure wave by simulating a nonlinear
three-element model of the aortic input impedance (Modelflow). During cardiac surgery, this method showed adequate tracking of bolus thermodilution cardiac output (TDCO) over a range of 3.1-6.9 l/min for several hours. It remains uncertain, however, how this method performs in high output states, e.g., hyperdynamic septic shock, because vasodilatation associated with severe septic shock may alter the arterial system. This, consequently, may affect cardiac output estimation from the arterial pressure wave.

The aims of this study were to evaluate in patients with septic shock whether continuous cardiac output monitoring by model simulation is reliable in the course of treatment, i.e., over 1 or 2 days, and at various hemodynamic stages, compared with an improved bolus thermodilution technique.

Materials and Methods

Patients

Thirty-two patients with septic shock requiring invasive arterial pressure monitoring, pulmonary artery catheterization, and inotropic therapy were studied. Patients were admitted to the intensive care units of the Academic Medical Center and the Academic Hospital of the Free University between September 1996 and July 1998. Septic shock was defined according to the criteria of Bone et al. Informed consent was obtained from the patient’s next-of-kin, and the study design was reviewed and approved by the ethics committee of the participating hospitals. Patients aged less than 19 yr or more than 74 yr or with a life expectancy of less than 24 h were not included in the study.

Patient characteristics are summarized in table 1. All patients required mechanical ventilation with positive end-expiratory pressure ranging between 5 and 15 cm H₂O and were sedated with opiates and benzodiazepines. Patients received broad-spectrum antibiotic coverage. The antibiotic regimen was adjusted according to the culture results.

Inotropic Drug Regimen

Patients were included after initial fluid resuscitation. Twenty-seven patients received dopamine, mean dosage of 13.6 µg · kg⁻¹ · min⁻¹ (range, 0.63-51); 11 patients received dobutamine, mean dosage of 10.3 µg · kg⁻¹ · min⁻¹ (range, 2.38-20); 26 patients received norepinephrine, mean dosage of 0.44 µg · kg⁻¹ · min⁻¹ (range, 0.02-3.2); and one patient received epinephrine (0.12 µg · kg⁻¹ · min⁻¹).

Twelve patients were studied over a 1-to 5-h period of standard critical care management. Eleven patients were studied during the replacement of norepinephrine (maximum dosage, 0.14-0.35 µg · kg⁻¹ · min⁻¹) by dopamine (maximum dosage, 7-25 µg · kg⁻¹ · min⁻¹) in a crossover design, with arterial pressure maintained at a constant level. Within 1 h, after a steady state for arterial pressure was reached, the inotropic regimen with norepinephrine was restored. Nine patients were studied when dobutamine was added to the vasoactive drug regimen. In approximately 2 h the dobutamine dosage was increased in a stepwise manner to 5, 8, 12.8, and 20 µg · kg⁻¹ · min⁻¹. The dobutamine infusion was terminated at dosages of 8 and 12 µg · kg⁻¹ · min⁻¹ in six patients because of large changes in heart rate or arterial pressure.

As long as the patients met the inclusion criteria, the study performed on the first day was repeated on two consecutive days. Fifteen patients were studied on day 2, six of them during standard critical care management, four during the replacement of norepinephrine by dopamine, and five during the addition of dobutamine (only one patient received the maximal dosage of 20 µg · kg⁻¹ · min⁻¹). Five patients were studied on day 3, two of them during standard critical care management, one during norepinephrine replacement, and two during the addition of dobutamine.

Blood Pressure Monitoring

Radial (25 patients) or femoral (7 patients) artery and pulmonary artery pressures were recorded using a standard Hewlett-Packard model 78342A arterial pressure monitor (Hewlett-Packard, Medical Products Group, Andover, MA). The resonance frequency of the catheter-manometer system was checked with the tapping method before the start of the protocol and ranged between 15 and 25 Hz for radial or femoral artery pressure and > 8 Hz for pulmonary artery pressure. Arterial pressure was measured with the patient in the supine position after calibrating and zeroing to the midaxillary level.

Bolus Injection Thermodilution Cardiac Output

A Baxter COM-2 or SAT-2 device (Baxter Edwards Critical Care, Irvine, CA) was used to compute TDCO. The respiratory signal of the ventilator provided the time pulses to trigger injections of 10 ml ice-cooled 5% glucose solution with a computer-controlled injectate
## Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Underlying Disease</th>
<th>Blood Culture</th>
<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
<th>Maximal Dose of Inotropics (µg·kg⁻¹·min⁻¹)</th>
<th>Number of CIG Measurements</th>
<th>Range of TDCO (l/min)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>44</td>
<td>Pneumonia</td>
<td>Coagulase negative, Staphylococcus, Pseudomonas aeruginosa</td>
<td>78</td>
<td>115</td>
<td>D:21.8/Db:20</td>
<td>7</td>
<td>4.9-6.2</td>
<td>d</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>30</td>
<td>Pneumonia</td>
<td>Staphylococcus epidermidis</td>
<td>70</td>
<td>129</td>
<td>D:23.8/N:0.024</td>
<td>4</td>
<td>18.2</td>
<td>d</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>Pneumonia</td>
<td>Coagulase negative, Enterobacter</td>
<td>63</td>
<td>124</td>
<td>D:17/N:0.024/Db:8</td>
<td>4</td>
<td>13.3-15</td>
<td>s</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>67</td>
<td>Urosepsis</td>
<td>Klebsiella pneumoniae</td>
<td>53</td>
<td>119</td>
<td>D:13.7/Db:12.8</td>
<td>5</td>
<td>10.3-11.5</td>
<td>s</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>Pneumonia</td>
<td>Enterobacter</td>
<td>81</td>
<td>110</td>
<td>D:10/Db:20</td>
<td>4</td>
<td>5-7.4</td>
<td>s</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>48</td>
<td>Cholecystitis</td>
<td>Escherichia coli</td>
<td>72</td>
<td>112</td>
<td>D:12/Db:8</td>
<td>5</td>
<td>7-8.8</td>
<td>s</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>69</td>
<td>Pneumonia</td>
<td>Staphylococcus epidermidis</td>
<td>78</td>
<td>115</td>
<td>D:13/Db:20</td>
<td>6</td>
<td>7-8.8</td>
<td>s</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>70</td>
<td>Colitis</td>
<td>Negative</td>
<td>80</td>
<td>75</td>
<td>D:8.2/N:0.23</td>
<td>5</td>
<td>4.9-6.7</td>
<td>s</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>31</td>
<td>Pancreatitis</td>
<td>Staphylococcus epidermidis</td>
<td>75</td>
<td>140</td>
<td>D:22/N:0.08</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>65</td>
<td>Endocarditis</td>
<td>Staphylococcus epidermidis</td>
<td>80</td>
<td>120</td>
<td>N:0.19</td>
<td>2</td>
<td>10.5-12</td>
<td>s</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>36</td>
<td>Acute leukemia</td>
<td>Negative</td>
<td>85</td>
<td>130</td>
<td>N:0.19</td>
<td>2</td>
<td>9.3-11.2</td>
<td>s</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>50</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>64</td>
<td>70</td>
<td>N:0.19</td>
<td>4</td>
<td>5.6-8.9</td>
<td>d</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>45</td>
<td>Limb abscess</td>
<td>Negative</td>
<td>60</td>
<td>60</td>
<td>N:0.34</td>
<td>3</td>
<td>5.9-7.4</td>
<td>s</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>75</td>
<td>Pneumonia</td>
<td>Enterococcus</td>
<td>90</td>
<td>135</td>
<td>N:0.95/Db:2.38</td>
<td>3</td>
<td>5-7.3</td>
<td>s</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>46</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>99</td>
<td>85</td>
<td>N:0.19</td>
<td>3</td>
<td>7-11</td>
<td>s</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>26</td>
<td>Gas gangrene</td>
<td>Negative</td>
<td>80</td>
<td>92</td>
<td>D:5/N:0.02</td>
<td>3</td>
<td>5-8</td>
<td>s</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>75</td>
<td>Pneumonia</td>
<td>Enterococcus</td>
<td>86</td>
<td>95</td>
<td>D:17.1/N:0.09</td>
<td>4</td>
<td>6-7.9</td>
<td>d</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>54</td>
<td>Sepsis</td>
<td>Neisseria meningitidis</td>
<td>70</td>
<td>97</td>
<td>N:0.11</td>
<td>6</td>
<td>6-8.3</td>
<td>s</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>28</td>
<td>Pneumonia</td>
<td>Enterococcus faecalis</td>
<td>70</td>
<td>97</td>
<td>D:0.63/N:0.14</td>
<td>5</td>
<td>10.2-13.1</td>
<td>s</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>72</td>
<td>Pneumonia</td>
<td>Enterococcus enterococcus</td>
<td>85</td>
<td>106</td>
<td>D:13/N:0.04</td>
<td>1</td>
<td>5.1</td>
<td>d</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>30</td>
<td>Pneumonia</td>
<td>Pseudomonas aeruginosa</td>
<td>90</td>
<td>115</td>
<td>D:32/N:3/E:0.1</td>
<td>2</td>
<td>5.4-6.6</td>
<td>d</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>52</td>
<td>Pneumonia</td>
<td>Enterococcus</td>
<td>65</td>
<td>116</td>
<td>D:32/N:3/E:0.1</td>
<td>3</td>
<td>11.5-12.5</td>
<td>s</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>42</td>
<td>Pancreatitis</td>
<td>Enterococcus</td>
<td>70</td>
<td>75</td>
<td>D:51/N:2.9</td>
<td>2</td>
<td>10.5-11</td>
<td>s</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>52</td>
<td>Colitis</td>
<td>Negative</td>
<td>70</td>
<td>110</td>
<td>D:4/N:0.3</td>
<td>5</td>
<td>4.1-7</td>
<td>s</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>46</td>
<td>Ileus/pneumonia</td>
<td>Pseudomonas aeruginosa</td>
<td>68</td>
<td>114</td>
<td>D:30/N:0.9</td>
<td>2</td>
<td>4.7-5.1</td>
<td>s</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>47</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>88</td>
<td>100</td>
<td>D:16.7/N:1</td>
<td>3</td>
<td>4.1-4.7</td>
<td>s</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>58</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>91</td>
<td>115</td>
<td>D:14/N:0.35/Db:8</td>
<td>8</td>
<td>4.5-10.6</td>
<td>s</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>55</td>
<td>Pneumonia</td>
<td>Pseudomonas aeruginosa</td>
<td>93</td>
<td>118</td>
<td>D:14/N:0.2/D:8</td>
<td>5</td>
<td>5.2-7.5</td>
<td>s</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>55</td>
<td>Pancreatitis</td>
<td>Pseudomonas aeruginosa</td>
<td>82</td>
<td>113</td>
<td>D:11.8/N:0.2/Db:5</td>
<td>4</td>
<td>6-7.3</td>
<td>s</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>56</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>80</td>
<td>88</td>
<td>D:10/N:0.1</td>
<td>3</td>
<td>9.1-11.6</td>
<td>s</td>
</tr>
<tr>
<td>31</td>
<td>M</td>
<td>58</td>
<td>Pneumonia</td>
<td>Negative</td>
<td>88</td>
<td>79</td>
<td>D:5/N:0.1</td>
<td>3</td>
<td>7-8.4</td>
<td>s</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>57</td>
<td>Sepsis</td>
<td>Staphylococcus aureus</td>
<td>82</td>
<td>86</td>
<td>D:8/N:0.2</td>
<td>3</td>
<td>7-8.2</td>
<td>s</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure at the start of the study; HR = heart rate at the start of the study; TDCO = thermodilution cardiac output; D = dopamine; N = norepinephrine; E = epinephrine; Db = dobutamine; d = died in hospital; s = survived.

Pump. The injectate (temperature < 10°C) was delivered through the proximal port of the pulmonary artery catheter in approximately 2 s. The syringe was refilled automatically using a two-way valve. The two-way valve and cooling unit were parts of a closed injection system (CO-set, Baxter). An interface box between the Baxter device and a personal computer provided electric isolation of the patient. The interface box facilitated three options for the automated thermodilution injections: "flush," "start," and, in case of an emergency, "break."

To improve the accuracy of the TDCO estimates, we used the technique of phase-controlled injections,
equally spread over the ventilatory cycle. Injections were performed four times within 3 min. Each injection was delayed from the start of a ventilatory period over 0%, 25%, 50%, and 75% of the duration of the period, with at least 36 s between injections. Each series of four thermodilution estimates was averaged, delivering one TDCO value. The entire series of four thermodilution estimates was rejected if, during an injection, the Baxter device, the ventilator, or the model-simulation software displayed an alert signal, if the injectate temperature was above 10°C, or if the curve of the dilution was abnormal. In case of rejection, the entire series of four thermodilution and model-simulated estimates was repeated.

Model-simulated Cardiac Output
Beat-to-beat cardiac output was estimated from the arterial pressure wave with the Modelflow method. The method uses a nonlinear three-element model of the aortic input impedance to compute an aortic flow waveform (see Appendix).

Protocol
Each day, the first TDCO value was obtained in a steady-state period, i.e., at least 30 min after a change in dosage of catecholamines or sedatives, infusion rate, or ventilatory settings. The first TDCO value of each day was used to calibrate the model by multiplying uncalibrated model-simulated cardiac output (MCO) by the TDCO-to-MCO ratio. The next cardiac output measurements were performed at least 15 min after a change in catecholamine dose, and at time intervals varying from 15 min to 2 h between successive measurements. An example of TDCO and continuous MCO monitoring with substantial changes in hemodynamic status is shown in figure 1.

Data Acquisition and Analysis
The analogue intrarterial pressure and electrocardiogram signals were recorded at a sampling rate of 100 Hz and stored on hard disk for off-line analysis together with values for blood temperature and thermodilution injectate temperature. To facilitate comparison with intermittent TDCO values, continuous MCO values were averaged over two ventilatory cycles beginning at each phase-controlled injection. Each pair of TDCO and MCO values in the comparison, therefore, consisted of an average of four phase-controlled thermodilution estimates and four simultaneously obtained MCO estimates.

The first paired MCO and TDCO measurements of the first day (n = 32) were used to quantify the bias (average difference between MCO and TDCO) and TDCO-to-MCO ratio before calibration (precalibration comparison). To assess the influence of hemodynamic status and measurement site on the precalibration bias and ratio, two groups were analyzed according to the level of TDCO (< 8 and ≥ 8 l/min), heart rate (< 110 and ≥ 110 beats/ min), mean arterial pressure (< 80 and ≥ 80 mmHg), systemic vascular resistance (< 800 and ≥ 800 dyne · s · cm⁻²), and the site of measurement (radial or femoral artery). In the case of measurements on day 2 (15 patients) and day 3 (5 patients), the first paired MCO and TDCO measurements of the corresponding day were analyzed to quantify the bias and the TDCO-to-MCO ratio on consecutive days.

Apart from the first paired measurements on each day, used for calibration (n = 32 on day 1, n = 15 on day 2, and n = 5 on day 3, respectively), all sets of MCO and TDCO values were analyzed in the post-calibration comparison (n = 137). The influence of hemodynamic status and measurement site on the post-calibration bias was analyzed. Post-calibration tracking of changes in cardiac
output by the model was analyzed by relating sign and magnitude of changes in MCO to changes in TDCO.

The robustness of cardiac output tracking throughout consecutive days was assessed by comparing TDCO with off-line recalculation of MCO values from day 2 (15 patients) and day 3 (5 patients) with the use of the TDCO-to-MCO ratio obtained on day 1 only.

**Statistical Analysis**

Average TDCO and MCO values are given as mean ± SD. Differences between simultaneous MCO and TDCO values were plotted against their mean. The agreement (pre- and post-calibration) between the methods was expressed as the bias (mean ± SD). The distribution of the difference between MCO and TDCO was tested for normality. Limits of agreement are given as mean ± 1.96 SD. Influence of the measurement site, level of cardiac output, heart rate, mean arterial pressure, and systemic vascular resistance were analyzed by Student t test. The changes in the TDCO-to-MCO ratio of the patients studied on three successive days were analyzed by nonparametric repeated measures analysis of variance. Tracking of TDCO by MCO was analyzed by linear regression. A P value of less than 0.05 was considered statistically significant.

**Results**

A total of 189 paired cardiac output measurements were obtained in 52 patients. TDCO ranged from 4.1 to 18.2 l/min. The number of paired measurements for each patient ranged from one to six per day (see table 1).

On the second day, 15 of 32 patients were studied (17 patients dropped out), and on the third day, 5 of 15 patients (10 patients dropped out). After the first day, measurements were discontinued in five patients because of a life expectancy less than 24 h, and in eight patients because their clinical conditions improved sufficiently to allow removal of the pulmonary artery catheter. In addition, measurements were discontinued in four patients after the first day because of failure in the communication between computer and the Baxter device or computer hardware problems, with only one paired measurement available in three of four patients.

After the second day, measurements were discontinued in two patients because of life expectancies of less than 24 h, in three patients because of improvement of the clinical condition and removal of the pulmonary artery catheter, and in five patients because of malfunc-

**Precalibration Comparison**

On day 1, uncalibrated MCO was 6.47 ± 2.1 l/min (mean ± SD) and TDCO was 8.38 ± 3.4 l/min (n = 32) with a bias of −1.92 ± 2.3 l/min (95% limits of agreement, −6.5 to 2.6 l/min; fig. 2) and a TDCO-to-MCO ratio of 1.30 ± 0.33. The precalibration bias was not significantly related to the level of mean arterial pressure, heart rate, systemic vascular resistance, or site of pressure monitoring (radial vs. femoral; table 2). The bias increased at higher levels of cardiac output (P < 0.05).

In the 15 patients studied on 2 consecutive days, the TDCO-to-MCO ratio before calibration was 1.39 ± 0.28 (mean ± SD) on day 1 and did not change on day 2 (1.39 ± 0.34). In the five patients studied on a third day, the precalibration ratio was 1.46 ± 0.27 on day 1, 1.50 ± 0.29 on day 2, and 1.49 ± 0.21 on day 3 (NS). Individual values are given in table 3.

**Post-calibration Comparison**

The average calibrated MCO was 8.9 ± 3.0 l/min (mean ± SD), and TDCO was 9.0 ± 3.0 l/min, with a bias of −0.1 ± 0.8 l/min (95% limits of agreement, −1.6 to 1.4 l/min; fig. 3). The post-calibration bias was not related to the level of cardiac output, mean arterial pressure, heart rate, systemic vascular resistance, or site of pressure monitoring (radial vs. femoral; table 2).

Figure 4 illustrates the tracking of changes in TDCO by corresponding MCO after calibration of the model. Of the 137 post-calibration comparisons, 82% (n = 112) of the differences between MCO and TDCO were < 1 l/min, and 58% (n = 79) were < 0.5 l/min. In 18 of 137 comparisons the sign of the changes in MCO versus TDCO was opposite with a difference < 1 l/min in 14 measurements and < 0.5 l/min in 7.

In 14 of 15 patients changes in TDCO on consecutive days were tracked adequately by MCO, when the model was calibrated with the first TDCO of day 1 only (fig. 5).

**Discussion**

The present study compared in patients with septic shock intermittent cardiac output estimates by bolus injection thermodilution with a beat-to-beat method estimating cardiac output from the arterial pressure wave...
with a three-element model of the aortic input impedance (see Appendix). Measurements were obtained under the conditions of standard critical care management with a vasoactive drug administered at a constant rate and with cardiac output varying substantially by changing vasoactive drug infusion rate. The main findings are that an initial calibration with a reference method is needed, that MCO reflects TDCO over a range of cardiac output values with 82% of the differences < 1 l/min after initial calibration, and that a single calibration of the model appears sufficient to monitor cardiac output continuously from arterial pressure over a 2-day monitoring period with a bias of -0.1 ± 0.8 l/min.

Bolus Injection Thermomilution Cardiac Output

Several factors affect the accuracy of the bolus injection thermomilution technique, including mechanical ventilation, variations in heart rate, injectate temperature, injection volume, duration of the injection, and timing of the injection within the respiratory cycle, in

Table 2. Bolus Thermomilution versus Model Simulation

<table>
<thead>
<tr>
<th></th>
<th>Precalibration Measurements of Day 1</th>
<th>Postcalibration Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Bias (l/min)</td>
</tr>
<tr>
<td>TDCO &lt; 8</td>
<td>18</td>
<td>-0.86 ± 1.51</td>
</tr>
<tr>
<td>TDCO ≥ 8</td>
<td>14</td>
<td>-2.45 ± 1.92</td>
</tr>
<tr>
<td>HR &lt; 110</td>
<td>16</td>
<td>-1.88 ± 1.78</td>
</tr>
<tr>
<td>HR ≥ 110</td>
<td>16</td>
<td>-1.96 ± 2.82</td>
</tr>
<tr>
<td>MAP &lt; 80</td>
<td>15</td>
<td>-2.06 ± 2.82</td>
</tr>
<tr>
<td>MAP ≥ 80</td>
<td>17</td>
<td>-1.80 ± 1.85</td>
</tr>
<tr>
<td>SVR &lt; 800</td>
<td>15</td>
<td>-2.66 ± 2.79</td>
</tr>
<tr>
<td>SVR ≥ 800</td>
<td>17</td>
<td>-1.26 ± 1.61</td>
</tr>
<tr>
<td>Radial</td>
<td>25</td>
<td>-2.32 ± 2.35</td>
</tr>
<tr>
<td>Femoral</td>
<td>7</td>
<td>-0.48 ± 1.59</td>
</tr>
</tbody>
</table>

Number = number of cardiac output measurements; Bias = mean difference ± SD; k = ratio of thermomilution cardiac output to model simulated cardiac output; TDCO = thermomilution cardiac output, in l/min; HR = heart rate, in beats per minute; MAP = mean arterial pressure, in mmHg; SVR = systemic vascular resistance, in dyne.s.cm⁻⁵; Radial = radial artery pressure; Femoral = femoral artery pressure.

* P < 0.05 low versus high values.

Anesthesiology, V 90, No 5, May 1999
particular in mechanically ventilated patients.\textsuperscript{18–20} To improve the accuracy of the thermodilution estimates in the present study, phase-controlled automated injections of ice-cooled fluids were used. This technique reduces the standard deviation of a single injection of 13% to 3.2% for a series of four injections.\textsuperscript{20}

Validation of Model-simulated Cardiac Output

Prerequisite to proper computation and validation of MCO is sufficient quality of the arterial pressure signal, with maintenance of the pressure transducer at heart level and avoidance of motion.

In 32 septic patients investigated in this study, the precalibration bias was found to be considerably larger compared with a smaller series of cardiac surgery patients.\textsuperscript{12} This difference might be related to the considerably higher level of cardiac output in patients with septic shock, associated with increased vasodilation.\textsuperscript{14} The precalibration bias was larger in septic patients with a cardiac output of 8 l/min (table 2). However, as the hyperdynamic phase regressed over days, the TDCO-to-MCO ratio did not change significantly (table 3). These data suggest that the larger ratio found cannot be attributed to the higher level of cardiac output. Thus, this study does not provide an explanation for the consistent underestimation of uncalibrated MCO.

After calibration, the bias became small for a range of cardiac output values and independent of the level of cardiac output. This underscores the need for an initial calibration of the model by a reference cardiac output

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Patient Number & Protocol Day & TDCO (l/min) & MCO (l/min) & $\kappa$ & $\kappa$/Day 1 \\
\hline
2 & 1 & 18.15 & 9.78 & 1.86 & 1 \\
 & 2 & 13.25 & 7.255 & 1.83 & 0.98 & 1 \\
5 & 1 & 7.66 & 7.79 & 0.98 & 1 \\
 & 2 & 7.14 & 7.06 & 1.01 & 1.03 & 1 \\
6 & 1 & 10.13 & 8.08 & 1.25 & 1.16 & 1 \\
 & 2 & 10.73 & 7.36 & 1.46 & 1.11 & 1 \\
 & 3 & 6.97 & 5.00 & 1.39 & 1.11 & 1 \\
7 & 1 & 7.80 & 5.84 & 1.34 & 1 \\
 & 2 & 7.31 & 5.93 & 1.23 & 0.92 & 1 \\
9 & 1 & 15.40 & 11.16 & 1.38 & 1 \\
 & 2 & 10.52 & 8.19 & 1.28 & 0.93 & 1 \\
 & 3 & 11.18 & 7.92 & 1.41 & 1.02 & 1 \\
10 & 1 & 5.64 & 4.15 & 1.36 & 1 \\
 & 2 & 5.91 & 4.13 & 1.43 & 1.05 & 1 \\
14 & 1 & 6.95 & 4.24 & 1.64 & 1 \\
 & 2 & 7.94 & 4.45 & 1.79 & 1.09 & 1 \\
22 & 1 & 11.48 & 7.37 & 1.56 & 1 \\
 & 2 & 10.53 & 6.75 & 1.56 & 1.00 & 1 \\
 & 3 & 10.50 & 6.61 & 1.59 & 1.02 & 1 \\
24 & 1 & 4.69 & 3.50 & 1.34 & 1 \\
 & 2 & 4.13 & 3.14 & 1.32 & 0.98 & 1 \\
25 & 1 & 8.89 & 7.32 & 1.22 & 1 \\
 & 2 & 5.19 & 4.24 & 1.22 & 1.00 & 1 \\
 & 3 & 6.74 & 5.35 & 1.26 & 1.04 & 1 \\
26 & 1 & 9.12 & 8.24 & 1.11 & 1.00 & 1 \\
 & 2 & 7.84 & 8.61 & 0.91 & 0.82 & 1 \\
27 & 1 & 7.45 & 5.87 & 1.27 & 1.00 & 1 \\
 & 2 & 7.29 & 6.40 & 1.14 & 0.9 & 1 \\
29 & 1 & 15.00 & 8 & 1.88 & 1.00 & 1 \\
 & 2 & 14.78 & 7.54 & 1.96 & 1.05 & 1 \\
 & 3 & 13.58 & 7.57 & 1.79 & 0.96 & 1 \\
30 & 1 & 11.53 & 6.92 & 1.67 & 1.00 & 1 \\
 & 2 & 10.11 & 5.52 & 1.83 & 1.1 & 1 \\
31 & 1 & 6.08 & 6.06 & 1.00 & 1.00 & 1 \\
 & 2 & 4.8 & 4.86 & 0.99 & 0.99 & 1 \\
\hline
\end{tabular}
\caption{Day-to-day Comparison of the TDCO-to-MCO Ratio in 15 Patients with Septic Shock}
\end{table}

$k =$ ratio of thermodilution cardiac output to model simulated cardiac output; TDCO = thermodilution cardiac output, in L/min; MCO = model simulated cardiac output, in L/min.
method in high-output states, as in patients with hypodynamic septic shock.

The TDCO-to-MCO ratio did not change over a 2-day monitoring period. This finding implies that a single calibration with a standard cardiac output method enables continuous cardiac output monitoring in septic patients with vasodilation and high cardiac output. Pharmacologic vasodilation with nitroprusside in cardiac surgery patients had been shown not to influence the difference between MCO and TDCO. The finding that the bias after calibration was not affected by the level of cardiac output implies that systemic vascular resistance as part of the aortic input impedance is simulated appropriately by the model in septic patients as well (table 2).
CARDIAC OUTPUT FROM A MODEL OF THE AORTIC INPUT IMPEDANCE

Fig. 5. Recalculated values for thermodilution cardiac output (TDCO) and model-simulated cardiac output (MCO) on day 2 (15 patients) and day 3 (5 patients) calibrated with the first TDCO of day 1. Each symbol denotes a separate patient. For clear presentation of the individual cardiac output tracings three panels were created. Solid lines = TDCO; dashed lines = MCO.

Clinical Implications

In the management of septic shock, interventions should be aimed ideally at modifying systemic flow (cardiac output) given an adequate perfusion pressure.\textsuperscript{21} From this point of view, this recent development in continuous monitoring of cardiac output may advance manipulation of systemic blood flow as a major determinant in a goal-based treatment of patients with septic shock. The thermodilution technique is the most accepted clinical method to estimate cardiac output, but it requires the presence of a pulmonary artery catheter for as long as cardiac output monitoring is needed. This study shows that comparable information on changes in cardiac output after calibration may be obtained from arterial pressure. This is relevant in the ongoing debate on the pros and cons of pulmonary artery catheterization for the purpose of cardiac output monitoring.\textsuperscript{22,23}
Appendix: Modelflow Method

The Modelflow method digitally computes an aortic-flow waveform from a peripheral arterial pressure signal.\textsuperscript{12} It uses a nonlinear three-element model of the aortic input impedance. Integrating the computed aortic-flow waveform per beat provides left ventricular stroke volume. Cardiac output is computed by multiplying stroke volume and instantaneous heart rate.

A Three-element Model of the Human Aortic Input Impedance

The behavior of the aorta in opposing ejection of blood by the left ventricle can be described by a three-element model of the human aortic input impedance, relating aortic pressure and aortic inflow.\textsuperscript{24–27} The three-model elements represent the major properties of the aorta and arterial system: aortic characteristic impedance, arterial compliance, and peripheral vascular resistance.\textsuperscript{28}

The first element in the model is aortic characteristic impedance ($Z_0$); it describes the relation between pulsatile flow and pulsatile pressure at the entrance of the aorta. When the left ventricle contracts, blood is ejected into the aorta. As the aorta already contains blood, the existing aortic pressure opposes left ventricular outflow. In reaction to the accelerated blood volume, aortic pressure increases. The increase in pressure depends on instantaneous flow, cross-sectional area of the aorta, and aortic compliance. Hence, $Z_0$ represents the aortic opposition to pulsatile inflow from the contracting left ventricle. $Z_0$ has the dimension of pressure divided by flow.

The second model element is the arterial compliance ($C_a$); it describes how much the aorta pressure increases for a certain amount of blood. When a volume of blood is expelled into the aorta, the aorta expands elastically and aortic pressure increases. The increased pressure opposes further inflow into the aorta until left ventricular pressure also increases. A compliant aortic wall expands easily, producing only a small increase in aortic pressure (Windkessel function), as is the case for the aortic wall of young subjects. Compliance decreases, however, with increasing age.\textsuperscript{29} $C_a$ represents the aortic opposition to an increase in blood volume. The dimension of compliance is defined as a change in volume (dV) divided by a change in pressure (dP).

The third element in the model is peripheral vascular resistance ($R_p$). $R_p$ is a measure for the case of constant blood drainage from the compliant aorta (Windkessel) into the peripheral vascular beds. $R_p$ is defined as the ratio of mean pressure to mean flow and is not a major determinant of systolic inflow.\textsuperscript{12}

The first two elements of the model, $Z_0$ and $C_a$, are thus dependent on the elastic properties of the aorta.

Elastic Properties of the Aorta

The elastic properties of thoracic and abdominal human aorta were studied by Langwouters et al.\textsuperscript{30} They found that the cross-sectional area of the aorta increases with aortic pressure in a nonlinear manner: at lower pressures the area increases quickly; at higher pressures the area increases slowly (fig. 6, top). In that study, the elastic behavior of the human thoracic and abdominal aorta, i.e., the relation of cross-sectional area (A) to pressure (P), was described mathematically by an arc tangent equation with three parameters:

$$A(P) = A_{\text{max}} \left[ 0.5 + \frac{1}{\pi} \arctan \left( \frac{P - P_0}{P_1 - P_0} \right) \right]$$

with $A(P)$, aortic cross-sectional area for any pressure $P$; $A_{\text{max}}$, the maximal cross-sectional area of the aorta at very high pressure; $P_0$, position of the inflection point on the pressure axis at 0.5 $A_{\text{max}}$; and $P_1$, steepness of the curve at 0.75 $A_{\text{max}}$ (fig. 6, top left).

As described in the first section, two elements ($C_a$ and $Z_0$) of the three-element model are dependent on the elastic properties of the aorta. They can be derived from the pressure–area equation by algebraic manipulation: the dimension of compliance is defined as a change in volume (dV) divided by a change in pressure (dP). Assuming that aortic length (l) is constant, changes in volume ($V = \pi \cdot r^2 \cdot l$) or $\pi$-

![Fig. 6. (Top) Pressure–area curves for human thoracic aortas with moderate atherosclerosis (solid line) and severe atherosclerosis (dotted line) at the ages of 40, 60, and 80 yr, respectively. Area = aortic cross-sectional area, in cm²; pressure = aortic pressure, in mmHg; $A_{\text{max}}$, maximal cross-sectional area at high pressure; $P_0$, position of the inflection point on the pressure axis; $P_1$, steepness of the curve. (Bottom) The matching compliance curves on a semilogarithmic scale, in $10^{-3}$ cm³·mmHg⁻¹. Compliance decreases when pressure increases because an aorta can expand elastically only until the collagen fibers in its wall are fully stretched. (Modified from data in Langwouters et al.\textsuperscript{31}}]
CARDIAC OUTPUT FROM A MODEL OF THE AORTIC INPUT IMPEDANCE

A·Δ) are proportional to changes in cross-sectional area. Consequently, compliance is computed by C = dA/dP (fig. 6, bottom). When the compliance is computed, Z₀ can be derived from the standard formula:

\[ Z₀ = \sqrt{\rho/\lambda A C} \]

with \( \rho \) the density of blood. In summary, if values for P₀, P₁, and Aₘₐₓ in the pressure-area equation are known, values for C₀ and Z₀ can be derived for any pressure P.

The shape of the pressure-area curve and consequently values for P₀, P₁, and Aₘₐₓ change with subject age, gender, and degree of atherosclerosis. With increasing age, the steep part of the pressure-area curve moves to the left along the pressure axis (i.e., P₀ and P₁ decrease; fig. 6, top). The parameters P₀ and P₁ regress tightly on age and are different for men and women. Aₘₐₓ does not regress with age. The average value for Aₘₐₓ is significantly larger for men than for women and scatters considerably. Human atherosclerotic thoracic aortas have an increased Aₘₐₓ (fig. 6, top) and an increased stiffness (i.e., a decreased P₁). The net effect of both increments is that they compensate each other for the effect on compliance; the compliant behavior of a severely atherosclerotic aorta is almost identical to that of a moderately atherosclerotic aorta over the physiologic pressure range (fig. 6, bottom).

Computations of Continuous Cardiac Output from an Arterial Pressure Waveform

With the arterial pressure waveform, subject gender, and age as input, the Modelflow software (TNÖ-BMI Biomedical Instrumentation, Amsterdam, The Netherlands) computes values of the model elements C₀ and Z₀ (fig. 7). Because the aortic properties depend nonlinearly and strongly on pressure, values are computed for each new pressure sample taken at 100 Hz. Instantaneous values of C₀ and Z₀ are used in the model simulation, resulting in the computation of an aortic flow waveform. Integrating the aortic flow waveform per beat provides left ventricular stroke volume. Cardiac output is computed by multiplying stroke volume and heart rate. The third model element, peripheral vascular resistance, is calculated for each heartbeat as the quotient of measured arterial pressure and computed MCO.

Modelflow applies the values for P₀ and P₁ from a built-in database with subject age and gender as input. The parameter Aₘₐₓ scatters considerably among patients, and the uncertainty of the absolute level of computed cardiac output depends linearly on the uncertainty in Aₘₐₓ. The scatter in Aₘₐₓ is approximately 15% SD, and its 95% confidence interval is ±50%. However, the precision of tracking percentage changes in cardiac output is not affected by the uncertainty in Aₘₐₓ. Although the error in Aₘₐₓ seems substantial, it is comparable to the error of a single thermodilution estimate. If better absolute accuracy is required, one can calibrate MCO with a more accurate method (as is done in present study) to obtain a proper individual value for Aₘₐₓ.

Aortic pressure, theoretically preferred in the model, is not routinely available in clinical practice, but peripheral arterial pressure resembles the aortic pressure sufficiently to compute stroke volume. It appeared that the computed flow waveform was distorted because the peripheral pressure wave was distorted. However, the area under the flow waveform (stroke volume) was affected only minimally.

Good quality of the intraarterial pressure signal is a prerequisite for proper computation of MCO. The tubing of the catheter–manometer system has to be noncompliant and the catheter system free of clots and air bubbles. Sufficient signal quality should be assessed by checking the dynamic performance of the arterial pressure measurement system.

References


Anesthesiology. V 90, No 5, May 1999


31. Langemans GJ. Visco-elasticity of the Human Aorta In Vitro in Relation to Pressure and Age (thesis). Amsterdam, Free University Amsterdam; 1982


Anesthesiology, V 90, No 5, May 1999