Clinical evaluation of circulating blood volume in critically ill patients—contribution of a clinical scoring system

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The circulating blood volume (CBV) of critically ill patients may be difficult to estimate on the basis of history and physical examination. The aim of this study was to evaluate the ability of seven clinical signs and central venous pressure (CVP) to predict CBV in critically ill patients; CBV was evaluated with the [¹²⁵I]human serum albumin technique. A scoring system was constructed using a combination of independence Bayes method and logistic regression. Sixty-eight patients constituted a ‘model development’ sample and 30 patients a validation sample. Thirty-six patients (53%) in the model development sample were found to have a low CBV (measured CBV at least 10% lower than the predicted mean normal CBV). Neither the haemodynamic variables monitored in ICU, nor the spot urinary sodium concentrations were different between patients with and without a low CBV. Individually, none of the clinical signs tested have a good positive or negative predictive value. For CVP, only extreme values seem to have clinical significance. To construct the score, the signs tested were ranked according to their discriminating efficacy. The probability of a low CBV was obtained by adding the weights of each sign tested and converting the score obtained into a probability. On a validation sample of 30 patients, the predictions are reliable as assessed by $Z$ statistics ranging between $-2$ and $+2$. Our results suggest that: (1) individually, no clinical sign presented a clinical useful predictive value; and (2) a clinical scoring system may be helpful for the evaluation of CBV in critically ill patients.

Keywords: blood volume; intensive care; measurement techniques, Bayes’ theorem; measurement techniques, radioactive labelled albumin; complications, hypovolaemia; clinical trials

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Direct measurement of circulating blood volume (CBV) is currently of interest for improving patient care,¹,² as CBV is distinct from all other haemodynamic variables and is related to preload. Volume-deficit hypovolaemia has been associated with a significant increase in morbidity and mortality.³ On the other hand, fluid overload is deleterious in patients with acute respiratory distress syndrome.⁴ Circulating blood volume monitoring may help to identify such a volume deficit or excess and act as a guide for fluid therapy. However, even nowadays, CBV determination is complex, labour-intensive and time-consuming. Therefore, a reliable clinical evaluation of CBV would be most useful.

However, volume-deficit hypovolaemia is quite difficult to detect on the basis of history, urine volumes, sodium concentration or physical examination,⁵–⁸ with a 50% incidence of false-negative results.⁶,⁷ Moreover, in critically ill patients hospitalized for many days, complete examination is often unhelpful or impractical and renal function is rarely preserved.

Clinical evaluation of CBV could encounter two potential problems. First, knowing absolute CBV is less important than the effective CBV in determining pre-load responsive-

¹ This article is accompanied by Editorial I.
ness or in defining the determinants of a particular haemodynamic state. For the physician, hypovolaemia means low pre-load, not just low CBV. Circulating blood volume is one of the most important factors that affect heart pre-load; changes in the compliance of veins maintain the correct relationship between vascular space and CBV. Second, the clinical signs used are really aimed at measuring total body ‘extracellular’ volume which includes intravascular volume and interstitial volume, and therefore, one would not expect them to closely predict intravascular volume.

The aim of this study was to evaluate the ability of the routine clinical parameters used to estimate fluid volume status to predict CBV, and to compare with measurements of CBV using the [125I]albumin technique. The study was divided into two parts: first, clinical variables that best discriminated between patients with and without low CBV were determined; and second, a scoring system which combines elements of Bayes’s theorem with those of logistic regression was constructed and prospectively assessed in another group of patients.

**Patients and methods**

**Study population**

Our institution’s clinical investigation review board approved the study procedure, and informed consent was obtained from each patient or their relatives.

The patient population consisted of subjects admitted to our ICU during a 2-yr period between January 1996 and December 1997, in whom clinical assessment of CBV status had to be confirmed by laboratory measurement, because, after several days in the ICU, the physician was uncertain about the CBV status. Bedside CBV determination is readily available at our institution. The initial study population consisted of 68 patients and represented the model development sample from which the prediction system was derived. Another 30 patients were then included to constitute the test data set. The main reasons for admission to ICU included 39 post-operative cases (orthopaedic, thoracic, vascular and abdominal surgery); 45 cases of sepsis as previously defined, six cases of gastrointestinal haemorrhage and eight miscellaneous causes.

The following information was recorded: age, sex, height and usual weight, new Simplified Acute Physiology Score (SAPS II), duration of ICU stay, time of CBV determination after ICU admission, need for mechanical ventilation or vasoactive drugs, and mortality in ICU.

**Clinical assessment of extracellular fluid volume**

Each patient underwent two independent physical examinations by two attending physicians before CBV determination. Results of these examinations were subsequently compared. When a disagreement occurred, a third physician was required to make final decision. A chest x-ray was available for all patients. According to previous reports and guidelines, clinical examination paid special attention to seven signs readily available at the bedside: (1) presence or absence of fluid losses since ICU admission (chest and abdominal drainage, aspiration of gastric contents); (2) fluid balance in the last 24 h by recording intake and output (positive fluid balance if above 400 ml); (3) skin mottling; (4) presence of pulmonary congestion based on detection of pulmonary rales and crackles on physical examination, and/or alveolar oedema and pulmonary vasculature redistribution on chest x-ray; (5) presence of congestive heart failure supported by a past medical history, cardiac enlargement and pulmonary oedema on physical and chest x-ray examination, and gallop rhythm; (6) peripheral oedema; and (7) detection of an enlarged third space: ascites (bulging flanks, fluid wave, shifting dullness), and pleural effusion (dullness on physical examination, compatible chest x-ray). The following variables were also recorded: systolic and diastolic arterial pressure, heart rate, temperature, urine output over the last 24 h, plasma and urinary sodium concentrations, serum total proteins, haemoglobin and haematocrit values.

Central venous pressure (CVP) was measured with a pressure transducer (PVB, Kirchsceon, Germany). Pressures were obtained after calibration, zeroing to atmospheric pressure and using the mid-chest level as reference. Transducers were connected to bedside amplifiers (HP M10469102B, Hewlett Packard). Central venous pressure was recorded at end-expiration.

**Circulating blood volume determination**

Measurement of CBV was performed with [125I]human serum albumin (SERALB-125°; CIS bio international, Gypsum sur Yvette, France) and CBV equipment (Volumetron°; AMES Co, Div. Miles Lab. Inc.; Elkhart, IN, USA), which automatically calculated the volume from the radioactivity injected and from the radioactivity of a post-injection whole blood sample, as previously described.°

SERALB-125° was supplied as a sterile solution of human serum albumin labelled with iodine 125, made isotonic with sodium chloride. The radioactive concentration was 185 kBq ml⁻¹ (5 µCi ml⁻¹) at the calibration date; SERALB-125° contains 9 mg of human serum albumin ml⁻¹. Not less than 97% of the total radioactivity was bound to human serum albumin. After treatment any acute episode of severe hypotension, 3.5 µCi of SERALB-125° were injected i.v. (#0.7 ml of solution). The radioactivity injected was assumed to be the difference of the activities contained in the syringe before and after injection. Blood was withdrawn from a vein of the contralateral arm after 10 min, as previously recommended.° The concentration of test substance in the sample was obtained from simultaneous measurements of fixed volumes of pre-mixing and post-mixing blood samples.
Plasma volume and cell volume were calculated from CBV and peripheral haematocrit corrected for the body-venous haematocrit ratio (0.91). Interpretation of results was based on comparison between observed values and expected values in healthy subjects of the same sex, height, weight and age. The expected values for healthy subjects have been previously reported. Precision of CBV determination is ±5% (Dr F. Paillard, personal communication). Hypovolaemia was defined as a CBV at least 10% lower than the predicted mean normal CBV.

Statistical analysis

Hypovolaemic and non-hypovolaemic patients were compared using the chi-squared test or Fisher’s exact test for categorical variables, and Student’s t- or Mann–Whitney U-test for continuous variables. A two-sided formulation with a P value <0.05 was required for statistical significance. Results are expressed as mean (SD) for continuous variables, and as per cent for categorical variables.

Agreement between physicians on the presence or absence of a clinical sign was assessed by the kappa measurement of agreement. Kappa values exceeding 0.75 represent excellent agreement, values between 0.4 and 0.75 indicate fair to good agreement, and values less than 0.4 indicate poor agreement. Standard formulas were used to calculate sensitivity (true positives/[true positives+false negatives]), specificity (true negatives/[true negatives+false positives]), positive predictive value (true positives/[true positive+false positives]), and negative predictive value (true negative/[true negatives+false negatives]) for each clinical parameter.

To decide the optimum cut off point for CVP, a Receiver Operating Characteristics (ROC) curve was constructed, which plots true- and false-positives rates (sensitivity and 1 minus specificity, respectively) for a series of cut off points.

Calculation of Spiegelhalter–Knill-Jones weightings

Many statistical methods have been developed to improve the physician’s judgment. Over the past few years, Spiegelhalter and Knill-Jones have proposed a simple scoring system which adds precision to risk assessment in individual patients. This statistical method combines elements of Bayes’ theorem with those of logistic regression. The result is a system that neatly sidesteps some of the main disadvantages of the two original techniques. For example, it does not assume that all risk factors are acting independently within each outcome class (the ‘independence Bayes’ assumption, which is central to many bayesian analyses) because an adjustment is made, while at the same time predictions are presented in a form which is less mathematical and much more clinically relevant than the output of a conventional logistic regression analysis. Another reason why this method may be preferred over simple logistic regression is the ability to integrate zero for missing data. Finally, the weights of evidence may be viewed as tools for refining risk prediction by taking into account key clinical parameters in the individual patient. Once the Spiegelhalter–Knill-Jones weightings have been derived they can be used by the non-mathematician, but the process of derivation from the training data set requires statistical skill (see Appendix). The Spiegelhalter–Knill-Jones scoring system, applied to the evaluation of CBV could, therefore, improve the physician’s clinical judgment.

Validation of the clinical scoring system

The predictive accuracy of the Spiegelhalter and Knill-Jones weighting system was measured in the 30 patients constituting the test data set. The predictive probabilities have been grouped into four categories and the observed number of hypovolaemic patients (O) in each category is noted. The four categories are defined according to the range of probabilities of expected hypovolaemia: category 1, 0–10%; category 2, 11–49%; category 3, 50–70%; and category 4, 71–100%.

The expected number of hypovolaemic patients (E), assuming the prediction is completely reliable, is also shown. According to the null hypothesis that the predictions are reliable, O would be approximately distributed with the mean E and a standard error (SE) equal to √E(1–E/n)1/2. Hence, Z=(O–E)/(SE) will be approximately a standard normal statistic according to the null hypothesis of perfect reliability. Values of Z greater than 2 suggest that the ‘probability’ attributed to hypovolaemia is too low, while values of Z less than –2 suggest that the probabilities are too high.

Results

Clinical characteristics of initial study population and CBV determination

The clinical characteristics of the 68 patients, with and without hypovolaemia according to CBV determination, are shown in Table 1. In the model development sample, 36 patients were classified as hypovolaemic (53%). Results of CBV determination for the two groups are summarized in Table 1.

Diagnostic value of laboratory parameters and haemodynamic measurements

Results are presented in Table 2. Neither the haemodynamic parameters usually monitored in ICU, nor the spot urinary sodium concentrations were different between hypovolaemic and non-hypovolaemic patients. However, serum total protein and haemoglobin concentrations were higher in hypovolaemic patients.
Agreement between physicians and accuracy of each clinical parameter

Agreement between physicians was excellent for the elicited physical signs. Kappa values were 0.78 for the presence or absence of pulmonary congestion; 0.82 for the presence or absence of peripheral oedema; 0.84 for the presence or absence of congestive heart failure; 0.86 for detection or absence of third spacing; and 1.00 for the presence or absence of skin mottling.

The accuracy of each of the seven clinical signs in the model development sample is shown in Table 3. Sensitivity was 0.94 for absence of congestive heart failure, which was marginally higher than the sensitivity of absence of pulmonary oedema or absence of third spacing (both equal to 0.92). Specificity was highest for the presence of fluid losses and presence of skin mottling (both equal to 0.78), and lowest for absence of third spacing (0.19). Positive predictive value was highest for the absence of peripheral oedema (0.62). Negative predictive value was highest for the presence of skin mottling (0.49), closely followed by the presence of fluid losses (0.48).

Calculation of Spiegelhalter–Knill-Jones weightings and application to individual patients

Table 4 gives the starting score and adjusted weights of evidence needed to predict the chances of hypovolaemia from the seven clinical signs and CVP measurement. The goodness of fit of the stepwise logistic regression was 0.51.

The cut off value for CVP was obtained from the upper left corner of the ROC curve. For a cut off value of CVP <2 mm Hg, the sensitivity was 0.38 and the specificity was 0.84 (data not shown).

Two steps are required to predict the risk of hypovolaemia in an individual patient. First, by referring to Table 4, the starting score is added to the appropriate adjusted weights of evidence for that patient. Then, by referring to Figure 1, the total score obtained is converted into a probability of hypovolaemia. These steps are illustrated in the following example. A patient presented with septic shock after cholangitis. Three days after ICU admission, physical examination showed peripheral oedema, fluid losses, and a negative fluid balance. No signs of pulmonary congestion, congestive heart failure, skin mottling, or

Table 1 Clinical characteristics and blood volume estimations by the radiiodine-labelled human serum albumin technique in hypovolaemic and non-hypovolaemic patients. *P values are reported when <0.2, otherwise non-significant (NS). Definitions of abbreviations: SAPS II=simplified acute physiology score; BV=blood volume. Values are expressed as mean (SD)

<table>
<thead>
<tr>
<th>Reasons for ICU admission</th>
<th>Hypovolaemic (n=36)</th>
<th>Non-hypovolaemic (n=32)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative cases (%)</td>
<td>47</td>
<td>28</td>
<td>0.18</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>36</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage (%)</td>
<td>8.5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr) (range)</td>
<td>61 (35–88)</td>
<td>66 (18–89)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>24/12</td>
<td>22/10</td>
<td>NS</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>36 (16)</td>
<td>41 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.3 (0.9)</td>
<td>37.2 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Need for mechanical ventilation (%)</td>
<td>69</td>
<td>31</td>
<td>0.002</td>
</tr>
<tr>
<td>Need for vasoactive drugs (%)</td>
<td>44</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of ICU stay (days)</td>
<td>13 (20)</td>
<td>13 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>25</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Time of BV determination after ICU admission (days)</td>
<td>3.5 (6)</td>
<td>4.6 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>3350 (590)</td>
<td>4089 (1176)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood volume excess or deficit</td>
<td>&lt;514 (194)</td>
<td>88 (273)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Index (ml m−2)</td>
<td>range –236, –111</td>
<td>range –234, +806</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood volume, relative change (%)</td>
<td>–22 (8)</td>
<td>4 (12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Venous haematocrit (%)</td>
<td>33.5 (7.0)</td>
<td>29.6 (3.9)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 2 Haemodynamic and laboratory variables between hypovolaemic and non-hypovolaemic patients. *P values are reported when <0.2, otherwise non-significant (NS) is state. #Spot urinary sodium concentration was included only for 47 patients without diuretic treatment (24 hypovolaemic and 23 non-hypovolaemic patients). Values are expressed as mean (SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypovolaemic (n=36)</th>
<th>Non-hypovolaemic (n=32)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats min−1)</td>
<td>103 (18)</td>
<td>102 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>124 (23.4)</td>
<td>120 (20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>68 (17.5)</td>
<td>62 (13.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Urine output over the last 24 h (ml)</td>
<td>1620 (1013)</td>
<td>1593 (769)</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Na+ (mmol litre−1)</td>
<td>135 (5.5)</td>
<td>137 (5.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Spot urinary Na+ (mmol litre−1) #</td>
<td>68 (42)</td>
<td>63 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum total protein (g litre−1)</td>
<td>39 (12)</td>
<td>34 (8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haemoglobin (g dl−1)</td>
<td>11.5 (2.7)</td>
<td>9.6 (1.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
increased third space was found. Central venous pressure could not be measured. The adjusted weights of evidence for pulmonary congestion (+20), peripheral oedema (~29), skin mottling (~10), congestive heart failure (~11), third spacing (~27), fluid losses (~14), fluid balance (~41), and CVP (0) were added to the starting score (~5 in every case) (Table 4). The total score was +74. A total score of +74 corresponds to a predicted probability of hypovolaemia of 70% (Fig. 1).

Predictive accuracy of the Spiegelhalter–Knill-Jones scoring system
The Spiegelhalter–Knill-Jones scoring system was tested on a prospective series of 30 patients. This population of patients was comparable with the training data set in terms of sex ratio, need for mechanical ventilation, main reasons for ICU admission, SAPS II score (mean 39 (SD 12) vs 39 (18)), and time of CBV determination after ICU admission (4 (3) vs 4 (5) day).

Figure 2 gives the reliability of adjusted predictions. The percentage of hypovolaemia observed in patients in the test data set is plotted against the percentage of hypovolaemia expected from the calculated predictions. The line produced is close to the line of identity. The results indicate that the predicted probabilities are reliable, especially for patients with a high probability—that is, patients predicted to have, say 60% chance of hypovolaemia will actually have hypovolaemia about 60% of the time.

**Discussion**
Our study demonstrates that the usual haemodynamic parameters monitored in ICU and spot urinary sodium concentration are unreliable in differentiating patients with

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of fluid losses</td>
<td>0.25</td>
<td>0.78</td>
<td>0.56</td>
<td>0.48</td>
</tr>
<tr>
<td>Negative fluid balance</td>
<td>0.44</td>
<td>0.71</td>
<td>0.61</td>
<td>0.39</td>
</tr>
<tr>
<td>Presence of skin mottling</td>
<td>0.28</td>
<td>0.78</td>
<td>0.59</td>
<td>0.49</td>
</tr>
<tr>
<td>Absence of peripheral oedema</td>
<td>0.64</td>
<td>0.56</td>
<td>0.62</td>
<td>0.38</td>
</tr>
<tr>
<td>Absence of pulmonary oedema</td>
<td>0.92</td>
<td>0.31</td>
<td>0.60</td>
<td>0.40</td>
</tr>
<tr>
<td>Absence of third spacing</td>
<td>0.92</td>
<td>0.19</td>
<td>0.56</td>
<td>0.44</td>
</tr>
<tr>
<td>Absence of congestive heart failure</td>
<td>0.94</td>
<td>0.20</td>
<td>0.58</td>
<td>0.44</td>
</tr>
</tbody>
</table>

**Table 3** Accuracy of the seven clinical variables used to predict hypovolaemia

- **Prior probability**
- **Pulmonary oedema**
  - Yes: 3/36 (0.25)
  - No: 33/36 (0.94)
- **Peripheral oedema**
  - Yes: 13/36 (0.36)
  - No: 23/36 (0.64)
- **Skin mottling**
  - Yes: 10/36 (0.28)
  - No: 26/36 (0.72)
- **Congestive heart failure**
  - Yes: 2/36 (0.06)
  - No: 34/36 (0.94)
- **Third spacing**
  - Yes: 3/36 (0.09)
  - No: 33/36 (0.91)
- **Fluid losses**
  - Yes: 9/36 (0.25)
  - No: 27/36 (0.75)
- **Fluid balance**
  - Positive or nil: 18/36 (0.5)
  - Negative: 14/36 (0.4)
- **Central venous pressure**
  - ≤2 mm Hg: 13/36 (0.36)
  - >2 mm Hg: 21/36 (0.58)

**Table 4** Crude weights for symptoms of hypovolaemia and normo/hypervolaemia, and effect of adjustment of crude scores by logistic determination. The goodness of fit chi-square of this model remained non-significant during the eight steps (P=0.51 at the last step).

- Third spacing: ascites, pleural effusion.
- Central venous pressure was measured in 65 patients only.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Hypovolaemic (n=36)</th>
<th>Normo or hypervolaemic (n=32)</th>
<th>LR</th>
<th>Crude weights</th>
<th>Logistic coefficients (SE)</th>
<th>Adjusted weight</th>
<th>Range of adjusted weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior probability</td>
<td>0.53</td>
<td>0.47</td>
<td>12</td>
<td>~5 (1.8)</td>
<td>~5</td>
<td>~5</td>
<td>110</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td></td>
<td></td>
<td></td>
<td>~5 (1.8)</td>
<td>~5</td>
<td>~5</td>
<td>110</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>10</td>
<td>0.27</td>
<td>~131</td>
<td>~0.69 (0.9)</td>
<td>~0.90</td>
<td>~90</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>22</td>
<td>1.33</td>
<td>29</td>
<td>0.65 (0.7)</td>
<td>0.54</td>
<td>54</td>
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<tr>
<td>Peripheral oedema</td>
<td></td>
<td></td>
<td></td>
<td>~45</td>
<td>~0.65 (0.7)</td>
<td>~0.54</td>
<td>54</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>18</td>
<td>0.64</td>
<td>38</td>
<td>1.22 (0.8)</td>
<td>1.12</td>
<td>39</td>
</tr>
<tr>
<td>No</td>
<td>23</td>
<td>14</td>
<td>1.46</td>
<td>38</td>
<td>1.22 (0.8)</td>
<td>1.12</td>
<td>39</td>
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<tr>
<td>Skin mottling</td>
<td></td>
<td></td>
<td></td>
<td>~8</td>
<td>~1.03 (1.1)</td>
<td>~0.95</td>
<td>~95</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>7</td>
<td>1.27</td>
<td>24</td>
<td>1.03 (1.1)</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>25</td>
<td>0.92</td>
<td>~8</td>
<td>~1.03 (1.1)</td>
<td>~0.95</td>
<td>~95</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td>~10</td>
<td>~1.03 (1.1)</td>
<td>~0.95</td>
<td>~95</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>5</td>
<td>0.36</td>
<td>~102</td>
<td>1.03 (1.1)</td>
<td>1.03</td>
<td>116</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>27</td>
<td>1.12</td>
<td>11</td>
<td>~1.03 (1.1)</td>
<td>~1.03</td>
<td>116</td>
</tr>
<tr>
<td>Third spacing</td>
<td></td>
<td></td>
<td></td>
<td>~11</td>
<td>~1.03 (1.1)</td>
<td>~1.03</td>
<td>116</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>6</td>
<td>0.44</td>
<td>~82</td>
<td>2.25 (1.3)</td>
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</tr>
<tr>
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<td>26</td>
<td>1.13</td>
<td>12</td>
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<tr>
<td>Fluid losses</td>
<td></td>
<td></td>
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<td>~4</td>
<td>~1.09 (0.8)</td>
<td>~1.09</td>
<td>18</td>
</tr>
<tr>
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<td>9</td>
<td>7</td>
<td>1.14</td>
<td>13</td>
<td>1.09 (0.8)</td>
<td>1.09</td>
<td>18</td>
</tr>
<tr>
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<td>25</td>
<td>0.96</td>
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<td>~1.09</td>
<td>18</td>
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<tr>
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<td>~1.09</td>
<td>18</td>
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<td>41</td>
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<td>65</td>
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<tr>
<td>Central venous pressure</td>
<td></td>
<td></td>
<td></td>
<td>~65</td>
<td>~1.36 (0.8)</td>
<td>~1.36</td>
<td>159</td>
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<tr>
<td>≤2 mm Hg</td>
<td>13</td>
<td>5</td>
<td>2.37</td>
<td>86</td>
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<td>~1.36</td>
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<tr>
<td>&gt;2 mm Hg</td>
<td>21</td>
<td>26</td>
<td>0.74</td>
<td>~31</td>
<td>~1.36 (0.8)</td>
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and without a low CBV, several days after their ICU admission. However, careful physical examination, resulting in a clinical scoring system, improves the clinical ability to determine the patient’s CBV status. Our study design was not addressed to patients with acute illness who became hypotensive in the emergency department or several hours after ICU admission, as these situations are totally different from patients hospitalized for several days in ICU, in whom either large fluid volumes or diuretics may have been recently administered. In such cases, the clinical diagnosis of CBV status constitutes a real challenge for the physician.

We chose the radioactive-labelled albumin method for quantitative CBV determination as the standard. However, using this method in ICU patients raises several problems. First, measurement of CBV depends on adequacy of mixing of [125I]albumin throughout the vascular system and rapid whole body disappearance of the tracer. In the present study, the measurement of CBV 10 min after tracer injection corresponded to the best compromise between complete mixing of the tracer with plasma and its disappearance. However, despite a close correlation with other techniques, this method could lead to a slight overestimation of CBV. Second, septic patients have altered capillary permeability. However, [125I]albumin disappearance rate has been reported to be almost unmodified after endotoxin administration and determination of CBV has been shown to be accurate in septic patients. Third, CBV measurements are commonly compared with predicted CBV values derived from measurements in a normal population. However, the ‘normal’ values of CBV could be different in critically ill patients. Unfortunately, to our knowledge, there are no published data concerning normal CBV values in critically ill patients. Despite these concerns, direct measurement of CBV by a radioactive tracer in ICU patients has been shown to be accurate and reproducible.

We have defined hypovolaemia in term of intravascular volume because CBV is one of the most important factors affecting pre-load. In most clinical studies, the term hypovolaemia refers to either volume depletion or dehydration. One could argue that measurement of CBV only refers to intravascular volume and ignores interstitial and intracellular volumes, but it has been demonstrated that CBV correlates well with extracellular fluid volume. Both CBV and vascular capacitance determine the ‘effective’ CBV. It could, therefore, be hypothesized that septic patients could have an unchanged CBV despite a decreased pre-load. However, Rothe and colleagues reported that, in an endotoxin shock model, CBV decreased by nearly 30% after endotoxin infusion. It has also been shown that ‘effective’ vascular compliance is already decreased in patients under mechanical ventilation with sepsis syndrome, or when sympathetic nervous system tone is elicited. It could also be argued that the division into hypovolaemia and non-hypovolaemia on the basis of a greater than 10% reduction in the measured CBV could be too stringent. However, the mean CBV deficit was –948 ml in hypovolaemic patients and only two non-hypovolaemic patients overlapped with this threshold.

Previous studies have indicated that clinical estimates of a patient’s fluid volume status are not reliably perceived by physical examination alone, with an accuracy range from 30 to 50%. One possible explanation is that physicians...
do not optimally use clinical information when assessing fluid volume status. In our series, hypovolaemia was present in about one half of ICU patients, as reported by Shoemaker and colleagues using the same method in a comparable patient population. Ourselves and others have noted that the use of routine haemodynamic variables are of little value to differentiate hypovolaemiac and non-hypovolaemic patients. Likewise, spot urinary sodium concentration is not useful in this setting in contrast with its value in stable, non-critically ill patients. Renal losses of sodium and water are often a result of an osmotic diuresis. One common culprit is glycosuria, but other causes (e.g. post-obstructive diuresis, profuse diuresis during recovery from acute renal failure) may account for such differences.

The value of haemoglobin concentration has several limitations. During rapid and severe bleeding, the patients may exsanguinate before transcapillary migration of interstitial fluid can significantly reduce the haemoglobin value. On the other hand, haemoglobin changes become almost uninterpretable when patients have been given large volumes of packed red cells and fluids.

The clinical signs that were used are really aimed at measuring total body extracellular volume and are not directly indicative of intravascular volume. However, there is a relationship between clinical features such as oedema and aspiration crackles and CBV. On the other hand, the appearance of reduced CBV in the face of expanded extracellular fluid has been described. As a consequence, based on the values of the likelihood ratio and as shown in Table 3, none of these findings is particularly helpful when present in isolation, as previously reported. On the other hand, combinations of physical signs appear to be more helpful. Inspection of the range of adjusted weights given in Table 4 allows comparison of the value of the symptoms. The wider the range of an indicator, the greater its potential value as a diagnostic item. However, it is possible to have a very powerful symptom that is so rarely present that it would not normally be ascertained in clinical evaluation. Central venous pressure was the last variable taken into account in the score, as CVP is commonly measured in critically ill ICU patients. However, we found that only a value <2 mm Hg provided evidence in favour of hypovolaemia. CVP may vary considerably in critically ill patients, because of heart–lung interactions, especially in mechanically ventilated patients, and therefore only extreme values seem to have any clinical significance.

Regarding the Spiegelhalter–Knill-Jones system, three points must be stressed. First, the predictive accuracy of the system appears reliable. However, the system seems to be less reliable for patients with a low probability of hypovolaemia (Figure 2). Second, some cardiopulmonary signs have been suggested to be of questionable reliability. However, most of the signs used to construct the system frequently occur in the ICU setting, and unreliability of the signs seems to be linked to their low frequency of appearance. Finally, if the criteria of hypovolaemia change, the sensitivity and specificity of each of the signs may be different, affecting the prediction of the model.

Following recent concerns and doubts about the efficacy and safety of using Swan-Ganz catheterization to assess haemodynamic status, there are no guidelines to help the physician to decide when to use or to withhold invasive monitoring in individual patients. We believe the application of such a method could lead to a more judicious selection of diagnostic tests. In conclusion, physicians working in ICU are daily called upon to predict the patient’s fluid volume status on the basis of existing symptoms and signs, physical findings, and laboratory results. As illustrated by the Spiegelhalter–Knill-Jones method, a science of clinical prediction has been developed, and it is now possible to make quantitative predictions by using statistical models and to more rigorously assess the accuracy of these predictions.

Appendix

Summary of statistical techniques used to derive Spiegelhalter–Knill-Jones weightings.

(1) Calculation of the likelihood ratio (LR)

To calculate the LR for a given sign, the patients were divided into hypovolaemic and non-hypovolaemic patients. A standard 2x2 table allowed calculation of sensitivity, specificity, and LR for the presence or absence of a given sign:

\[
\text{LR for the presence of a particular sign} = \frac{\text{sensitivity}}{1-\text{specificity}}
\]

\[
\text{LR for the absence of a particular sign} = \frac{1-\text{sensitivity}}{\text{specificity}}
\]

(2) Bayes’ theorem for calculation of the post-test probability of disease

The independence Bayes equation may be expressed as:

\[
\text{Posterior odds} = \text{prior odds} \times \text{LR of sign 1} \times \text{LR of sign 2} \times \ldots \times \text{LR of sign } N
\]

where posterior odds is the predicted odds of hypovolaemia in an individual, and prior odds is the odds of hypovolaemia in the study population.

(3) Converting LR into scores and weights

To convert LR into a simple score that can be added up, we took the natural logarithm of this LR, as the logarithm can be added rather than multiplied, thus simplifying the process. For further simplicity, this value was multiplied by 100 and rounded off so that crude weights could be expressed as whole numbers.

Equation (1) therefore becomes:

\[
100 \ln \text{posterior odds}=100 \ln \text{prior odds}+100 \ln \text{LR of sign 1}+100 \ln \text{LR of sign 2} \ldots +100 \ln \text{LR of sign } N
\]
By using the terminology of the Spiegelhalter and Knill-Jones method, equation (2) becomes:

Total score ($T$)=starting score+crude weights of sign 1+crude weights of sign 2+...+crude weights of sign $N$ (3).

The starting score reflects the prior probability of hypovolaemia and could be different according to the specificity of the ICU.

(4) Adjustment of crude weights

The use of Bayes theorem could lead to considerable problems in overestimating the probabilities of hypovolaemia, as the assumption of independence of different signs is rarely satisfied in practice. A statistical method of making an adjustment must therefore be defined. The Spiegelhalter and Knill-Jones method calculates ‘adjusted weights of evidence’, which are obtained by entering the value of the crude weights as independent variables in a logistic regression equation. Data were computerized (Compaq prolinea 575E) and analysed using BMDP statistical packages (BMDP Statistical Software, 7.0 software release 1992; Inc. Los Angeles, CA, USA). Goodness of fit was assessed by the Hosmer and Lemeshow chi-squared test. The resulting regression coefficients $a_0$, $a_1$, $a_2$, $a_n$ are displayed, together with their standard error (SE). After multiplication of crude weights by their respective regression coefficient, equation (3) becomes:

Total score ($T$)$=a_0+a_1$adjacently weighted signs of sign 1+$a_2$adjacently weighted signs of sign 2+...+$a_n$adjacently weighted signs of sign $N$ (4).

(5) Converting scores back to probability of disease

Because $T$=100 (Ln posterior odds) and because odd-s=(probability of event)/(1−probability of event), it may be calculated that probability of hypovolaemia (in %)=$e^{T/100}/1+e^{T/100}\times100=1/(e^{-T/100}+1)\times100$. This can be performed more rapidly by using a simple graph.

References

36 Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. Lancet 1988; i: 873–5