BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 86, Number 6, June 2001

Editorial I

Circulating volume and clinical assessment of the circulation

Experience teaches that to place reliance upon a single sign is precarious. Compare this sign and that, and confident recognition of the patient's state grows as these signs group themselves together to form a harmonious picture.

Sir Thomas Lewis[1]

One of the biggest critical care challenges is a septic patient with massive apparent fluid losses. The losses result from increased capillary permeability and third space sequestration, confounded by reduced vascular tone mediated through induced nitric oxide production, which might be associated with myocardial dysfunction.[2] These changes lead to a fall in cardiac output and profound hypotension, which result in poor organ perfusion, multiple organ failure and death. It would probably come as a surprise to most scientists, therefore, that, whereas clinicians have good techniques for measuring cardiac output, there are no easily undertaken bedside methods for measuring total circulating blood volume.

Circulating volume is a major determinant of cardiac output and it has been the response of the latter to fluid challenges that provides us with proxy assessments of circulating volume. Furthermore, it has been the achievement of good cardiac output rather than circulating volume which has consistently been related to better outcomes.[3–7]

Given the complex cause of changes in volume, blood pressure and cardiac output in sepsis, how should they be restored? Start by providing large quantities of intravenous fluid (6–10 litres of crystalloid or 2–4 litres of colloid) in order to obtain a blood pressure and a hyperdynamic state.[8] The type of fluid probably does not matter, but colloids tend to be less likely to cause pulmonary oedema at higher filling pressures.[9–11] Once volume resuscitation is 'complete', organ perfusion should be restored by increasing blood pressure to pre-morbid values with vasoconstrictors, because organ autoregulation is lost and perfusion becomes pressure dependent.[12] Norepinephrine on a full circulation seems to be in favour if dopamine is ineffective or has caused side-effects.[13] The resulting improved global circulatory state should provide a sustainable cardiac output for adequate organ function while specific therapies such as timely surgery and antibiotics prevent further insult.

What about the effect of all that fluid on systemic oedema and tissue oxygenation? Systemic oedema is an inevitable late development that follows fluid loading in patients with disturbed tissue permeability. It should not be a distraction to the prime target of achieving a full circulation. Furthermore, the effect of tissue oedema on tissue oxygenation is not necessarily deleterious.[14 15]

What about haemodynamic targets and monitoring? Use clinical end-points of perfusion in the first instance and insert an arterial line. If cardiac output is low, some measurement of pre-load and cardiac output is appropriate to guide inotrope requirements and avoid cardiac overload.

The foregoing guide sounds simple and should sound familiar. These are some of the latest evidence-based recommendations of the American College of Critical Care Medicine (ACCM) for the treatment of septic shock.[16] This excellent document exudes common sense but mostly surprises with its emphasis on clinical assessment in spite of the apparent advantages of technology that allows more and more accurate ways to measure pre-load and cardiac output.

The paper by Stephan and colleagues in this issue therefore comes as a timely reminder that clinical assessment of circulating volume as a first aim to adequate cardiac output in an individual still has a role.[17] But how can we seamlessly merge clinical art form and scientific measurement?

The importance of generous volume replenishment in septic shock was first seriously promoted by William Shoemaker and colleagues.[4 18–21] Shoemaker's approach at the time was brave considering that most intensivists were focused on drying patients to improve Pa_{O_2} in order to reduce FI_{O_2} to <0.6. Now most would agree that Shoemaker was right. However, when he suggested numerical haemodynamic targets that were subsequently applied prospectively in controlled studies the results were ambiguous.[5–7 22] Where patients did badly the proponents of goal-directed

therapy suggested that the targets had been achieved with far too much use of inotropes. Unwittingly, the proponents had struck on the real problem, namely that the targets were population based rather than individually tailored, leading to some patients being driven with inotropes (possibly with insufficient volume) beyond their normal physiological limit. A recent study confirms the importance of physiological reserve for outcome.[23]

The effect of these studies was to tilt the emphasis towards volume resuscitation and to use inotropes to achieve pre-morbid blood pressure rather than specific oxygen transport targets. Then a spanner was thrown in the works when Connors and colleagues demonstrated that patient management guided by pulmonary artery flotation catheter, the current tool for guiding volume replacement, was associated with a poorer outcome.[24] At the time it was thought unlikely that this was due to complications of catheter placement,[25] which are relatively low,[26 27] but was more related to the way in which the information it provided was used.[28–31] So, paradoxically, after having been told that our clinical ability to assess haemodynamics is poor,[32 33] it seems that clinicians without the flotation catheter get better results.[24] Perhaps it is no longer time to ask what is the cardiac output but rather, is cardiac output effective?

How can we define an effective cardiac output (ECO)? The great Paul Wood, doyen of circulatory clinical assessment, firmly established the value of applying Ohm's law to bedside assessment and physiological measurement.[34] Blood pressure, which is directly related to the product of cardiac output and systemic vascular resistance, if compromised by fluid loss, stimulates sophisticated neuroendocrine compensat[illegible]ctivity. When acute this activity is revealed through clinical signs such as vasoconstriction, tachycardia and sodium retention (oliguria) in order to restore an effective cardiac output and, consequently, blood pressure. Chronic forms of compensated ineffective cardiac output are well recognized in conditions such as cirrhosis, nephrosis and chronic congestive cardiac failure where a sustained state of fluid retention and neuroendocrine activity coexists with a constant risk of organ failure at any further change in circulating volume status.[35]

An effective cardiac output, on the other hand, should have little need for compensatory mechanisms and individuals should be able to simultaneously have toes that are warm to the touch, and sustain their normal blood pressure preferably with a heart rate below 100 beats min^{-1}.[36 37] The absolute cardiac output is irrelevant in such circumstances. In the context of critical illness, a reasonable aim for an individual would be to achieve these same clinical end-points with some combination of fluids, vasoactive agent and inotrope. The advantage of clinical end-points for global perfusion is that they remain the same regardless of the phase of illness. The ACCM recommends additional end-points such as urine output and cerebral function; these could be included in a definition of ECO but may be unrelated to global perfusion due to previous established damage. Inevitably, clinical assessment is likely to vary with observer experience and therefore should be used with markers of improving cellular respiration. Furthermore, some patients, particularly those with poor cardiac function, may never reach these end-points; this is perhaps an omen of the likely outcome.

Do clinical end-points mean we can safely abandon all physiological measurement? Almost certainly not.[16] Measurements complement clinical assessment but do not replace it. They sometimes provide immediate diagnostic information, can provide confidence to undertake fluid challenges and help monitor trends towards the clinical target. Most significantly, measurement provides us with a language for information exchange. Whereas pulmonary artery catheter data may have been criticised for being poorly acquired, badly used or misleading,[38] alternative techniques have not yet been so tainted. Modern continuous methods such as oesophageal Doppler[39 40] and thermodilution-calibrated arterial pulse wave contour cardiac output[41] are widely used. These techniques might not confirm warm feet from their derived calculations but, when combined with clinical examination, might provide an appropriate numeric target for planning management during that specific phase of the illness.

Improved global perfusion should be associated with improving cellular metabolism. In spite of some well known problems such as lead time bias[42 43] and lack of specificity, indicators such as mixed venous oxygen saturation, acid–base balance and blood lactate are widely accepted as measures of anaerobic metabolism.[16] Progressive acidosis in spite of adequate global perfusion is suggestive of concealed regional ischaemia such as ischaemic hepatitis or bowel infarction. These conditions easily overwhelm buffering capacity and are rarely reversible by further increases in cardiac output. Perhaps the most successful tool for regional perfusion has been gastrointestinal tonometry,[44] which with hepatic venous flow and saturation changes[45–47] might find a niche for monitoring intestinal ischaemia particularly following vasoconstrictor therapy.

So where does the work of Stephan and colleagues[17] fit in? They have attempted to correlate clinical indicators—four markers of fluid overload and three suggestive of volume loss—with measurements of absolute circulating blood volume. They carefully selected stable critically ill patients to minimize confounding variables and defined hypovolaemia as a 10% deviation from expected calculated values for normal circulating blood volume. Their study concluded that a score based on clinical indicators of extracellular volume status reasonably predicted measured circulating hypovolaemia when that loss was approximately 1 litre. The study might be criticised for having some overlap in clinical indicators, using a nomogram as the control for circulating volume or possibly for assuming that a stable vascular compliance allows one to equate absolute circulating volume with effective circulating volume.

However, the message is clear: clinical assessment can be reasonably used to indicate volume status.

So might now be the time to apply a similar methodology to assessment of effective cardiac output? A daring start might be to break with tradition and assume this time that physical signs are the gold standard for an individual, and make the measurements in the presence and absence of signs. The volume and inotrope requirements to return to ECO might provide interesting and relevant information, particularly as we embark on outreach critical care.

M. Palazzo
Director of Critical Care
Charing Cross Hospital
London
UK

References

1 Lewis ST. *Disease of the Heart*, 3rd edn. London: Macmillan and Co., 1942
2 Parrillo JE, Parker MM, Natanson C *et al.* Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* 1990; **113**: 227–42
3 Shoemaker WC. Cardiorespiratory patterns of surviving and nonsurviving postoperative patients. *Surg Gynecol Obstet* 1972; **134**: 810–4
4 Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–86
5 Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; **102**: 216–20
6 Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *J Am Med Assoc* 1993; **270**: 2699–707
7 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New Engl J Med* 1994; **330**: 1717–22
8 Rackow EC, Kaufman BS, Falk JL, Astiz ME, Weil MH. Hemodynamic response to fluid repletion in patients with septic shock: evidence for early depression of cardiac performance. *Circ Shock* 1987; **22**: 11–22
9 Virgilio RW, Rice CL, Smith DE *et al.* Crystalloid vs. colloid resuscitation: is one better? A randomized clinical study. *Surgery* 1979; **85**: 129–39
10 Rackow EC, Falk JL, Fein IA *et al.* Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983; **11**: 839–50
11 O'Brien R, Murdoch J, Kuehn R, Marshall JC. The effect of albumin or crystalloid resuscitation on bacterial translocation and endotoxin absorption following experimental burn injury. *J Surg Res* 1992; **52**: 161–6
12 Bersten AD, Holt AW. Vasoactive drugs and the importance of renal perfusion pressure. *New Horiz* 1995; **3**: 650–61
13 Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; **103**: 1826–31
14 Baum TD, Wang H, Rothschild HR, Gang DL, Fink MP. Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. *Circ Shock* 1990; **30**: 385–97
15 Rackow EC, Astiz ME, Schumer W, Weil MH. Lung and muscle water after crystalloid and colloid infusion in septic rats: effect on oxygen delivery and metabolism. *J Lab Clin Med* 1989; **113**: 184–9
16 Task Force of the American College of Critical Care Medicine SoCCM. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; **27**: 639–60
17 Stéphan F, Flahault A, Dieudonné N, Hollande J, Paillard F, Bonnet F. Clinical evaluation of circulating blood volume in critically ill patients. *Br J Anaesth* 2001; **86**: 754–62
18 Shoemaker WC, Printen KJ, Amato JJ, Monson DO, Carey JS, O'Connor K. Hemodynamic patterns after acute anesthetized and unanesthetized trauma. Evaluation of the sequence of changes in cardiac output and derived calculations. *Arch Surg* 1967; **95**: 492–9
19 Shoemaker WC. Priorities of resuscitation and subsequent therapy after trauma. *N Y State J Med* 1972; **72**: 1948–54
20 Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. *Arch Surg* 1973; **106**: 630–6
21 Shoemaker WC, Kram HB, Appel PL. Therapy of shock based on pathophysiology, monitoring, and outcome prediction. *Crit Care Med* 1990; **18**: S19–25
22 Gattinoni L, Brazzi L, Pelosi P *et al.* A trial of goal-oriented hemodynamic therapy in critically ill patients. Sv_{O_2} Collaborative Group. *New Engl J Med* 1995; **333**: 1025–32
23 Velmahos GC, Demetriades D, Shoemaker WC *et al.* Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. *Ann Surg* 2000; **232**: 409–18
24 Connors AF, Speroff T, Dawson NV *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *J Am Med Assoc* 1996; **276**: 889–97
25 Soni N. Swan song for the Swan-Ganz catheter? *Br Med J* 1996; **313**: 763–4
26 Boyd KD, Thomas SJ, Gold J, Boyd AD. A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. *Chest* 1983; **84**: 245–9
27 Smart FW, Husserl FE. Complications of flow-directed balloon-tipped catheters. *Chest* 1990; **97**: 227–8
28 Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *J Am Med Assoc* 1990; **264**: 2928–32
29 Nadeau S, Noble WH. Misinterpretation of pressure measurements from the pulmonary artery catheter. *Can Anaesth Soc J* 1986; **33**: 352–63
30 Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? *Crit Care Med* 1997; **25**: 213–20
31 Komadina KH, Schenk DA, LaVeau P, Duncan CA, Chambers SL. Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. *Chest* 1991; **100**: 1647–54
32 Rackow EC, Connors AF. Controversies in pulmonary medicine.

Invasive measurements are required for assessing hemodynamic status in critically ill patients. *Am Rev Respir Dis* 1988; **138**: 1070–2

33 Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984; **12**: 549–53

34 Wood P. *Diseases of Heart and Circulation*, 2nd edn. London: Eyre and Spottiswoode, 1961

35 Rose B. *Clinical Physiology of Acid Base and Electrolyte Disorders*, 4th edn. New York: McGraw–Hill Inc., 1994

36 Joly HR, Weil MH. Temperature of the great toe as an indication of the severity of shock. *Circulation* 1969; **39**: 131–8

37 Palazzo M, Soni N. Critical-care studies: redefining the rules. *Lancet* 1998; **352**: 1306–7 [Erratum published in *Lancet* 1999; **353**: 848]

38 Gomez CM, Palazzo MG. Pulmonary artery catheterization in anaesthesia and intensive care. *Br J Anaesth* 1998; **81**: 945–56

39 Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. *Crit Care Med* 1991; **19**: 1132–7

40 Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Crit Care Med* 1989; **17**: 447–52

41 Buhre W, Weyland A, Kazmaier S *et al*. Comparison of cardiac output assessed by pulse-contour analysis and thermodilution in patients undergoing minimally invasive direct coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 1999; **13**: 437–40

42 Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983; **11**: 449–51

43 Falk JL, Rackow EC, Leavy J, Astiz ME, Weil MH. Delayed lactate clearance in patients surviving circulatory shock. *Acute Care* 1985; **11**: 212–5

44 Fiddian Green RG, Haglund U, *Gut*ierrez G, Shoemaker WC. Goals for the resuscitation of shock. *Crit Care Med* 1993; **21** (Suppl): S25–31

45 Ruokonen E, Soini HO, Parviainen I, Kosonen P, Takala J. Venoarterial CO_2 gradient after cardiac surgery: relation to systemic and regional perfusion and oxygen transport. *Shock* 1997; **8**: 335–40

46 Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Crit Care Med* 1991; **19**: 1365–9

47 De Backer D, Creteur J, Noordally O, Smail N, Gulbis B, Vincent JL. Does hepato-splanchnic VO_2/DO_2 dependency exist in critically ill septic patients? *Am J Respir Crit Care Med* 1998; **157**: 1219–25

British Journal of Anaesthesia **86 (6)**: 754–62 (2001)

BJA

CLINICAL INVESTIGATIONS

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

F. Stéphan[1*], A. Flahault[2], N. Dieudonné[1], J. Hollande[1], F. Paillard[3] and F. Bonnet[1]

[1]Service d'Anesthésie-Réanimation chirurgicale, [2]Antenne de Biostatistiques et d'Informatique médicale and [3]Laboratoire des Explorations Fonctionnelles, Hôpital Tenon, 4 rue de la Chine, F-75970 Paris Cedex 20, France

**Corresponding author*

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 [^{125}I]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.

Br J Anaesth 2001; **86**: 754–62

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

Accepted for publication: November 13, 2000

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-

† 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.[2 9] 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 [^{125}I]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,[10] 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),[11] 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,[6 12 13] 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 [^{125}I]human serum albumin (SERALB-125®; CIS bio international, Gyf 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.[5]

SERALB-125® was supplied as a sterile solution of human serum albumin labelled with iodine ^{125}I, 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.[5] 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-to-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.[14 15] 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–Witney *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.[16] 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.[16]

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.[17]

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.[17]

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.[18 19] 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, $Z=(O–E)/(\mathrm{SE})$ 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.[19]

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 radioiodine-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)

	Hypovolaemic (*n*=36)	Non-hypovolaemic (*n*=32)	*P* value*
Reasons for ICU admission			0.18
Post-operative cases (%)	47	28	
Sepsis (%)	36	63	
Gastrointestinal haemorrhage (%)	8.5	6	
Miscellaneous causes (%)	8.5	3	
Age (yr) (range)	61 (35–88)	66 (18–89)	0.18
Sex, male/female	24/12	22/10	NS
SAPS II score	36 (16)	41 (21)	NS
Temperature (°C)	37.3 (0.9)	37.2 (1.0)	NS
Need for mechanical ventilation (%)	69	31	0.002
Need for vasoactive drugs (%)	44	19	0.03
Duration of ICU stay (days)	13 (20)	13 (13)	NS
Mortality (%)	25	31	NS
Time of BV determination after ICU admission (days)	3.5 (6)	4.6 (4.7)	NS
Blood volume (ml)	3350 (590)	4089 (1176)	0.001
Blood volume excess or deficit	–514 (194)	88 (273)	<0.0001
Index (ml m^{-2})	range –236, –111	range –234, +806	
Blood volume, relative change (%)	–22 (8)	4 (12)	<0.0001
Venous haematocrit (%)	33.5 (7.0)	29.6 (3.9)	0.006

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)

	Hypovolaemic (*n*=36)	Non-hypovolaemic (*n*=32)	*P* value*
Heart rate (beats min^{-1})	103 (18)	102 (16)	NS
Systolic arterial pressure (mm Hg)	124 (23.4)	120 (20.0)	NS
Diastolic arterial pressure (mm Hg)	68 (17.5)	62 (13.0)	0.11
Urine output over the last 24 h (ml)	1620 (1013)	1593 (769)	NS
Plasma Na^+ (mmol $litre^{-1}$)	135 (5.5)	137 (5.0)	NS
Spot urinary Na^+ (mmol $litre^{-1}$)†	68 (42)	63 (38)	NS
Serum total protein (g $litre^{-1}$)	39 (12)	34 (8)	<0.05
Haemoglobin (g dl^{-1})	11.5 (2.7)	9.6 (1.2)	0.002

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 3 Accuracy of the seven clinical variables used to predict hypovolaemia

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

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. ‡Available for 63 patients only; value of fluid excess was 1553 (1154) ml (range 400–5840) and value of fluid deficit was –946 (1018) ml (range 230–3990). §Central venous pressure was measured in 65 patients only. LR: likelihood ratio

Symptom	Hypovolaemic (n=36)	Normo or hypervolaemic (n=32)	LR	Crude weights	Logistic coefficients (SE)	Adjusted weight	Range of adjusted weights
Prior probability	0.53	0.47		12	–5 (1.8)	–5	
Pulmonary oedema							
Yes	3	10	0.27	–131	0.69 (0.9)	–90	110
No	33	22	1.33	29		20	
Peripheral oedema							
Yes	13	18	0.64	–45	0.65 (0.7)	–29	54
No	23	14	1.46	38		25	
Skin mottling							
Yes	10	7	1.27	24	1.22 (0.8)	29	39
No	26	25	0.92	–8		–10	
Congestive heart failure							
Yes	2	5	0.36	–102	1.03 (1.1)	–105	116
No	34	27	1.12	11		11	
Third spacing†							
Yes	3	6	0.44	–82	2.25 (1.3)	–184	211
No	33	26	1.13	12		27	
Fluid losses							
Yes	9	7	1.14	13	1.09 (0.8)	14	18
No	27	25	0.96	–4		–4	
Fluid balance‡							
Positive or nil	18	22	0.79	–24	0.99 (0.7)	–24	65
Negative	14	9	1.51	41		41	
Central venous pressure§							
≤2 mm Hg	13	5	2.37	86	1.36 (0.8)	117	159
>2 mm Hg	21	26	0.74	–31		–42	

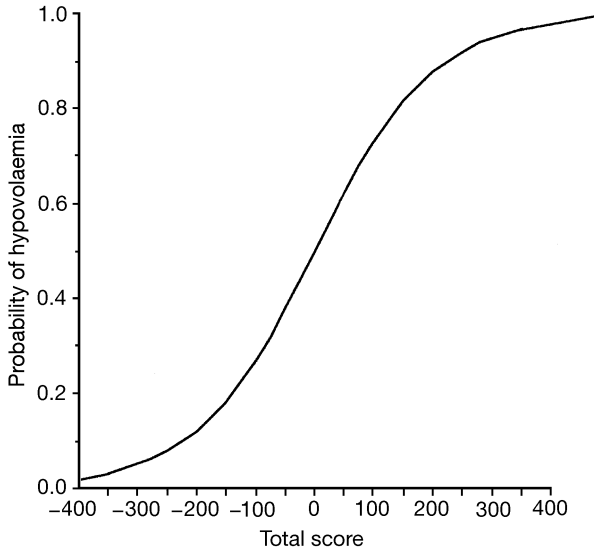

Fig 1 Relationship between hypovolaemia score and its theoretical probability. Probability=1/($e^{-T/100}$+1); Score=100 Ln [probability/(1–probability)].

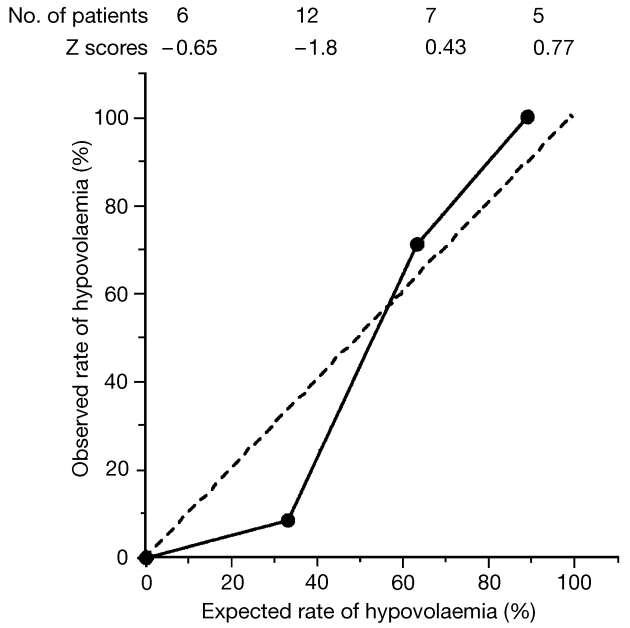

Fig 2 Observed and expected (predicted) rates of hypovolaemia status in test data set (30 ICU patients). A perfect predictor would exactly coincide with the diagonal line running from bottom left to top right (line of identity). As values of *Z* statistic lie within the range –2 to +2, the fit of the predictor to the line of identity is satisfactory. Predictions are therefore reliable.

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.[2] First, measurement of CBV depends on adequacy of mixing of [^{125}I]albumin throughout the vascular system and rapid whole body disappearance of the tracer.[20] 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.[5 21 22] However, despite a close correlation with other techniques,[23] this method could lead to a slight overestimation of CBV.[20 23] Second, septic patients have altered capillary permeability.[24] However, [^{125}I]albumin disappearance rate has been reported to be almost unmodified after endotoxin administration[21] and determination of CBV has been shown to be accurate in septic patients.[25] 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.[5 25 26]

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.[8] 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.[27] 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.[21] 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.[9] 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%.[5–8 28–31] One possible explanation is that physicians

do not optimally use clinical information when assessing fluid volume status. [32] 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.[26] Ourselves and others[25 33] have noted that the use of routine haemodynamic variables are of little value to differentiate hypovolaemic 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.[6] 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 aspiratory crackles and CBV.[27] On the other hand, the appearance of reduced CBV in the face of expanded extracellular fluid has been described.[26] 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.[8] On the other hand, combinations of physical signs appear to be more helpful.[8] 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.[32] 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,[34] 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.[35 36] 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.[35 36] Finally, if the criteria of hypovolaemia change, the sensitivity and specificity of each of the signs may be different,[8] 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,[37] there are no guidelines to help the physician to decide when to use or to withhold invasive monitoring in individual patients.[29] 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 2×2 table allowed calculation of sensitivity, specificity, and LR for the presence or absence of a given sign:

LR for the presence of a particular sign=sensitivity/(1–specificity)

LR for the absence of a particular sign=(1–sensitivity)/specificity.

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

The independence Bayes equation may be expressed as:

Posterior odds=prior odds×LR of sign 1×LR of sign 2 . . .×LR of sign *N* (1)

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 posterior odds=100 Ln prior odds+100 Ln LR of sign 1+100 Ln LR of sign 2 . . .+100 Ln LR of sign *N* (2).

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+adjusted weights of sign 1+adjusted weights of sign 2 . . .+adjusted weights of sign N (4).

(5) Converting scores back to probability of disease

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

References

1 Tschaikowsky K, Meisner M, Durst R, Rügheimer E. Blood volume determination using hydroxyethyl starch: A rapid and simple intravenous injection method. *Crit Care Med* 1997; **25**: 599–606

2 Jones JG, Wardrop CAJ. Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth* 2000; **84**: 226–35

3 Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic patterns in surviving and nonsurviving shock patients. *Arch Surg* 1973; **106**: 630–6

4 Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Resp Dis* 1992; **145**: 990–8

5 Williams JA, Fine J. Measurement of blood volume with a new apparatus. *N Engl J Med* 1961; **264**: 842–8

6 Chung H-M, Kluge R, Schrier RW, Anderson RJ. Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 1987; **83**: 905–8

7 Cook DJ. Clinical assessment of central venous pressure in the critically ill. *Am J Med Sci* 1990; **229**: 175–8

8 McGee S, Abernethy WB, Simel DL. Is this patient hypovolemic? *JAMA* 1999; **281**: 1022–9

9 Stéphan F, Novara A, Tournier B, *et al*. Determination of total effective vascular compliance in patients with sepsis syndrome. *Am J Respir Crit Care Med* 1998; **157**: 50–6

10 American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee. Definitions for sepsis and organ failures and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74

11 Le Gall J-R, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957–63

12 Brezis M, Rosen S, Epstein KH. Acute renal failure. In: Brenner BM, Rector Jr FC eds. *The Kidney*, 4th edn. Philadelphia: WB Saunders Company, 1991; 993–1061

13 Greco BA, Jacobson HR. Fluid and electrolyte problems with surgery, trauma, and burns. In: Koko JP, Tannen RL, eds. *Fluids and Electrolytes*, 3rd edn. Philadelphia: WB Saunders Company, 1996; 729–58

14 Wennesland R, Brown E, Hopper J, *et al*. Red cell, plasma and blood volume in healthy men measured by radiochromium cell tagging and hematocrit: influence of age, somatotype and habits of physical activity on the variance after regression of volumes to height and weight combined. *J Clin Invest* 1959; **38**: 1065–77

15 Brown E, Hopper J, Hodges JL, Bradley B, Wennesland R, Yamauchi H. Red cell, plasma, and blood volume in healthy women measured by radiochromium cell-labelling and hematocrit. *J Clin Invest* 1962; **41**: 2182–90

16 Armitage P, Berry G. *Statistical Methods in Medical Research*, 6th edn. Oxford: Blackwell Scientific Publications, 1994

17 Griner PF, Mayewski RJ, Mushlin AI, Greenland P. Selection and interpretation of diagnostic tests and procedures. Principles and applications. *Ann Intern Med* 1981; **94**: 553–600

18 Spiegelhalter DJ, Knill-Jones RP. Statistical and knowledge-based approaches to clinical decision-support system, with an application in gastroenterology. *J R Statist Soc A* 1984; **147**: 35–77

19 Spiegelhalter DJ. Probabilistic prediction in patient management and clinical trials. *Stat Med* 1986; **5**: 421–33

20 Bent-Hansen I. Initial plasma disappearance and distribution volume of ^{131}I-albumin and ^{125}I-fibrinogen in man. *Acta Physiol Scand* 1989; **136**: 455–61

21 Rothe CF, Murray RH, Bennett TD. Actively circulating blood volume in endotoxin shock measured by indicator dilution. *Am J Physiol* 1979; **236**: H291–H300

22 Payen J-F, Vuillez J-P, Geoffray B, *et al.* Effects of preoperative intentional hemodilution on the extravasation rate of albumin and fluid. *Crit Care Med* 1997; **25**: 243–8

23 Thomsen JK, Fogh-Andersen N, Bülow K, Devantier A. Blood and plasma volumes determined by carbon monoxide gas, ^{99m}Tc-labelled erythrocytes, ^{125}I-albumin and the T^{1824} technique. *Scand J Clin Lab Invest* 1991; **51**: 185–90

24 Ellman H. Capillary permeability in septic patients. *Crit Care Med* 1984; **12**: 629–33

25 Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; **12**: 107–12

26 Shoemaker WC, Bryan-Brown CW, Quigley L, Stahr L, Elwyn DH, Kark AE. Body fluid shifts in depletion and poststress states and their correction with adequate nutrition. *Surg Gynecol Obstet* 1973; **136**: 371–4

27 Bogaard HJ, de Vries JPPM, de Vries PMJM. Assessment of refill and hypovolaemia by continuous surveillance of blood volume and extracellular fluid volume. *Nephrol Dial Transplant* 1994; **9**: 1283–7

28 Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984; **12**: 549–553

29 Connors AF Jr, Dawson NV, Shaw PK, Montenegro HD, Nara AR, Martin L. Hemodynamic status in critically ill patients with and without acute heart disease. *Chest* 1990; **98**: 1200–6

30 Steingrub JS, Celoria G, Vickers-Lahti M, Teres D, Bria W. Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. *Chest* 1991; **99**: 1451–5

31 Mimoz O, Rauss A, Rekik N, Brun-Buisson C, Lemaire F, Brochard L. Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. *Crit Care Med* 1994; **22**: 573–9

32 Connors AF, Dawson NV, McCaffree DR, Gray BA, Siciliano CJ. Assessing hemodynamic status in critically ill patients: do physicians use clinical information optimally? *J Crit Care* 1987; **2**: 174–80

33 Lazrove S, Waxman K, Shippy C, Shoemaker WC. Hemodynamic, blood volume, and oxygen transport responses to albumin and hydroxyethyl starch infusions in critically ill postoperative patients. *Crit Care Med* 1980; **8**: 302–6

34 Pinsky MR. The hemodynamic consequences of mechanical ventilation: An evolving story. *Intensive Care Med* 1997; **23**: 493–503

35 Koran LM. The reliability of clinical methods, data and judgments (first of two parts). *N Engl J Med* 1975; **293**: 642–6

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

37 Connors A, Speroff T, Dawson N, Thomas C, Knauss W. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA* 1996; **276**: 889–97