

HeartSmart® for routine optimization of blood flow and facilitation of early goal-directed therapy

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Abstract: The empirical physiological formulae of the new continuous cardiac dynamic monitoring HeartSmart® technology, which involves the use of a new inverse square rule of the heart, were investigated with pulmonary artery catheter (PAC) thermodilution in the estimation of CI in diverse patients. Clinical trial data collected from 268 adult surgery or intensive care patients requiring PAC placement were obtained from 7 NHS Trust hospitals, providing 2720 paired sets of CI estimations for comparison between HeartSmart® and PAC thermodilution. For 95% of pairs of measurements, HeartSmart® values were between 57% and 164% of PAC measurements; additionally, the larger limit of agreement between HeartSmart® and PAC thermodilution ($1.26 \text{ L min}^{-1} \cdot \text{m}^{-2}$) suggests that HeartSmart® agrees with PAC thermodilution as closely as PAC thermodilution agrees with itself. HeartSmart® can also estimate CI in the extreme circumstances of shock/sepsis, as indicated by PAC thermodilution CI values that were hypo- or hyperdynamic based on systemic inflammatory response syndrome criteria. In CI measurements for hypo- or hyperdynamic values that were matched between HeartSmart® and PAC thermodilution, the difference in total volumes and average CI measurements between the two methods was less than 5%. For unmatched hypo- or hyperdynamic values, the difference between total volumes and average CI measurements was less than 33% – an acceptable percentage of difference or error even for normal values of CI. HeartSmart® tracked PAC thermodilution CI hypodynamic values 98.2% of the time and hyperdynamic values 97.6% of the time. These findings show that CI estimations provided by the HeartSmart® empirical physiological formulae are comparable to those obtained using PAC thermodilution. HeartSmart® removes many of the technical barriers that prevent the routine adoption and practice of early goal-directed therapy, and represents a simple, reliable method of estimating CI and other hemodynamic variables at the bedside or in departments other than the Intensive Care Unit.

Keywords: cardiac index, early goal-directed therapy, HeartSmart®, cardiodynamics, blood flow

The importance of estimating cardiac output (CO ; L min^{-1}) or the more clinically relevant cardiac index (CI ; $\text{L min}^{-1} \cdot \text{m}^{-2}$) has long been recognized; indeed, measuring cardiac output as part of an appropriate goal-directed therapy protocol has been shown to reduce both mortality and morbidity in certain groups of surgical and intensive care patients, including those with early sepsis.¹⁻⁵ However, there is considerable controversy regarding which of the plethora of available technologies provides results that are sufficiently consistent and reliable to allow routine optimization of blood flow, thus facilitating early goal-directed therapy. This debate is centered around the issue of when, why, and which fluid therapy should be implemented. This question has, until now, remained largely unanswered due to the lack of a simple, reliable hemodynamic monitoring technology that can monitor all the main hemodynamic variables and which could, therefore, tell

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us which cardiodynamic variables indicate the need for 'wet or dry' therapy with the appropriate intravenous/vasopressor fluid regimens for the optimization of blood flow and facilitation of early goal-directed therapy.

Historically, routine optimization of blood flow using goal-directed therapy – or, more importantly, early goal-directed therapy – has not been possible, mainly because existing technologies are not suitable for this purpose: they generally require an exceptional amount of operator input, with long and steep learning curves. Despite somewhat erroneous and controversial criticisms,^{6,7} the pulmonary artery catheter (PAC) thermodilution method is still considered the 'gold standard' for hemodynamic monitoring at the bedside, and all new methodologies for estimating cardiac index are compared with this technique.⁸

All bedside hemodynamic monitoring methodologies, at best, only estimate CO/CI. None of the technologies currently available can give a 'true' CO, for which there is no true reference technique for clinical determination. Comparison of the reproducibility and accuracy of the PAC thermodilution method with both the Fick and the dye-dilution methods reveals that all three are of equal merit and can be used as independent references.⁹ However, an assessment of the thermodilution technique demonstrates that a difference of at least 15% between the means of the three CO/CI estimations is required to reach clinical significance.⁹

Continuous cardiac dynamic monitoring (CCDM)-HeartSmart® technology (HeartSmart Ltd, Harlow, Essex, UK) involves the use of a new inverse square rule of the heart in the regulation of CI/CO, along with empirical physiological formulae derived from routinely measured physiological variables (central venous pressure, heart rate, mean arterial pressure, height, weight, temperature, and age), to estimate CI and other hemodynamic variables.¹⁰ This new technology provides a robust methodology that can be used to facilitate early goal-directed therapy in order to optimize blood flow.^{11,12} The aim in this paper was to present clinical trial data that compare these empirical physiological formulae with PAC thermodilution in the estimation of CI in a diverse groups of patients in order to determine whether the CCDM software could be used interchangeably with – or perhaps replace – the thermodilution method.

Methods

Between 1995 and 2005, clinical trial data collected from 268 adult patients requiring placement of a PAC for routine monitoring were collected from seven separate NHS Trust hospitals: St George's Hospital in London, Papworth Hospital

in Cambridge, Bradford Royal Infirmary, Leeds General Infirmary, the Royal Hallamshire Hospital in Sheffield, and Grimsby and Scunthorpe General Hospitals. We obtained ethical approval from each institution, and patients or their relatives gave written consent to be enrolled into the study. These studies comply with the Declaration of Helsinki.

The Medical Economics Research Centre Sheffield was also commissioned by Medics Limited to collect clinical data from patients taking part in the PAC-MAN study.⁶ The Royal Hallamshire with the Grimsby and Scunthorpe General Hospitals were taking part in the intensive care national audit research committee ICNARC study ordered by the Department of Health into the benefits and risks of pulmonary artery catheterization;⁶ the authors of this study were simultaneously performing a double-blind study of the ICNARC study data as they were being recorded. With the exception of one investigator, investigators from the Royal Hallamshire and the Grimsby and Scunthorpe Hospitals had no knowledge of, or contact with, the HeartSmart® investigators, and vice versa.

Data for 23 patients (141 paired sets of measurements) were obtained from St George's Hospital in London; eight of those patients were being evaluated for heart transplants and the remainder for scheduled cardiac surgery. Papworth Hospital in Cambridge provided data for five patients (23 paired sets of measurements) undergoing cardiac investigations. The Bradford Royal Infirmary provided data for 63 patients (545 paired sets of measurements) from the adult general intensive care unit. These three hospitals were used in the development and testing stage (1994–1997) of the HeartSmart® computer software, and in the design of future clinical studies. We are able to include all these data for analysis, even though there are multiple paired sets of measurements.

Leeds General Infirmary provided data for 101 patients (1635 paired sets of measurements), from whom 11 random patient data sets were used to establish the HeartSmart® empirical formulae prior to carrying out two sets of different patient studies. These studies involved 67 patients undergoing scheduled corrective open heart surgery (two studies of 22 and 45 patients) and 23 patients admitted to the neurological intensive care unit.

The Royal Hallamshire Hospital in Sheffield, along with Grimsby and Scunthorpe General Hospitals, provided data for a total of 60 patients (360 paired sets of cardiac index measurements); 80% of these patients were diagnosed with sepsis/shock and admitted to general intensive care units (unpublished). It is this group that has the highest number of

hypo- and hyperdynamic flow values consistent with those pathologies.

We also included one retrospective study performed at the Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands,¹³ observing 90 adult patients in a study of hemodynamic patterns in ST-elevation myocardial infarction. The incidence and correlates of elevated filling pressures were measured, averaging down to 16 single sets of defined PAC thermodilution measurements. This was a blinded retrospective study in which the hemodynamic values of central venous pressure, heart rate, systolic and diastolic pressure, and core body temperature (36.9°C) were read out to the first author, who computed the results prior to analysis and comparison of both sets of results.

The above hospital clinical trials provided a total of 2720 paired sets of CI estimations in very diverse groups of patients for analysis against the PAC thermodilution intermittent method. We analyzed 2720 paired sets of data and then looked specifically at the low CI values (hypodynamic) and high CI values (hyperdynamic) usually encountered with patients in sepsis and shock. Finally, we undertook a deeper analysis of our study in scheduled corrective cardiac surgery patients.

The majority of the HeartSmart® clinical trials from 1997 onwards followed the same design requiring that the patient's treatment would normally require right heart catheterization using a standard PAC using the intermittent thermodilution method for hemodynamic monitoring. The manufacturer's instructions for performing cardiac output studies were closely adhered to, and each patient had six full sets of studies recorded or multiples of six sets of studies. Only patients or their relatives who gave full consent were admitted into the studies; if there were problems anatomically with the insertion of the PAC, then these patients were also made exempt from the study. The objective in these studies was to investigate how well the HeartSmart® empirical physiological formulae compared with the accepted standard PAC thermodilution method. The risks of complications associated with pulmonary artery catheterization are well reported, while such risks associated with catheterization of the superior and inferior vena cava using a standard central venous pressure catheter are known to be very much less; hence, HeartSmart® may confer a potential benefit with respect to safety even if there are no other benefits. Of course, the costs associated with the two methods of hemodynamic monitoring via right heart catheterization are markedly different.

CO was estimated using standard PAC thermodilution and simultaneous values obtained from HeartSmart®. CI estimations were made from six paired sets of measurements from each individual patient, providing 2720 sets of paired measurements from PAC thermodilution. When reporting our findings on specific clinical trials from any one of the above hospitals, we include six sets of measurements per patient (or multiples of six measurements in hemodynamically unstable patients), as per the original study design protocol (1994) that was prepared for future clinical trials.¹⁰

The principles underpinning the new inverse square rule of the heart

We start with some very simple components that are important for regulating the normal range of the CI/CO. The four constituents that are involved in regulating CO, and which are represented in the HeartSmart® software, are as follows:

- a. Heart rate
- b. Contraction
- c. Preload
- d. Afterload

The components of the empirical physiological formulae in the new inverse square rule of the heart are heart rate in beats per minute, constants (K), the mean central venous pressure (CVP) in mmHg (preload), mean arterial pressure (MAP) in mmHg (afterload), and core body temperature in degrees Celsius – all of which are physiological parameters of a–d above. These physiological parameters are used to produce the biophysical expression $CI = CVP \cdot K \cdot T / HR^2$.¹⁰ Figure 1 shows a grid of K values produced from bandwidths of right atrial pressure (RAP) or CVP to bandwidths of heart rate; it is effectively a look-up table for any variation of RAP and heart rate.¹¹

The K empirical value per set of values is derived from the grid CVP – HR in Figure 1. The K values over a wide range of CVP and HR bandwidths in Figure 1 were validated by the University of Sheffield, School of Mathematics in 1998, covering all bandwidths of CVP (0 mmHg–30 mmHg) and bandwidths of heart rates up to 300 beats per minute. In essence, the grid in Figure 1 is just another representation of the Frank–Starling Law.

If it were possible to measure CI directly at the arch of the aorta, then the K value could change using this type of heuristic empirical research technique, which we have used until now, thus providing a more accurate value of K. In our study,^{10,11} we compared the HeartSmart® CI against the cardiopulmonary bypass machine CI flow values (unpublished),

and the statistical analysis showed an even closer relationship to the PAC versus HeartSmart® reported in this paper.

In this paper, there is scope to briefly discuss only one aspect of the new inverse square rule of the heart that regulates CI/CO comparable with stroke volume index (SVi), calculated $SVi = Ci/HR$. This concerns the direct relationship between RAP, core body temperature in conjunction with the constant K's components of capacitance, compliance, and elasticity (combined with resistance, which is the energy force behind blood flow through the heart and lungs), and heart rate. CCDM-HeartSmart® technology shows that our knowledge of cardiodynamics and the associated cardiovascular physiology has, so far, been incomplete. This new inverse square rule shows that each of the physiological parameters can work individually or collectively in the regulation of CI/CO. In contrast, the K grid in Figure 1 shows that bands of RAP/CVP within bands of heart rates will deliver a uniform change in blood flow per change in heart beat, provided that the RAP/CVP and core temperature remain constant. For example, if the core temperature is 36.9°C, the RAP/CVP is 7 mmHg, and the heart rate is 78 beats per minute (bpm), then $K = 90$ and the estimated CI is $3.61 \text{ L min}^{-1} \cdot \text{m}^{-2}$. At heart rates of 79 bpm, 80 bpm, and 81 bpm, the CI is 3.52, 3.43, and $3.35 \text{ L min}^{-1} \cdot \text{m}^{-2}$, respectively. Each heartbeat uniformly changes the SVi by $0.09 \text{ L min}^{-1} \cdot \text{m}^{-2}$. If the RAP/CVP is increased by 2 mmHg over a heart-rate range of 78–81 bpm, where $K = 80$, the CIs delivered would be 4.37, 4.26, 4.15, and $4.05 \text{ L min}^{-1} \cdot \text{m}^{-2}$, respectively. Again, as the heart rate changes, it uniformly increases stroke volume by approximately $0.10 \text{ L min}^{-1} \cdot \text{m}^{-2}$. If RAP/CVP decreases by 2 mmHg from 7 mmHg over the

same heart-rate range (78–81 bpm), where $K = 100$, the CIs delivered would be decreased to 2.88, 2.81, 2.74, and $2.67 \text{ L min}^{-1} \cdot \text{m}^{-2}$, respectively. Each change in heart rate in that specific range decreases stroke volume by approximately $0.09 \text{ L min}^{-1} \cdot \text{m}^{-2}$. If we take the value of RAP/CVP at the lowest heart rate of 78 bpm (ie, RAP/CVP = 7 mmHg), the CI is $3.61 \text{ L min}^{-1} \cdot \text{m}^{-2}$. Increasing RAP/CVP by 2 mmHg at 78 bpm gives a CI of $4.37 \text{ L min}^{-1} \cdot \text{m}^{-2}$, and decreasing RAP/CVP by 2 mmHg to 5 mmHg at 78 bpm produces a CI of $2.88 \text{ L min}^{-1} \cdot \text{m}^{-2}$. Therefore, an increase or decrease of 2 mmHg in RAP/CVP produces overall differences in CI of 0.76 and $0.73 \text{ L min}^{-1} \cdot \text{m}^{-2}$, respectively. For relatively small changes in RAP/CVP, changes in K increase or decrease incrementally by a factor of 10 in response to the changes in RAP/CVP with heart rate.

We can now conclude that RAP/CVP equates to venous return over a wide range of heart rates and CVP values. Increasing or decreasing RAP/CVP produces increases or decreases in K (elasticity/stretch, compliance), respectively, resulting in increased or decreased CI/CO depending on the increase or decrease in heart rate over a specific range of change in RAP/CVP. In turn, this increases or decreases the stroke volume index by a uniform set amount, thus regulating CI/CO over that specific range (Figure 1). We can also deduce that the empirical physiological formula $CI = CVP \cdot K \cdot T/HR^2$ for CI permits enormous scope for optimizing blood flow using early goal-directed therapy and regulating CI/CO over a very large range of values.

Statistical analysis

The mean values of three thermodilution CO estimates were used (provided that each measurement lay within 10% of the others), and were then compared with the CCDM-HeartSmart® estimates. The results of the measurements obtained were analyzed by the repeatability of tests within 95% limits of agreement method¹² using the adaptation for repeated pairs of observations. The repeatability of this method was assessed by the first and second authors with assistance from each of the hospital investigators, who analyzed all clinical trial data reported in this paper (including outlying plots). All calculations were performed using StatsDirect, a Statistical Computer Software Resource for Medical Research. The significance of the bias was tested using a paired *t* test on the mean bias for each patient.

Results

The limits of agreement have been calculated using the method for multiple pairs of measurements (described by

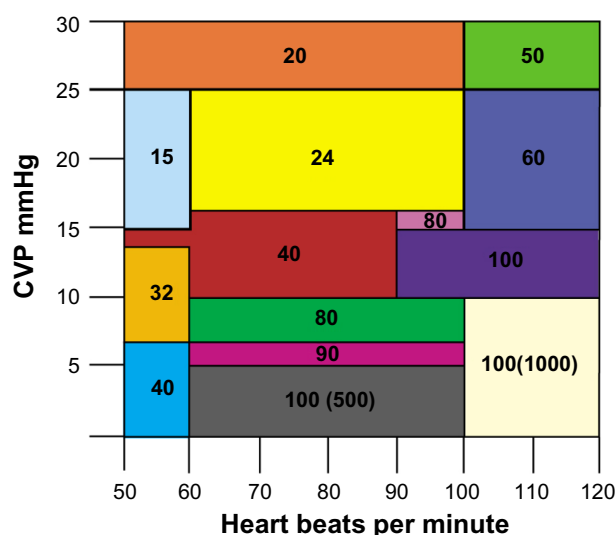


Figure 1 The continuous cardiac dynamic monitoring algorithm: relationship of the constant K with heart rate (beats per minute) and central venous pressure (CVP; mmHg).¹¹

Bland and Altman)^{14,15} for these 2720 paired sets of CI estimations. First, we check whether the differences between PAC and HeartSmart® appear to be independent of the magnitude of the measurement, by plotting the difference in CI against the average of the two measurements (Figure 2). As shown in Figure 2, there appears to be a relationship between difference and average, such that the differences become more variable as the magnitude of CI increases. We tried a logarithmic transformation of CI (Figure 3), and this appears to be much better. There are two outliers for which the differences are further from zero than any others and for which the average is smaller. The logarithmic transformation were therefore used for the remaining calculations.

The estimated standard deviation of differences was $0.2665 \text{ L min}^{-1} \cdot \text{m}^{-2}$ and the mean difference was $-0.0280 \text{ L min}^{-1} \cdot \text{m}^{-2}$. As this mean difference is very close to zero, there is no evidence of a consistent bias between HeartSmart® and PAC. The limits of agreement are given by the mean difference ± 1.96 standard deviations, $-0.5504 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $0.4944 \text{ L min}^{-1} \cdot \text{m}^{-2}$. The range of antilogs of these limits is 0.57 to $1.64 \text{ L min}^{-1} \cdot \text{m}^{-2}$. Hence, we estimate that for 95% of pairs of measurements, HeartSmart® will be between 57% and 164% of the PAC measurement. The limits of agreement are shown in Figure 4.

A measurement cannot have closer agreement with another measurement than it does with itself and it is useful to compare the limits of agreement with the repeatability coefficient, within which will fall approximately 95% of differences between pairs of measurement by the same method. This is difficult to obtain for CI, which may be a continuously changing quantity. In the present data, we have repeated measurements for both methods. If we can assume that the CI is

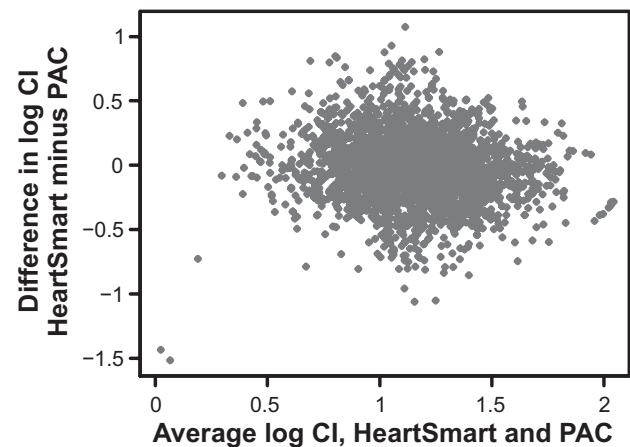


Figure 3 The relationship between the difference in the log cardiac index (CI) and the average log of CI of HeartSmart® minus pulmonary artery catheter (PAC) thermodilution logarithmic transformation of CI.

not changing greatly over the period of measurement, we can estimate the repeatability. For log PAC, the within-subject standard deviation was $0.2150 \text{ L min}^{-1} \cdot \text{m}^{-2}$. The repeatability coefficient, the 95% limit for differences, is $1.96\sqrt{2}$ times this, $0.5960 \text{ L min}^{-1} \cdot \text{m}^{-2}$. The antilog is $1.81 \text{ L min}^{-1} \cdot \text{m}^{-2}$, so that for 95% of pairs of PAC measurements, the larger measurement will be less than 181% of the smaller. This is actually larger than the limits of agreement. For HeartSmart®, the standard deviation of log CI was $0.2219 \text{ L min}^{-1} \cdot \text{m}^{-2}$ and the repeatability coefficient was $0.6152 \text{ L min}^{-1} \cdot \text{m}^{-2}$. The antilog is $1.85 \text{ L min}^{-1} \cdot \text{m}^{-2}$, very similar to that for PAC. Of course, these standard deviations include variation in CI over time, which is not present in the limits of agreement. In order to minimize this, we took pairs of CI observations adjacent in time. For PAC, this gave a standard deviation of $0.2116 \text{ L min}^{-1} \cdot \text{m}^{-2}$ and a repeatability of $0.5865 \text{ L min}^{-1} \cdot \text{m}^{-2}$,

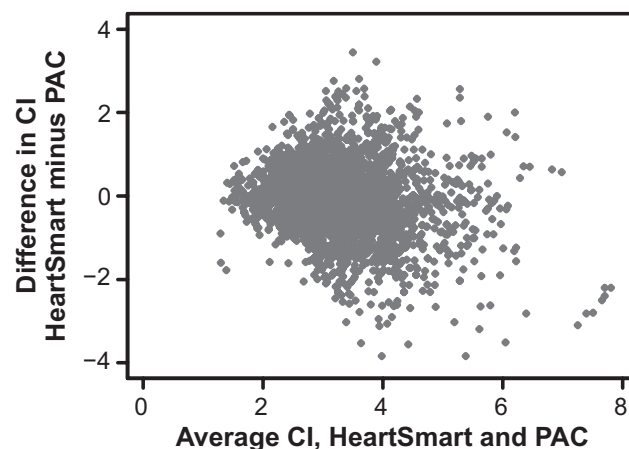


Figure 2 The relationship between difference in cardiac index (CI) and the average values provided by HeartSmart® and pulmonary artery catheter (PAC) thermodilution.

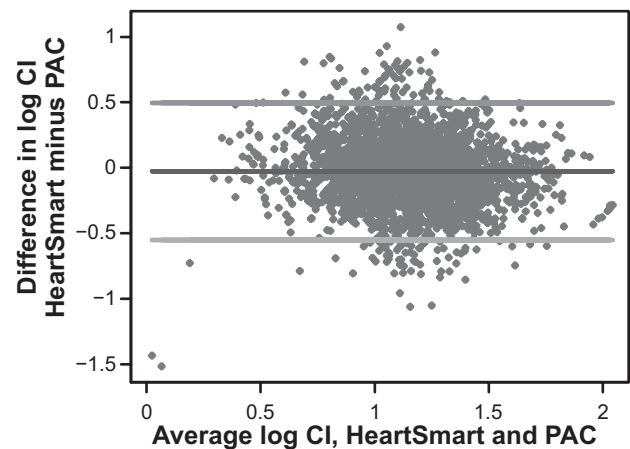


Figure 4 The relationship between the difference in the log cardiac index (CI) and the average log of CI of HeartSmart® minus pulmonary artery catheter (PAC) thermodilution logarithmic transformation of CI.

which has an antilog of $1.80 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For HeartSmart®, it gave a standard deviation of $0.2242 \text{ L min}^{-1} \cdot \text{m}^{-2}$ and a repeatability of $0.6216 \text{ L min}^{-1} \cdot \text{m}^{-2}$, which has an antilog $1.86 \text{ L min}^{-1} \cdot \text{m}^{-2}$. Hence, the numbers are almost the same for the adjacent pairs of observations. There is still temporal variation in this estimate, but the figures certainly suggest that we could not get better agreement between any measurement and PAC than that found with HeartSmart®. Our analysis would indicate that operator error may be responsible for the majority of these differences.

We now consider the differences in our first published study,¹⁰ in which estimates using the Critcheley criteria¹⁶ found an average difference of 39.5% between HeartSmart® and PAC: approximately 33% in the pre-bypass group and approximately 46% in the post-bypass group. These differences between the two methods arise from several sources, including the inherent PAC thermodilution technical error of approximately 10%–15%, which is present even before any hemodynamic studies are performed. Some of the variation may be due to a failure of the thermistors to react correctly after rewarming when we made our first measurements immediately after patients came off bypass.

There is little or no information available on the measurement error of the PAC thermodilution method,¹⁷ and so we carried out some analysis on this for our data. From one of the Leeds General Infirmary studies, 45 adult patients were enrolled and 270 pairs of CI measurements were made after induction, when patients were in a stable condition. We observed that changes in cardiodynamics were small. We treated these pairs as repeated measurements of the same quantity, and estimated the repeatability coefficient, below which 95% of differences between pairs of measurements will be expected to lie if the participant's CI does not change. This is given by the standard deviation of differences between the first and second measurements multiplied by 1.96. We checked for systematic changes between first and second measurements using a paired *t* test. The mean difference was close to, and not significantly different from, zero. The repeatability for CI was estimated to be $1.25 \text{ L min}^{-1} \cdot \text{m}^{-2}$, ie, 95% of measurement pairs for CI in a stable patient would differ by $<1.25 \text{ L min}^{-1} \cdot \text{m}^{-2}$. This statistic is similar to the limits of agreement for two different methods of measurement.

The larger limit of agreement between HeartSmart® and PAC thermodilution was $1.26 \text{ L min}^{-1} \cdot \text{m}^{-2}$, and we interpret this as showing that HeartSmart® agrees with the PAC thermodilution method as closely as the PAC thermodilution method agrees with itself.

Crucially, it is important to show that the CCDD empirical physiological formulae can estimate CI in the most extreme circumstances of sepsis/shock, and we believe this study achieves that goal in detail. We now look to see whether the PAC thermodilution CI values were hypodynamic or hyperdynamic based on systemic inflammatory response syndrome (SIRS) criteria.

Of the 2720 paired sets of measurements, there were 642 PAC thermodilution estimations (23.6%) indicative of sepsis/shock. Of those 642 estimates, 415 (64.34%) were hypodynamic values of $<2.5 \text{ L min}^{-1} \cdot \text{m}^{-2}$; 213 values matched HeartSmart®, having a CI of $<2.5 \text{ L min}^{-1} \cdot \text{m}^{-2}$, and 202 HeartSmart® values were $>2.5 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For the 213 matched hypodynamic PAC thermodilution values, the CI total volume amounted to $419.85 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $1.96 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $1.40 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $2.41 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For the HeartSmart® matched values, the CI total volume was $428.84 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $2.01 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $1.47 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $2.48 \text{ L min}^{-1} \cdot \text{m}^{-2}$. There is a difference of 3.1% between the total volumes and a difference of 2% between the average values of CI.

For the 202 unmatched hypodynamic PAC thermodilution values, the CI total volume amounted to $424.95 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $2.09 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $1.33 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $2.41 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For HeartSmart® unmatched values, the CI was a total volume of $628.46 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $3.1 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $2.47 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $5.22 \text{ L min}^{-1} \cdot \text{m}^{-2}$.

There is a difference of 32.38% between the total volumes and a difference of 32.58% between the average values of CI.

For the 100 matched hyperdynamic PAC thermodilution values, the CI total volume amounted to $551.26 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $5.46 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $4.50 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $8.90 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For HeartSmart® matched values, the CI was a total volume of $530.17 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $5.23 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $4.50 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $7.90 \text{ L min}^{-1} \cdot \text{m}^{-2}$. There is a difference of 3.83% between the total volumes and a difference of 4.23% between the average values of CI.

Of the 127 unmatched hyperdynamic PAC thermodilution values, the CI total volume amounted to $650.07 \text{ L min}^{-1} \cdot \text{m}^{-2}$, giving an average value per measurement of $5.12 \text{ L min}^{-1} \cdot \text{m}^{-2}$ over a range of $4.50 \text{ L min}^{-1} \cdot \text{m}^{-2}$ to $7.50 \text{ L min}^{-1} \cdot \text{m}^{-2}$. For HeartSmart® matched values, the

CI was a total volume of $469.05 \text{ L min}^{-1}\cdot\text{m}^{-2}$, giving an average value per measurement of $3.69 \text{ L min}^{-1}\cdot\text{m}^{-2}$ over a range of $2.50 \text{ L min}^{-1}\cdot\text{m}^{-2}$ to $4.48 \text{ L min}^{-1}\cdot\text{m}^{-2}$. There is a difference of 27.85% between the total volumes and a difference of 27.93% between the average values of CI. There were 227 (35.66%) paired sets of hyperdynamic CI estimations $>4.5 \text{ L min}^{-1}\cdot\text{m}^{-2}$, 100 (44.35%) of which paired with PAC thermodilution $>4.5 \text{ L min}^{-1}\cdot\text{m}^{-2}$ and 127 of which (55.65%) did not match with PAC thermodilution estimates.

These data show that, in the matched CI measurements for hypo- or hyperdynamic values, the difference between the total volumes and the average CI measurements is less than 5%. For the unmatched hypo- or hyperdynamic values, the difference between total volumes and average CI measurements is less than 33%. This percentage difference or error is acceptable even for normal values of cardiac index.¹⁶ HeartSmart[®] tracked PAC thermodilution CI hypodynamic values 98.2% of the time and hyperdynamic values 97.6% of the time.

Discussion

There are eight desirable characteristics for CO monitoring techniques:¹⁸ accuracy; reproducibility with precision; fast response time; operator independence; ease of use; continuous use; cost effectiveness; and reduced risk of mortality and morbidity.

CCDM-HeartSmart[®] introduces a very simple, safe way of performing hemodynamic studies and regulating CO using a new inverse square rule of the heart, which is embedded in its software. We believe that analyses comparing this new inverse square rule of the heart to the industry standard method, as performed in the current study (which involves various NHS Trust hospitals and widely differing populations of adult medical and surgical patients), are specific requirements for establishing this new technology. Such a substantial combined study was also necessary to demonstrate the reliability of the new method over a broad spectrum of clinical conditions.

The results from this collection of seven sets of clinical studies show that CO measurements derived using these new empirical physiological formulae are comparable with those obtained using PAC thermodilution in a substantial number of patients admitted to general and cardiac intensive care units. We used a well-validated method¹² to compare PAC thermodilution with the CCDM software: the 95% limits of agreement analysis assesses the agreement between two methods of measurement of a variable, and the means of the differences are an estimate of the average bias of

PAC thermodilution relative to that of the new CCDM technology.

The results showed strong correlations between the two groups of variables: data showed that the 95% limits of agreement and the mean bias were statistically sufficiently close across the full range of CI measurements observed, suggesting that this physiological platform is comparable to the PAC thermodilution mathematical platform of estimating CI. However, we believe that there may be a disparity of as much as 50% between the recorded CI/CO measurements and the real values in shock situations. Both methods follow these CI/CO trends, especially when aggressive fluid therapy regimens are applied.

While the pulmonary artery catheter permits the operator to see whether there are 'giant' a and/or cv waves in the CVP waveform, these waves are just one of the indicators used to diagnose some form of heart valve incompetence that may lead to sepsis/shock conditions. Practitioners therefore need to compare other hemodynamic parameters – especially the RAP and left atrial pressure (LAP) with right and left ventricular end diastolic pressures (RVEDP and LVEDP) – when spurious CI/CO results are derived, along with other physiological signs and the patient's symptoms, to establish whether the flow rates shown on the monitor are consistent with the clinical picture. Results of this large study, along with those gained in other ongoing or completed studies, indicate that the empirical physiological formulae embedded in the software are robust and have the potential to replace – or to be used interchangeably with – PAC thermodilution when estimating CO in a number of different situations.¹⁰ Early perioperative fluid therapy is one of the most controversial topics in perioperative care; however, premature deaths have been recorded when such a procedure has not been used.

The CCDM software allows for the introduction of early goal-directed therapy as a standard procedure prior to, during, and after major surgery for patients at the highest risk of death and complications.⁵ Results of this study also confirm that CCDM empirical physiological algorithms are capable of achieving the physiological targets for 'early goal-directed therapy in early sepsis'.⁵ However, perhaps a more important consideration is that, like the PAC thermodilution method, this physiological method is able to derive left heart pressures¹⁰ in order to characterize shock and septic conditions that can quickly lead to morbidity and mortality if not recognized and treated immediately. The ability to eliminate the need for PAC insertion is an exceptional asset in the treatment and management of not only critically ill patients,

but also those patients where fluid management is part of routine treatment.

Catheterization of the internal jugular vein, or even using a short central venous pressure catheter placed *in situ* in the superior vena cava, is a relatively simple procedure that can be performed on patients in Accident and Emergency departments or on the wards under local anesthetic prior to any major procedure. Heart rate, blood pressure, and temperature are routine measurements, and entering these physiological parameters into the HeartSmart® program provides an instantaneous hemodynamic evaluation so that corresponding decisions can be made with regard to commencement of early goal-directed therapy by optimizing blood flow. Indeed, this HeartSmart® software removes many of the technical barriers that prevent early goal-directed therapy from being performed and globally adopted as routine practice. The goal is to improve the rates of morbidity and mortality associated with sepsis and shock so that they parallel those observed in other groups of patients (eg, those with acute myocardial infarction, trauma, and stroke), whilst also significantly reducing the annual number of premature deaths. In order to achieve this, we need to combine the well-researched principles and benefits of early recognition with i) monitoring of left heart pressures and levels of blood glucose and lactate (which can be indicators of the status of the microcirculation); and ii) a combined multidisciplinary approach to early goal-directed therapy that involves physicians, surgeons, and anesthetists.

The empirical physiological formulae embedded in the software represent groundbreaking science in terms of our knowledge of cardiodynamics, their effect on hemodynamics, and the almost limitless possibilities for use in medical scientific studies in the future. We also believe that the size of this combined clinical study, along with its outcomes, provides compelling evidence for the utility of this physiological platform as a standard procedure for performing routine hemodynamic monitoring whilst optimizing blood flow using early goal-directed therapy in medical and surgical patients. Should this new method of estimating CI with left heart pressures be adopted by the profession, so that hemodynamic monitoring becomes a standard procedure, then the controversy surrounding both optimization of blood flow using goal-directed therapy and the use of vasoactive drugs in different groups of patients could be fully investigated.

In many studies the economical benefits provided to healthcare providers¹⁹ by implementing early goal-directed therapy as quickly as possible in those patients suffering from sepsis or septic shock conditions have been found.

HeartSmart® can assist in this by removing one of the main obstacles to performing routine early goal-directed therapy, ie, the technological barrier posed by the need to provide a simple yet effective method of monitoring hemodynamics at the bedside.

Whenever a new innovative method is brought into industry, it is necessary to provide substantive evidence of its efficacy. This is never truer than in the highly regulated environment of healthcare. We conclude that this large combined study has confirmed the accuracy, precision, and robustness of the new inverse square rule of the heart governing regulation of CI, whilst lowering the risk of complications with increasing benefits for the patient and healthcare provider. Our data also highlight the efficacy of the empirical physiological platform in providing continuous cardiac dynamic monitoring and confirm that it is a simple, reliable method of estimating CO and other hemodynamic variables at the bedside or in any department other than Intensive Care Units.

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Disclosure

Dr Kenneth Warring-Davies is the inventor of CCDMHeartSmart. MERCS at the Royal Hallamshire Hospital, Sheffield, was commissioned to independently collect clinical data from NHS Hospitals in that NHS Hospital Trust. No financial contributions were made to any other institution or person.

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