Cardiac Dynamic Monitoring in Patients with Systemic Inflammatory Response Syndrome: a Double-Blind Study

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Abstract — Sepsis and Systemic Inflammatory Response Syndrome (SIRS) represent a major factor in morbidity and mortality in intensive care units. The pathophysiological mechanisms underlying these syndromes are becoming increasingly better understood by monitoring haemodynamic variables. Intensive monitoring and aggressive management of perioperative haemodynamics (i.e. early goal directed therapy, EGDT) have been reported to significantly reduce the morbidity and mortality associated with high-risk surgery. The advantages bestowed by pre- and perioperative optimization using early GDT (POEGDT) are largely dependent upon the technology used. In this double-blind study, conducted in patients with a diagnosis of SIRS, the pulmonary artery catheter thermodilution (PACTD) and Oesophageal Doppler Method (ODM2) were compared to HeartSmart, a continuous cardiac dynamic monitoring system with empirical physiological formulae (EPF) algorithms embedded in its software module. HeartSmart was found to be equally comparable to the PACTD and ODM2, calculating cardiac index with other haemodynamic variables. This study demonstrates that the continuous cardiac dynamic monitoring with the EPF’s algorithms embedded in HeartSmart software module, appears to offer an estimation of cardiac index and cardiac output that are comparable to that measured by the PACTD and ODM2, in a population of SIRS patients.

Keywords — Doppler, oxygen supply, haemodynamic monitoring, SIRS, thermodilution, cardiac index.

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I. INTRODUCTION

The National Health Service (NHS) reforms in UK1,2 have for the first time given real incentives for NHS Hospital Trust and other health care providers, to reduce the length of time patients spend in hospital3,4. Reducing hospital admissions and caring for people more appropriately outside of hospital is essential. However, when hospital care is needed, the NHS and other health care providers5, need to minimize the time that patients spend in hospital, while not undermining patient safety or quality of care. Haemodynamic monitoring is a major technology in achieving such goals; however, until now there has not been available an easy, friendly, inexpensive, less invasive method of performing haemodynamic monitoring with the right and left haemodynamic variables at the bedside. Such a method would reduce length of stay in hospital with improving levels of care, so that patients recover more quickly with marked improvements to the risks of morbidity or mortality occurring5,6.

In the harsh financial world health care providers find themselves, purchasers holding the ‘purse strings’ want immediate cost savings on products being purchased, as well as ongoing cost savings, while at the same time clinical staff want to maintain standards and levels of training etc. All too often the aims and viewpoints of clinicians and hospital managers do not meet7,8. Additionally, the NHS in the UK is reported as being the slowest adopter of new and groundbreaking technology in health throughout the western world9.

In the current climate of mounting NHS and other health care providers deficits throughout the world, and with the impending Comprehensive Government Spending Reviews since 2008, productivity and efficiency are paramount. Cash in the healthcare provider’s coffers worldwide will need to be spent more cautiously, with clear evidence of both clinical and cost effectiveness. In cardiovascular disease and open heart surgery haemodynamic monitoring is key to the patient’s routine treatment and recovery, the costs of performing such with post operative intensive and high dependency care units, especially pediatric cases, can quickly spiral out of control. Bearing in mind that the average cost for a patient to stay in an NHS surgical ward is £300-600 per day, rising to £1200-1500 per day for special care unit beds, and even higher special care costs in other countries3, then, the financial benefits of reducing length of stay are clear. Technology has a significant role to play in realizing these savings2, which will then allow health care providers to finance other services identified by clinicians and specialties — in other words, enabling improvements to be partly self-financing, especially in private hospitals and clinics and to medical insurers9,10.
Role of Assistance or Technicians
The role and job description of the Operating Department Practitioner (ODP) in the UK is changing, with some aspects of it being partly based on the US system of physician assistant, surgical assistant, nurse and technical anaesthetic assistant. Furthermore, in some establishments OPD’s are already responsible for purchasing hardware and other consumables for operating theatres and wards etc. Adoption of new technologies can be a major route providing better treatment for the patient and many cost savings in time and money to any healthcare institution.

Haemodynamic monitoring is one important area for consideration, and very often their surgical, medical and nursing colleagues often rely on technical staff to give advice in the decision-making process to purchase new equipment etc. Assistance and technical staff are involved daily with many types of haemodynamic monitoring methods, from simple intravenous drips with various pumps, central venous pressure monitoring, to full haemodynamic monitoring procedures used during thoracic and cardiac surgery. The haemodynamic monitoring market size is valued at approximately $8 billion/year11.

Thereby, with clear clinical advantages, it is important that assistance is made aware of the advantages of the technology described in this article11. The HeartSmart monitoring software has been described in previous articles12-15. HeartSmart has been shown to accurately calculate beat-by-beat the cardiac index in patients admitted onto the general intensive care unit. HeartSmart has been compared against the pulmonary artery flotation thermodilution catheter (PACTD) the accepted ‘gold standard’ that all haemodynamic monitoring technologies should be compared to, when making claims of what the technology and products provide, and compared to the Oesophageal Doppler Method (ODM2)16.

Advantages of Perioperative optimization (PO)
Perioperative optimization is the preventive manipulation of physiological parameters during the perioperative period. This strategy specifically aims, in addition to standard anesthetic and surgical care, to decrease morbidity and mortality following surgery. Studies assessing the effectiveness of specific strategies exist in the following areas17,18:
- Increasing tissue oxygen delivery
- Prevention of myocardial ischaemia
- Maintenance of normothermia
- Maintenance of normoglycaemia

Benefits of Early Goal Directed Therapy (EGDT)
The empirical physiological formulae (EPF’s) embedded in the continuous cardiac dynamic monitoring (CCDM) software module technology HeartSmart19,20, allows medical staff to use fluids and vasopressors/inotropes to optimize the flow of blood throughout the body, thus maintaining an adequate supply of oxygen (SO2) to the body’s organs and tissues in order that metabolic functions of the cells can be maintained. The physiological parameters required by the EPF’s are: heart rate (HR), systolic and diastolic blood pressure (BP), core body temperature in degrees Celsius (T) and right atrial or central venous pressure in mmHg (CVP), the only invasive parameter21,22. HeartSmart calculates the main parameters usually delivered by the right heart floatation catheter for performing PACTD. A short CVP catheter will suffice, as there is no requirement by HeartSmart technology for the catheter to enter into the heart. EGDT can then be performed, with all the reported benefits3,4,22.

When pathological conditions of reduced circulating blood volume are present, this is known as hypovolemia. The effect is similar to dehydration, which often leads to insufficient amounts of oxygen being delivered to the organs, due in part to a low cardiac index or output (Ci/CO).

Insufficient oxygen supply (SO2) and oxygen demand (DO2) cause medical and surgical complications, including peripheral and major organ dysfunction or multiple organ failure syndromes25. These lead to slower recovery, with longer lengths of stay in hospital, and in some cases increased morbidity, increased number of premature deaths, and/or subsequent latent mortality after hospital discharge3,6. It is estimated that there are some 20,000 premature deaths in the UK annually that could have been averted if the patient had been optimized using goal directed therapy during major surgery3.

Pre- and perioperative optimization using early goal directed therapy (POEGDT) is a subject that every practitioner should be conversant with, to help provide the full range of clinical benefits to the patient. So, what is the object of POEGDT? Quite simply, POEGDT is a technique that uses intravenous fluid administration to improve cardiac index (or output), to deliver slightly higher blood volume to every square meter of tissue per minute. It ensures that cells have enough oxygen to meet their metabolic functions or needs. We emphasize haemodynamic indexes because they are clinically more relevant than absolute values, including cardiac index in liters per square meter per minute rather than cardiac output in liters per minute, for example.

When cells do not receive the correct amount of oxygen supply (SO2), they release catecholamines, which is the first step of septic shock sepsis, leading to multiple organ dysfunction syndrome (MODS)26, with irreversible shock and mortality to follow. Goal-directed therapy has been used perioperatively for medical and surgical cases, and in cases of severe sepsis and septic shock, such conditions are known as ‘Systemic Inflammatory Response Syndrome (SIRS)’, see Table 1. Dealing with the septic patients with existing cardiac pathologies or any other co-morbidity presents a real challenge to the practitioner, and monitored fluid resuscitation therapy is a key element to the patients survival. The POEGDT approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand to every cell in the body, using fluids and vasopressors/inotropes management. In the SIRS patients, flow rates seen are hypo- and hyper-dynamic – each results in lack of oxygen capacity in the blood, with the dangerous complications that invariably follow on.
In patients with serious infections, including meningitis, pneumonia or tuberculosis, starting haemodynamic monitoring as soon as possible is essential. POEGDT can correct cardiac flow rate abnormalities, and is absolutely key to increase chances of survival. It is in this arena where haemodynamic monitoring really is a useful tool throughout the emergency treatment phase. Consider two scenarios: 1) the patient is cold, with a core temperature < 36°C, and vasoconstricted low cardiac index or output states (hypodynamic) are encountered. 2) Conversely, the patient is pyrexial, with a core body temperature > 38°C, with tachycardia and high cardiac index and outputs (hyper-dynamic). In either scenario, the cells in the body are not receiving enough oxygen to meet the metabolic demands. Hence, organs begin to fail and after time the situation becomes irreversible and death invariably ensues. It is important to understand that the patient’s clinical appearance and symptomatology does not always meet exactly with the SIRS criteria depicted in Table 1; often these patients alter between phases of hypo-dynamic, normo-dynamic and hyper-dynamic flow rates, in the normal course of the incident.

Sepsis and SIRS are becoming more common, and represent a major factor in morbidity and mortality in intensive care units and the critically ill patient. The pathogenesis of these syndromes is becoming increasingly better understood by monitoring the haemodynamic variables, including cardiac index and left heart pressures, while maintaining the patient’s blood glucose and lactate levels, with normal body temperature. These physiological parameters provide an insight into the status of the microcirculation when the lactate and blood glucose levels are measured simultaneously, giving a more valuable clinical view of the haemodynamic status of the patient.

SIRS is non-specific and can be caused by ischemia, inflammation, trauma, infection, or a combination of several insults. SIRS is not always related to infection, where infection is defined as ‘a microbial phenomenon characterized by an inflammatory response to the micro-organisms, or the invasion of normally sterile tissue by those organisms.’ Bacteremia is the presence of bacteria within the blood stream, but this condition does not always lead to SIRS or sepsis. Sepsis is the systemic response to infection and is defined as the presence of SIRS in addition to documented patholgy or presumed infection. Severe sepsis meets the aforementioned criteria and is associated with organ dysfunction, hypoperfusion, hypotension, pyrexia and hypothermia etc. Sepsis-induced hypotension is defined as ‘the presence of a systolic blood pressure of less than 90mmHg, or a reduction of more than 40mmHg from baseline in the absence of other causes of hypotension.’ Patients meet the criteria for septic shock if they have persistent hypotension and perfusion abnormalities, despite adequate fluid resuscitation. Multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) is a state of physiological derangements in which organ function is not capable of maintaining homeostasis.

Although not universally accepted terminology, ‘severe SIRS’ and ‘SIRS shock’ are terms that some authors have proposed. These terms suggest organ dysfunction or refractory hypotension related to an ischemic or inflammatory process, rather than to an infectious aetiology.

Any pathological condition or insult to the body that interferes with or alters the physiological haemodynamic parameters – CVP, BP, HR and core body temperature – that has effects upon the blood vessels, causing them to vasodilate or constrict respectively; then those variations in turn change the systemic and or the pulmonary vascular resistances (SVR & PVR), leading to a marked decrease or increase in cardiac index or output. Hence, the early intervention by the physician is an attempt to bring the patient’s CI/Co back into the normal range. Intensive monitoring and aggressive management of perioperative haemodynamics (i.e. GDT) have repeatedly been reported to reduce the significant morbidity and mortality associated with high-risk surgery. It may not matter what particular monitor is used to assess cardiac output providing the measured values are consistent, but it is essential to ensure adequate oxygen delivery is met. If this management cannot begin preoperatively, it is still worth beginning goal directed therapy in the immediate postoperative period.

**Barriers to Haemodynamic monitoring**

Until now, haemodynamic monitoring has not been routinely available to the populations of emergency or elective general medical and surgical patients. However, there are many studies that show that if those patients undergoing elective interventional invasive medical or surgical procedures had access to POEGDT, then the resultant reduced post-operative risks of complications, quicker recovery times, better prognoses, fewer times a doctor is required to save a life, lower use of expensive prescriptions and reduced need for intensive care admissions, combined will all lead to dramatic reductions in morbidity and mortality (by 80%) and costs. The key here is that the advantages bestowed by POEGDT are largely dependent upon the technology used. To that end a simple bedside haemodynamic monitoring system that can be operated by junior member of medical or nursing staff, that is, the technology providing reliable haemodynamic results consistently, breaks down one of the major barriers for not instituting fluid resuscitation as a routine practice. The HeartSmart technology, that relies on evidence based clinical trials in patients who are haemodynamically very unstable or undergoing corrective open heart surgery, is perhaps a step in that direction.

Several haemodynamic monitoring technologies are described as being non-invasive, minimally or less invasive; many of these claims are somewhat misleading – such descriptions are only true with respect to the placement of the catheter or probe not entering into the heart or lungs. HeartSmart does require that the medical and nursing staff ensure accurate measurement of relevant data by zeroing catheter lines correctly before data is entered to the HeartSmart program (which can be loaded to any personal computer or laptop). However, these physiological variables are the ones that are routinely recorded in most intensive care units, so the staff will be more familiar with ensuring the accuracy of the data when using a thermodilution catheter.
The vast majority of haemodynamic monitoring systems requires the patient to be anaesthetized and intubated in order to tolerate the catheter and/or probes which are in situ. Intrusive catheterization or induction of probes is not a simple, straightforward everyday tool that the average junior practitioners can readily use. Equally important, such invasive technologies are often ‘operator dependent’ to achieve, for example, the correct waveform shown in Figure 1, which is used to provide a suitable estimate of cardiac output.

It is recognized that invasive, intrusive haemodynamic monitoring systems, have been a barrier to POEGDT, being implemented routinely by clinicians. Worse still, the number of premature death as a consequence of the catheter or probe being wrongly placed by physician or nurse not being sufficiently skilled or able to interpret the haemodynamic values, has greatly compounded the problem. The knock on effect is that the use PACTD method as well as other haemodynamic monitoring technologies are in decline; indeed, anaesthetists and other members of the medical profession have been calling for a less or preferably a non invasive bedside haemodynamic monitor that is simple, reliable, cost effective system with fewer consumables for decades.

The Empirical Formula for Calculating Cardiac Index\(^{12}\).

**HeartSmart Ci expression:**

\[
Q = P \times K \times T / R
\]

\[
Q = P / R
\]

thus

\[
Q = CVP \times K \times T / HR^2
\]

Where \(Q\) = flow (cardiac index/output), \(K\) = empirical constant of energy; the constituent parts are compliance, capacitance with resistance; \(T\) = \(37^\circ C\) core body temperature at time of calculation, \(P\) = pressure (CVP), \(R\) = resistance; \(HR^2\) = beats per minute squared, an empirical surrogate for \(R\).

The \(K\) empirical value per set of values is derived from the grid CVP - HR depicted in Figure 2. The \(K\) values over a wide range of CVP and HR bandwidths in figure 1 has been validated by the University of Sheffield School of Mathematics in 1998 covering all bandwidths of CVP 0 - 30 mmHg and bandwidths of Heart Rates up to 300 beats per minute. In essence the grid in Figure 2 is just another but different representation of the Frank - Starling Law. \(K\) is an empirical value of the capacitance, compliance with viscosity/resistance combining to make the energy force/drive in every contraction or heartbeat, regulating and or optimising cardiac output/index.

Fig. 2 The K Grid over ranges of CVP & HR

**II. METHODS**

This is a double-blind study. This study meets the Helsinki declaration criteria. Having received institutional ethical approval, 60 adult patients gave their written consent and were enrolled into the study.

The criteria for acceptance into the study were: the subjects would require haemodynamic monitoring as part of their routine treatment, written patient consent usually by a relative, provision that the study subject could elect at any time to withdraw consent without detriment to treatment. In special cases 10% of the subjects the ODM2 was used initially and simultaneously with the PACTD, measuring the cardiac index/output against the HeartSmart calculations. We excluded patients with a too low chance of survival.
Table 1. SIRS criteria

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<th>SIRS</th>
<th>Two or more of:</th>
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<tr>
<td></td>
<td>1. Temperature &gt; 38°C or &lt;36°C</td>
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<td></td>
<td>2. Tachycardia &gt; 90 beats/minute</td>
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<td>3. Respiratory rate &gt; 20 breaths/minute or blood</td>
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<td></td>
<td>gas PaCO2 &lt; 4.3 kPa (32mmHg)</td>
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<td>4. White blood cell count &lt; 4000 cells/mm³ or</td>
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<td></td>
<td>&gt; 12000 cells/mm³ (&lt; 4 x 10⁹ or &gt; 12 x 10⁹</td>
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<td>cells/L), or the presence of greater than 10%</td>
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<tr>
<th>Severe sepsis</th>
<th>Sepsis due to evidence of pathological infection</th>
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<tr>
<td>1. Sepsis may</td>
<td>Present throughout a whole range of heart</td>
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<tr>
<td></td>
<td>rates.</td>
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<tr>
<td>2. Sepsis can</td>
<td>Present when temperature is raised or low.</td>
</tr>
<tr>
<td>3. Confirmed</td>
<td>Diagnosis by pathological findings.</td>
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| Septic shock  | Severe sepsis with hypotension (systolic BP < |
|---------------| 90mmHg) despite adequate fluid resuscitation or |
| Pyrexial shock| the requirement for vasopressors/inotropes to    |
| Blood pressure|      maintain blood pressure                     |
|               | Temperature 37.5°C with tachycardia > 120 per minute |

HeartSmart has undergone since 1995 many clinical studies, in which the EPFs have been compared against the PACDT method, and other technologies in eight major academic hospitals. The design of these studies has remained the same except for the size and population of the patient.

All of the subjects enrolled in this study had a diagnosis of SIRS. Each patient had six sets of paired measurements made – that is 360 measurements of the cardiac index (l/min/m²), mean pulmonary artery occlusion (wedge), and mean pulmonary artery pressures in mmHg, a total of 1080 measurements. In 6 patients (10%) 108 paired sets of cardiac indexes were measured by the ODM2, simultaneously.

The Bland–Altman statistical method called ‘Repeatability of Test Methods 95% Limits of Agreement’ was used to analyze the evidence based test data. The Bland–Altman methodology was incorporated into British Standard (BS 5497) in the late 1980s. Essentially, plots are measured, in this case cardiac index and other haemodynamic variables, by the old and new methods to see how closely the mean of the difference of the bias agrees to each other.

III. RESULTS

This study used a well-validated method to compare these two measurement techniques. The 95% limits of agreement analysis assesses how closely two methods of measurement of a variable agree. The means of the differences are an estimate of the average bias of the pulmonary artery catheter thermodilution method and ODM2 relative to that of the continuous cardiac dynamic monitoring method – HeartSmart.

Those subjects where 6 measurements of each haemodynamic variable or parts of were incomplete, or where there were errors recording the results of either a obvious clinical recording, for example a heart rate of 1710, were discarded, leaving 60 complete case studies: 27 female (45%) with an average age of 61.3 years, 33 male subjects (55%) with an average age of 71.75 years old. Each subject was evaluated on admission as being a septic shocked patient; pathology confirmed any pathological organism as the contributing aetiology in 37 cases (61.66%) and there were 9 further cases (15%) that developed pathological organisms within 36 hours of admittance to the intensive care unit.

Our results show a good correlation between the two groups of variables. Data collected as part of the institution taking part the NHS PacMan study, recording the 95% limits of agreement and the mean bias were statistically sufficiently close across the full range of cardiac index and mean artery occlusion pressures observed. This study used that data provided by the institutions researchers. The evidence based results are indicative that HeartSmart is equally comparable to the pulmonary artery catheter thermodilution (PACTD) and Doppler methods calculating cardiac index with other haemodynamic variables.

These results suggest that HeartSmart can provide a reliable estimation of cardiac index or output (with many other haemodynamic variables), that is comparable to the currently accepted ‘gold standard’ of measurement of cardiac output in clinical practice – the thermodilution method and Doppler ODM2. In addition, the HeartSmart software provides estimations for the mean pulmonary artery occlusion (wedge) pressure and mean arterial pressure. HeartSmart produces estimations of the haemodynamic variables provided by the pulmonary artery catheter thermodilution technology and the ODM2.

The results of the haemodynamic values were blinded to the HeartSmart investigator, who was provided with the physiological values of CVP, HR, BP and core body temperature by the institutions researchers, to calculate the results of cardiac index, the mean cardiac power index (CPI) the mean arterial pressure (MAP) the mean pulmonary artery pressure in mmHg (MPAP) the mean pulmonary artery occlusion or ‘wedge’ pressures (MPAOP), the systemic and pulmonary vascular resistances (SVR/PVR, respectively).

The scatter-grams in Figure 2 and Table 2 show that the results of cardiac index comparisons between both methods are not different.

IV. DISCUSSION

This study demonstrated that the continuous cardiac dynamic monitoring with the EPF’s algorithms embedded in CCDM HeartSmart software module, appears to offer an estimation of CI/CO with mean pulmonary artery pressure and mean pulmonary artery occlusion pressures, that are comparable to that measured by the PACTD and ODM2, in a population of septic – shock patients.
Routine implementation of POEGDT is reported to reduce the number of premature deaths, complications arising from major surgery and medical septic – sepsis, cases, with improved prognosis, derived by or through improved clinical excellent care from the healthcare provider. Whereas the PACTD and ODM technologies, including the cost of monitors, anaesthetic and staffing with consumables (a catheter and or probes costing £40 -£120 each in the UK48), compared to the cost of a standard CVP catheter of £12 required by HeartSmart, the cost savings on the equipment alone are very substantial to the healthcare provider41.

V. CONCLUSIONS

In a turbulent world where unheralded emergency medical scenarios unexpectedly occur so quickly, the requirement for resuscitative fluid management with the combined use of inotropes and vasopressors, is a key requirement of survival of the ‘accident and emergency’ A&E patient, at the same time delivering excellent clinical care. With a simple, safer less invasive portable haemodynamic monitor22,30, with the use of the measurement of the right atrial or central venous pressure, HeartSmart might become a useful asset in many situations where hitherto there was no provision for haemodynamic monitoring.

VI. ACKNOWLEDGMENTS AND DECLARATION OF INTEREST

The Author thanks Dr. John Martin Bland (Department of the School of Health Statistics, University of York), for reviewing the statistical data.

Medics Limited paid the institution for providing the patient data in this evidenced based study.

KJW-D is the inventor and developer of HeartSmart technology. He is director of HeartSmart Limited and Medics Limited.

VII. NOTES

‘HeartSmart®’ is a registered trademark™; all rights are acknowledged. HeartSmart empirical physiological formulae© (EPF’s) continuous cardiac dynamic monitoring software (CCDM), patents granted in the USA, New Zealand, and China, other applications are pending in UK, Europe and other countries.

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