Institution: King's College London

Unit of Assessment: UoA5

Title of case study: LiDCO: Minimally invasive measurement of cardiac output and haemodynamics by pulse contour analysis and lithium dilution

1. Summary of the impact (indicative maximum 100 words)

Researchers at King's College London developed an algorithm for a novel method of pulse contour analysis that allows continuous estimation of key haemodynamic parameters from an arterial line (PulseCO). They also invented a novel method for clinical measurement of cardiac output using lithium as an indicator and lithium-sensitive ion selective electrodes (LiDCO). Together, these allow rapid and minimally invasive measurements of haemodynamics and fluid status in high risk patients undergoing surgery or in an intensive care unit, facilitating goal directed therapy and reducing complications and costs. LiDCO and PulseCO form the key underpinning technologies for the clinical monitoring systems produced by LiDCO PLC, an AIM listed company with an international customer base.

2. Underpinning research (indicative maximum 500 words)

Monitoring of cardiovascular status in the high risk patient in an intensive care unit or during and after major surgery facilitates goal-directed therapy that helps minimise complications and maximise a successful outcome. One measure of such status is through analysis of cardiac output – the volume of blood pumped by the heart per minute (5 litres/min for an average size adult) – calculated as the amount of blood per heart beat (the stroke volume) times the number of heart beats in a minute (heart rate). Cardiac output is a determinant of the amount of oxygen delivered from the lungs to the body's tissues. Research led in the Physiology Department and Rayne Institute at King's College London (KCL) by Dr David Band (1964-2001, Reader in Applied Physiology) led to the development of novel, minimally-invasive ways of measuring cardiac output that involve a unique algorithm for analysis and a patented, flow-through, lithium-sensitive ion selective electrode.

Arterial pressure has long been used as a surrogate measure of cardiac output and techniques for deriving stroke volume and cardiac output from such have been used and refined for over a hundred years. However, these can be limited by, for instance, changes in systemic vascular resistance leading to calculation errors. Researchers at KCL developed a novel, non-morphological approach – the PulseCO algorithm – that transforms the arterial waveform from pressure to a stroke volume equivalent through a compliance and aortic volume correction maneuver. Autocorrelation of the volume waveform derives the heart rate and input pulsatile volume change, i.e. stroke volume. With this approach, the power and energy components are conserved within the beat data despite vasoconstriction or dilation; hence changes in waveform morphology and shape do not affect the autocorrelation measurement of stroke volume. To verify the accuracy of PulseCO in determining short-term changes in cardiac output, comparison was made between the ratios of consecutive PulseCO determinations with the ratios of corresponding, consecutive thermodilution cardiac output determinations in nine patients undergoing cardiac surgery. Agreement was found between the two (Linton NW et al., Br J Anaesth, 2001).

Development and refinement of the PulseCO required initial calibration of cardiac output. In high risk patients this is historically carried out by hot (via application of a heat source) or cold (via a bolus of cold glucose) thermodilution and a pulmonary artery catheter. This is, however, an invasive, complex procedure that can increase morbidity and may be compromised in major surgery by alterations in pulmonary artery blood temperature. The solution developed by KCL researchers was a novel indicator dilution method whereby a small bolus (150 mM) of an isotonic solution of lithium chloride (0.15 -0.30 mmol for an average adult) is injected via a vein and the concentration-time curve is generated by an *ex-vivo* lithium ion-selective electrode attached to the peripheral arterial pressure line. KCL research established that lithium can be applied via a peripheral vein, making the procedure minimally invasive, and that as lithium is not normally present in plasma, extremely small doses can be used without exerting pharmacological effects (Linton RA et al. Br J Anaesth, 1993). This system – known as LiDCO (lithium dilution of cardiac output) – was validated at KCL in comparison to thermodilution methods in post-operative, other high risk and paediatric patients. It was found to be at least as accurate as thermodilution but with

the advantages that it was safe and easy to perform, and could utilise existing venous and arterial lines (Linton R et al. Crit Care Med, 1997; Linton RA et al. Intensive Care Med, 2000).

3. References to the research (indicative maximum of six references)

Linton RA, Band DM, Haire KM. A new method of measuring cardiac output in man using lithium dilution. Br J Anaesth 1993;71:262-66 Doi: 10.1093/bja/71.2.262 (84 Scopus citations)

Linton RA, Band DM, O'Brien T, Jonas MM, Leach R. Lithium dilution cardiac output measurement: A comparison with thermodilution. Crit Care Med 1997;25:1796-800. Doi: (101 Scopus citations)

Linton RA, Jonas MM, Tibby SM, Murdoch IA, O'Brien TK, Linton NW, Band DM. Cardiac output measured by lithium dilution and transpulmonary thermodilution in patients in a paediatric intensive care unit. Intensive Care Med. 2000; 26(10):1507-511. Doi: 10.1007/s001340051347 (66 Scopus citations)

Linton NW, Linton RA. Estimation of changes in cardiac output from the arterial blood pressure waveform in the upper limb. Br J Anaesth 2001;86(4):486-96. Doi: 10.1093/bja/86.4.486 (85 Scopus citations)

4. Details of the impact

Research at King's College London (KCL) led to the development and validation of a monitoring system utilising a patented algorithm for continuous measurement of cardiac output and derivation of other haemodynamic variables using arterial pulse pressure contour analysis (PulseCO) and of a minimally invasive method for measuring cardiac output using lithium dilution and disposable lithium ion-sensitive electrodes (LiDCO). The key beneficiaries of this research are patients, healthcare providers and the cardiovascular monitoring industry. The LiDCO/PulseCO system has been independently validated, with studies suggesting that the system is at least as accurate as other means of measuring cardiac output but with the considerable advantages of being minimally invasive, usable in conscious subjects and easy and quick to set-up and interpret.

KCL research is turned into a worldwide commercial product

LiDCO Group PLC (1a) was founded in 1991 by Drs Terry O'Brien, David Band, Robert Linton and Jiri Kratochvil and by KCL. In 2012-2013 LiDCO Group PLC had an annual turnover of £7.21m, with sales predominantly in the UK, USA, EU and Japan (1b). LiDCO's first product – the LiDCO*plus* monitor – utilises the PulseCO algorithm and lithium dilution method developed by KCL researchers to provide a computer-based platform for real-time, continuous display of cardiac output, oxygen delivery and fluid volume. This was launched in 2001 with software updates occurring periodically (now on version 4) and sales continuing (1b,c). Its second product – the LiDCO*rapid* monitor – incorporates the PulseCO algorithm and was launched in 2008 (1d). Its newest product – the LiDCO*rapide*^{v2} with Unity Software monitor – additionally monitors parameters of continuous non-invasive blood pressure and level of consciousness and was launched in 2013 (1e).

The use of KCL research in goal-directed therapy during surgery

Uncorrected fluid shifts and blood loss during surgery may lead to periods of inadequate oxygen delivery and subsequent major organ dysfunction, post-operative morbidity and even mortality. Goal-directed therapy (GDT) to maximize flow-related hemodynamic variables during surgery and post operatively have significantly reduced complications and hospital stay. In the UK around 40,000 patients a year currently undergo surgery with the guidance of hemodynamic and fluid monitoring technologies. Under its latest initiatives, the NHS is seeking to increase this figure to 80,000 patients per year starting in April 2013, with the eventual aim of managing up to 800,000 patients a year (2a). The NHS's Enhanced Recovery Partnership states that it "fully supports the use of intra-operative fluid management technologies to deliver individualised goal-directed fluid therapy" (2b).

The LiDCO*rapid* monitor, which uses the PulseCO algorithm developed by KCL researchers, allows hemodynamic monitoring without the insertion of a catheter into an artery or probe into the oesophagus required by other monitoring systems. Unlike other systems, this monitor also allows

refinement of intervention. For instance, it can show if a fall in blood pressure is due to systemic vascular resistance change or a fall in stroke volume in cardiac output, ruling the difference between giving pharmaceutical or fluid intervention, or not needing intervention at all (1d,e). The PulseCO algorithm uses a patient-specific factor to adjust the aortic capacitance individually for each patient. The factor can be precisely determined by comparing a known cardiac output with the PulseCO estimate. Because the factor does not change for a patient over the short term, it was possible to develop a nomogram using the patient's characteristics (age, height and weight) to estimate it. The nomogram was developed from carefully controlled studies of the PulseCO algorithm with precise determinations of cardiac output using KCL's lithium indicator dilution method (2c). As the PulseCO is the same algorithm used in the earlier developed LiDCO*plus* monitor, data from studies involving the LiDCO*plus* also validated the LiDCO*rapid* monitor, aiding market acceptance (2d).

In February 2013, the NHS Technology Adoption Centre produced an 'Intraoperative Fluid Management Technologies (FMTs) Adoption Pack' commissioned by the Department of Health to help trusts implement such technologies. This pack provides information about the benefits and costs of FMTs and how to implement the technology and measure success. It discusses all of the current technologies including the LiDCO monitors (2e). The utility of Enhanced Recovery Programs (ERPs) which include goal-directed therapy via FMTs have been investigated in a number of trials. One such compared the LiDCO*rapid* system to attain GDT to standard care for 91 patients undergoing open liver resection. They found that ERP reduced the length of stay by 3 days with post-operative complications reduced to 7% versus 27% in the control arm (2f).

The successful uptake of use of LiDCO*rapid* monitors is reflected in the market sales with 228 monitors sold in the UK between January 2012 and July 2013, a rise of 57% from the previous year. In the US in 2012-3 the installed base of LiDCO*rapid* monitors stood at 254 units in 70 hospitals. In the East Asian market, predominantly Japan, there were 232 sales of LiDCO*rapid* monitors since launch in August 2012 (1b, 2g).

Monitoring patients in Intensive Care Units

While LiDCO's first product – the LiDCO*plus* monitor – was initially launched in 2001, it is still making an impact in Intensive Care Units (ICUs) where it is used for high-risk cardiovascular and shock patients for fluid management and stroke volume optimisation. This monitor was developed and refined due to a large number of KCL references, as detailed in LiDCO's reference section on Lithium Dilution (3a). In July 2010 LiDCO received accreditation from the UK Royal College of Nursing for its LiDCO*plus* monitor competency based study day. The course is designed for all critical care nurses, nurse educators, professional development nurses, nurse consultants and junior doctors (3b). Details of how useful the LiDCO*plus* system in the ICU setting has been shown in a number of trials. For instance, in one trial 21 extensively burned patients were randomly allocated for haemodynamic monitoring with LiDCO*plus* or to a control (unmonitored) group. Within the first 24 hours postburn, there was a significantly lower consumption of crystalloids in the LiDCO*plus* group due to improved cumulative fluid balance compared with fluid management based on standard parameters (3c). In a 2011 retrospective study comparing outcomes of 237 shock patients, while mortality rates for patients without hemodynamic monitoring was 37%, it was only 13% mortality rate for those monitored with LiDCO*plus*. This was compared to 20% with invasive central venous catheter monitoring and 32% with invasive pulmonary artery catheter monitoring and 37% in those with no (3d).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. **KCL research is turned into a worldwide commercial product**
   a. LiDCO Group PLC: http://www.LiDCO.com/
   b. LiDCO Group Plc Annual Report and Accounts for the year ended 31 January 2013: http://www.lidco.com/archives/report_accounts-2012.pdf
   c. LiDCOplus brochure: http://www.lidco.com/archives/LiDCOplus_brochure_1914.pdf
   d. LiDCO*rapid* brochure: http://www.lidco.com/archives/LiDCOrapid_brochure_2103.pdf
   e. LiDCO*rapid*^{v2} brochure: http://www.lidco.com/archives/LiDCOrapidv2_brochure_2719.pdf

Note: The references in these brochures do not cite Linton 2001 discussed above, however, the do cite the following paper which acknowledges the Linton paper as the first study of its kind, and also confirms the validity of the PulseCO algorithm: Hamilton TT, et al. PulseCO: a less-invasive method to monitor cardiac output from arterial pressure after cardiac surgery. Ann Thorac Surg 2002;74(4):S1408-12. Doi: 10.1016/S0003-4975(02)04059-6,

2. The use of KCL research in goal-directed therapy during surgery

a. Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg 2011;112(6):1392-402. Doi: 10.1213/ANE.0b013e3181eeaae5
b. NHS Improvement Enhanced Recovery Partnership: http://www.improvement.nhs.uk/enhancedrecovery2/Anaesthetics.aspx
c. LiDCO website. PulseCO - Pressure Waveform Analysis: http://www.lidco.com/clinical/lidco_science/waveform.php
d. LiDCO Group Plc Annual Report and Accounts for the year ended 31 January 2009: http://www.lidco.com/archives/report_accounts-2008.pdf
e. NHS Technology Adoption Centre. Intraoperative Fluid Management Technologies (FMTs) Adoption Pack. February 2013: http://www.ntac.nhs.uk/web/FILES/Intra_Operative_Fluid_Management/IOFM_Adoption_pack_update_Jan_2013.pdf
f. Jones C, Kelliher L, Dickinson M, et al. Randomized clinical trial on enhanced recovery versus standard care following open liver resection. Br J Surg. 2013;100(8):1015-024. Doi: 10.1002/bjs.9165.
g. LiDCO Group Plc Interim Report and Accounts up to July 2013: http://www.lidco.com/archives/Interims2013.pdf

3. Monitoring patients in Intensive Care Units

a. References on LiDCO website: http://www.lidco.com/clinical/lidco_science/lithium_dilution.php
b. Royal College of Nursing accreditation for LiDCO*plus* in LiDCO's 2010 annual report: http://www.lidco.com/archives/report_accounts-2010.pdf
c. Tokarik M, Sjöberg F, Balik M, et al. Fluid Therapy LiDCO Controlled Trial-Optimization of Volume Resuscitation of Extensively Burned Patients through Noninvasive Continuous Real-Time Hemodynamic Monitoring LiDCO. J Burn Care Res. 2013 [Epub ahead of print] doi: 10.1097/BCR.0b013e318278197e
d. Hata J, Stotts C, Shelsky C, et al. Reduced mortality with noninvasive hemodynamic monitoring of shock. J Crit Care 2011;26(2):224.e1-8. Doi: 10.1016/j.jcrc.2010.07.001