Goal Directed Fluid Therapy in Colorectal Surgery:

Strategies for the Low Risk Patient

Volume One of One

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Abstract

Morbidity and mortality following major surgery has considerable variation both nationally and globally, and hence considerable research has been focused on how post operative outcomes can be improved. In order to achieve improvement it is essential to be able to stratify a patient's risk, and hence direct appropriate therapy and interventions to those who will benefit.

Fluid therapy is used peri-operatively to expand the circulating volume to optimise cardiac output, and hence increasing oxygen delivery to tissues, allowing the patient to meet the metabolic demands of surgery. There has been considerable debate on the optimal fluid regime for major surgery. Goal directed fluid therapy utilises cardiac output monitoring to optimise haemodynamic status on an individualised basis. Various protocols have shown improved post-operative outcomes, and new non-invasive technologies are emerging which will allow uptake of targeted fluid therapy to be extended within the surgical population.

The oesophageal Doppler is an established technology used to target fluid therapy, and various studies have shown reduced morbidity when it is used in patients undergoing major abdominal surgery. Plethysmograph variability index (PVI) is a non-invasive technology, which evaluates variations in the plethysmographic waveform with the respiratory cycle indicating fluid responsiveness. However, currently there are no published outcome studies of its use for intra-operative goal directed fluid therapy.

The aim of this thesis is to examine the use of PVI in low-risk colorectal surgery patients, primarily investigating if similar volumes of fluids are administered when goal directed therapy is targeted using PVI or oesophageal Doppler. Fluid balance, post-operative morbidity and length of hospital stay are also compared to evaluate if PVI can be used as an alternative target for intra-operative goal-directed fluid therapy in this patient group.

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Author's Declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the Internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

1 INTRODUCTION AND BACKGROUND

There is much debate regarding the optimal fluid regime for patients undergoing major abdominal surgery. Over the past two decades studies have investigated numerous strategies to improve outcomes following surgery, ranging from liberal replacement of third space losses to strict maintenance of a zero balance. Goal directed therapy has emerged as a method of individualising intra-operative therapy based on haemodynamic values.

In this chapter I will examine global data on surgical outcomes and how these outcomes can be improved by identification of patients' risk status, leading to appropriate optimisation of haemodynamic status through fluid management.

1.1 Surgical morbidity and mortality

In order investigate how things can be improved it is important to first understand the scope of the issue, prior to reviewing published literature on intra-operative fluid management I will first examine surgical morbidity and mortality globally and in the United Kingdom in order to explore possible reasons for disparity in outcomes.

1.1.1 Global Surgical Outcomes

Mortality

It is estimated that there are between 187.2 million to 281.2 million surgical procedures carried out per year (1), meaning that there is approximately 1 surgical procedure performed for every 25 people worldwide. As the majority of surgery occurs in developed countries this would mean that this proportion is higher in a country such as the UK. An overall mortality rate of approximately 0.5% (1) has been conservatively estimated for surgery as a whole in the developed world, which equates to approximately 1 million deaths per year from surgical complications, a proportion of which can be assumed to be avoidable.

The European Surgical Outcomes Study (EuSOS) (2) examined postoperative mortality following non-cardiac surgery in 46 539 patients operated on over 7 days across 28 countries in Europe. The in-hospital mortality in this cohort was 4.0% for patients undergoing elective surgery. However, this is likely an underestimate of post-operative mortality for various reasons, firstly that urgent and emergency cases, which have higher mortality rates were excluded, and secondly post operative outcomes were limited to a 30 day follow up. Analysis of data from the Veterans Affairs National Surgical Quality Improvement Program (NSQIP) by Visser *and colleagues*(3) showed mortality in patients undergoing emergency or elective colectomy rose from 4.3% at 30 days to 9.1% at 90 days, hence the relatively short term follow up in the EuSOS investigation may mask significantly worse short to medium term outcomes.

Analysis of the EuSOS study by participating country (2) showed an in-hospital mortality rate of 3.6% for patients operated on in the United Kingdom, and variation in outcomes between the different participant countries (Table 1). There was a trend to higher mortality in the United Kingdom compared to other western and northern European countries such as Germany, France and Sweden, but no significant differences in adjusted mortality rates were found.

Country	Total no. of patients	Median length of Stay (IQR)	No. died in hospital (%)	Adjusted mortality OR* (CI)
United Kingdom	10630	2.0 (1.0-6.0)	378 (3.6)	1.0
Iceland	162	2.0 (1.0-4.0)	2 (1.2)	0.47 (0.07 – 3.41)
Estonia	727	3.0 (1.0-6.0)	11 (1.5)	0.60 (0.16 – 2.28)
Sweden	1314	2.0 (1.0-6.0)	24 (1.8)	0.58 (0.23 – 1.49)
Switzerland	1019	4.0 (2.0-8.0)	20 (2.0)	0.86 (0.25-2.97)
Germany	5284	4.0 (2.0-9.0)	133 (2.5)	0.85 (0.50-1.43)
France	2278	3.0 (1.0-6.0)	73 (3.2)	1.36 (0.72 – 2.56)
Ireland	856	3.0 (1.0-6.0)	55 (6.4)	2.61 (1.30 – 5.27)
Poland	297	5.0 (2.0-7.5)	71 (17.9)	6.92 (2.37 – 22.04)
Latvia	302	4.0 (2.0-8.0)	65 (21.5)	4.98 (1.22 – 20.29)
* Referenced against UK and adjusted for age, ASA grade, urgency, grade of surgery (minor, intermediate or major), specialty and co-morbid metastatic or liver disease				

Table 1 In-hospital mortality by country, adapted from the European Surgical Outcomes Study (2)

Similarly mortality outcomes from the UK compare poorly with those from the USA. Mortality adjusted for P-POSSUM variables in a study of 2 595 patients by Bennett-

Guerrero and colleagues(4) showed an in-hospital mortality rate to be four times higher in patients having surgery in the UK compared to the USA (OR 4.50 95% CI 2.81-7.19) across all risk groups. This difference in outcomes is likely to be multifactorial, two possible contributing factors are reduced health care spending and the relative lack of critical care beds in the UK compared to the US.

Variation in mortality between the United Kingdom and other European countries is also likely to be multifactorial with varying rates of co-morbidities and differing timing of surgery, but differences in financial provision for health care between countries and the availability of critical care beds is likely to be a key contributor. The United Kingdom has a significantly lower number of critical care beds corrected for population size in public sector health care compared to other countries such as Germany and France (5), alongside lower health care spending per capita (6).

Country	**Data from EuSOS study(2)**		**Number of critical care beds/100 000 population (5)**
	No. died in hospital (%)	**Adjusted mortality OR**	
United Kingdom	378 (3.6)	1.0	6.6
Estonia	11 (1.5)	0.60	14.6
Sweden	24 (1.8)	0.58	5.8
Switzerland	20 (2.0)	0.86	11.0
Germany	133 (2.5)	0.85	29.2
France	73 (3.2)	1.36	11.6

Table 2 In-hospital mortality figures related to population distribution of critical care beds

There is a strong degree of negative correlation (R=-0.82) between availability of intensive care beds per 100 000 population and ICU mortality (6), countries with high provision of critical care beds appear to have lower surgical mortality rates (Table 2). A relative lack of critical care beds means that only the sickness patients are admitted to these areas (who actually may be less likely to benefit) at the expense of patients who may have more treatable conditions, or indeed elective surgical patients who need post-operative surveillance. In addition there may be increased pressure for early discharge of patients from this environment due to bed pressures, particularly at night which is known to have a significant effect on mortality (OR 1.46, 95%CI 1.18-1.80) (7).

Jhanji and colleagues(8) looked at post-operative patients in a single UK trust over a 3 years period. Patients were classified as 'high risk' if they underwent a procedure with an expected mortality rate of greater than5%. Of these high risk patients only 35.3% of patients were admitted to a critical care unit at any point during their post-operative course, whilst over half of high risk patients who died were never admitted to a critical care unit at all. Amongst this cohort mortality rates were similar between those admitted to the critical care unit following surgery (5.3%) and those who were cared for on the ward (4.8%). However, premature discharge from ICU and unplanned admission to ICU from the ward were associated with high mortality rates (mortality rates 33.3% and 85.7% respectively). Amongst lower risk patients unplanned critical care admission was again associated with a higher mortality rate compared to a planned admission directly from theatre (21.2% v 0.94%). This data

suggests that even in a high-risk group a spectrum of risk exists, and that current methods of pre-operative risk stratification are not delineating between those that do well after surgery and those that do poorly. It is important both to identify the true high-risk group so that they can receive appropriate interventions and post operative care, but also to identify the low risk individual to avoid iatrogenic harm from these interventions, allowing these individuals need to be safely triaged to ward care following major surgery in order to achieve good post-operative outcomes for both groups.

Morbidity

Major abdominal surgery is not only associated with mortality, but also post operative complications, even in those at low risk of mortality post operative complications rates remain significant. Data from NSQIP has shown post-operative complications occur in between 24.6 to 26.9% of patients, with major complications occurring in 16.2 to 18.2% of patients(9).

Data from 84730 high risk general surgical and vascular patients from 186 centres in the American College of Surgeons National Surgical Quality Improvement Program shows a similar picture of post operative morbidity, but also highlights an interesting observation (9). Hospitals were ranked according to risk-adjusted mortality and divided them into 5 groups. Mortality following surgery varied from 3.5% (in the lowest mortality quintile) to 6.9% (in the highest). The incidence of complications was similar across all quintiles of hospitals at around 25%, however, the rate of

mortality following a major complication varied significantly. Mortality rates were 12.5% in the best performing hospitals compared with 21.4% in the worst performing. Therefore this study suggests that variation in mortality rates may not be related to the incidence of complications, but rather with the post operative management of these complications once they have occurred. This highlights the importance of effectively risk stratifying patients so that those at greatest risk of complications can be placed in the appropriate post operative environment so that identification and intervention can take place in a timely fashion, and also so that the low risk patients can be triage safely to a lower level of care.

Prevention of complications however, should still be the priority in order to effectively minimise both short term and long-term mortality, as post-operative complications appear to have a long term impact on health. Khuri *and colleagues*(10) who also used data from NSQIP, showed that the presence of a post-operative complication following major surgery in patients increased the risk of long-term mortality when compared to patients who do not experience complications. Using data from major surgical procedures between 1991 and 1999 this study showed that any patient who experienced a complication in the first 30 post-operative days had a 30 day mortality of 13.3% compared to 0.8% in those who did not encounter any complications. This difference was also seen in terms of an increase in long term mortality at 1 and 5 years respectively following surgery. Analysis of independent pre, intra and post-operative predictors of 30- day mortality showed, not unsurprisingly, that post-operative complications were strong predictors of short term outcome (Table 3), however the presence or absence of a

single complication within the first 30 days was one of the most important predictive variables of long-term survival (independent of survival in the first 30 days post-operatively) and was more predictive than any pre-operative variable. The long-term persistence of inflammatory cytokines following complications could contribute independently to post-30 day mortality.

30 day mortality		**Long-term mortality**	
Variable	**Odds Ratio (95% CI)**	**Variable**	**Hazard Ratio (95% CI)**
Cardiac Arrest	125.0 (106.3-147.3)	**Cardiac Arrest**	7.3(6.9-7.8)
Systemic Sepsis	3.6 (3.0-4.3)	**Disseminated cancer**	2.4 (2.3-2.5)
Disseminated Cancer	2.9 (2.4-3.5)	**BUN (>40mg/dL)**	1.4 (1.3-1.4)
Failure to wean	1.5 (1.3-1.8)	**ASA class**	1.4 (1.3-1.4)
Post-operative CVA	6.7 (5.1-8.7)	**Failure to wean**	1.3 (1.2-1.4)
Myocardial infarction	4.7 (3.7 -5.9)	**Smoking status**	1.3 (1.2-1.3)
Emergency Surgery	1.7 (1.5-2.0)	**History of COPD**	1.29 (1.26-1.33)
Renal Failure	4.8 (3.7-6.1)	**Functional status**	1.1 (1.1-1.2)
Serum Albumin	0.7 (0.6-0.7)	**Age**	1.035 (1.034-1.036)
ASA class	1.7 (1.6-1.9)	**Serum Albumin**	0.8 (0.8-0.9)

Table 3 Relative importance of top 10 predictors of 30 day and long-term mortality adapted from Khuri and colleagues (10)

Therefore interventions are required both to prevent the development of complications and to facilitate the early recognition and management of surgical morbidity, in order to reduce the risk of mortality both in the long and short term.

1.1.2. Outcomes following major colorectal surgery

With just under 30 000 patients being diagnosed with colorectal cancer per year in the United Kingdom there are significant public health implications from this disease. Data from the 2013 National Bowel Cancer Audit Report (11) shows that between April 2011 and March 2012 there were 17250 major resections in patients with colonic or rectal tumours. The majority of these patients were ASA grade 1 or 2 (64.9%) without nodal or metastatic spread of disease, in whom it is not unreasonable to assume were considered low risk for surgery in terms of mortality

Data from 19 895 colectomies between 1991 and 1999 in the NSQIP analysed by Khuri and colleagues (10) however, showed a 6.51% 30-day mortality colectomy, significantly higher than the mortality for elective repair of abdominal aortic aneurysms, infrainguinal vascular surgery and lung resection. This may reflect the patient population operated on, however, factors such as lack of recognition of importance of intra-operative optimisation and targeting patients likely to benefit from post-operative critical care in this patient group when compared to the more high surgical risk vascular and thoracic patients may have played a part. Specifically looking at elective colorectal surgery NSQIP data from 2005 to 2007 has shown a mortality rate of 1.9%, which may represent the inherently lower risk of purely elective surgery, the selective nature of surgery for the elective population, and improvements in surgical technique over time (12).

Data from then the National Bowel Cancer Audit (11) showed 58.6% of UK patients diagnosed with colorectal cancer underwent major resections between 2011 and 2012. Outcome data revealed an overall mortality of 2.9% and 4.5% at 30 and 90 days respectively days. This has decreased year on year since the introduction of the audit in 2008 (Table 4), reflecting improvements in both intra and post-operative care during this time period. Current mortality rates are similar to those following colorectal resections from other developed countries such as France (2.9%, 30 day mortality) (13) and the USA (1.9%, 30 day mortality) (12).

Year	**2008-9**	**2009-10**	**2010-11**	**2011-12**
30 day mortality (%)	4.0	3.9	3.4	2.9
90 day mortality (%)	6.1	5.8	5.3	4.5

Table 4 Mortality in UK patients undergoing major colorectal resections. Adapted from National Bowel Cancer Audit Report 2013 (11)

Further to mortality, morbidity following colorectal surgery can be significant and should have consideration paid when assessing post-operative outcomes Analysis of NSQIP data from elective colorectal patients by Ingraham *and colleagues*(12) showed a 23.9% incidence of complications, with the most frequently occurring being infective complications such as superficial surgical site infections, pneumonias, urinary tract infections or sepsis. As with mortality, morbidity varies between countries, a French study by Alves revealed a post-operative complication rate of 35% in patients undergoing colorectal surgery. Examining data from colorectal trials from the United Kingdom, there was a 32% overall post-operative

complication rate in the MRC CLASICC Trial at 30 days with no significant difference between patients undergoing laparoscopic or open surgery: seven percent of patients had on-going complications at 3 months, most commonly intestinal obstruction or persistent wound infections. In comparison controls receiving standard care within a study by Wakeling and colleagues experienced a complication rate of 59.3%. The complexities of interpreting and comparing data related to morbidity discussed are in sub-chapter 1.4.2. However, the extent of complications is illustrated within a study of colorectal surgical patients by Noblett and Colleagues (14) where 8% of patients receiving standard care required admission to intensive or high dependency care due to a life threatening complication.

In Ingraham and colleagues'(12) analysis of post-operative complications the top three predictors of development of complications were functional capacity, pre-operative anaemia requiring transfusion and ASA grade. Multivariate analysis of complications in a prospective multi-centre study of colorectal patients showed that risk of morbidity was increased in the presence of age over 70 years, neurological or cardiorespiratory co-morbidities, hypoalbuminaemia, operation duration greater than 120 minutes and peritoneal contamination (13).

Other measures of surgical outcome having impact on health services include length of stay and readmission. Median hospital length of stay was 7[IQR 5-12] for colonic resections and 8 [IQR 6-14] for rectal procedures within the 2012 National Bowel Cancer Audit (15) . Data from the 2012 audit showed that unplanned readmissions within 90 days were more likely in patients who had undergone a rectal resection

(15.2% compared to 13.8% in colonic resections). Readmissions were also more likely in patients under 65 years (16.7%) compared to those 65 to 74 years old (14.6%), 75-84 years old (12.1%) or over 85 years old (9.9%) with returns to theatre less likely in the over 80s.

The significant impact of developing post-operative complications on mortality and the relative lack of Critical Care resources in the United Kingdom means that identification of patients most likely to benefit from available resources is crucial, conversely the correct patients need to be identified as low risk in order that they can be safely streamed towards appropriate intra-operative and post-operative care. This can be achieved by both risk stratification of surgical procedures and patients pre-operatively.

1.2 Risk stratification and identification of patients at low risk of complications

Risk can be assessed by either categorising patients according to epidemiological and co-morbid factors or by quantitative assessment using investigative tests. Epidemiological and co-morbid factors are integrated into commonly used scoring systems that can be applied in the pre-operative setting. This allows the identification of a patient's risk of post-operative morbidity and mortality, allowing targeting of appropriate resources to improve both intra-operative and post-operative management. Identification of low risk patients is equally as important as identifying those at high-risk in order to avoid exposure to potentially harmful interventions and inappropriate use of scarce resources through unnecessary admissions to critical care.

1.2.1 Generic pre-operative assessment

Pre-operative assessment of patients at an outpatient clinic should be used to minimise risk to patients and identify high-risk patients according to the 2010 Safety Guideline (16) published by the Association of Anaesthetists of Great Britain and Ireland (AAGBI). At the time of the 2011 NCEPOD report entitled "Knowing the risk"(17), 84% of hospitals in the United Kingdom provided pre-admission anaesthetic assessment clinics. The AAGBI guidelines advise that a senior anaesthetist should see patients "*who are potentially at high-risk"* of mortality and morbidity and suggests nine markers that can be used to identify patients at high-

risk including: age, sex, socioeconomic status, aerobic fitness, diagnosed ischaemic heart disease, heart failure, ischaemic brain disease, kidney failure and peripheral artery disease. However, the lack of these factors in a patient's past medical history does not necessarily confer low risk status on a patient, and in addition the presence of certain co-morbidities historically associated with risk has recently been shown to be false(18). The presence of anaesthetist led pre-assessment allows further investigation of risk such as through objective measure of functional capacity such as cardiopulmonary exercise testing. Worryingly 21.8% of patients considered at high risk were not seen in a pre-operative assessment clinic according to the 2011 NCEPOD report (17).

Whilst pre assessment clinics appear to be a sensible approach to managing patients the question remains do they adequately assess patients' risk status and improve outcomes? An Investigation of elderly patients considered fit for surgery by anaesthetists showed that over 20% had severe cardiopulmonary disease found on invasive physiological assessment making them unfit for the planned surgery (19).

Wijeysundera and colleagues (20) retrospectively examined the impact of consultation with an anaesthetist prior to surgery on post operative outcomes. Using data gathered from billing information (for pre-operative anaesthetic consultations between 1994 to 2003) in the Canadian Institute for Health Information database, they compared outcome data of matched patients who had received a pre-operative consultation (n=104 716) before major surgery with those who had not (n=180 254). Patients who received a consultation had a statistically

significant, but clinically irrelevant reduced mean length of hospital stay (8.17 days v 8.52 days, P<0.001) but there was no difference in 30 day (RR 1.04 95% CI 0.96-1.13) or 1 year (RR0.98 95% CI 0.95-1.02) post-operative mortality. Whilst reduced length of stay would potentially allow for improved healthcare costs, this was offset by the finding that anaesthetic consultation lead to an increase in pre-operative testing, including echocardiography, angiograms, non-invasive myocardial stress testing and pulmonary function testing, compared to the matched cohort who did not receive a pre-operative consultation.

Pre-operative assessment fails to adequately identify risk unless further tools are used in order to stratify patients, therefore stratification tools and investigations need to be used in order to reliably identify patients at low risk of post operative morbidity and mortality and who will manage will with minimally invasive intra-operative strategies.

1.2.2 Epidemiological Factors

There has been a long tradition in anaesthesia of attempting to risk stratify surgical patients using epidemiological factors such as age and co-morbidities.

Age

Over 70% of colorectal cancers in the UK are diagnosed in patients aged 65 years and over (21). With an aging population the impact of age on surgical outcome is crucial

in both assessing an individual patient's peri-operative risk and in planning allocation of health care resources for the future.

A retrospective study of 33 238 Canadian Colorectal patients over the age of 50 undergoing surgery for cancer (22) looked at the effect of increasing age on surgical outcomes. Following univariate analysis, rates of death in hospital, length of stay and readmission within 30 days were all shown to climb with increasing age (Table 5), as did the chance of not being discharged home and need for home care.

Age (years)	**50-64**	**65-74**	**75-79**	**80+**
Death in hospital (%)	1.7	3.2	5.2	10.4
Mean length of stay (days) [SD]	10.2 [8.3]	11.8 [10.4]	13.8 [13.3]	16.9 [15.6]
Readmission within 30 days (%)	11.1	13.0	14.9	18.2

Table 5 Effect of age on in-hospital mortality, hospital length of stay and readmissions adapted from Devon and colleagues (22)

This effect is supported by evidence from a large retrospective study by Massaweh and colleagues (23). Patients undergoing all types of intra-abdominal surgery, except pancreatectomy, had an increased risk of death with advancing age. Adjusted odds of death at 90 days rose progressively with age; patients aged over 90 years old had odds of death of 4.1 (95% CI 3.6-4.7) compared to the reference category of patients aged 60-65 years of age. There was a 1% increase in the incidence of post-operative complications (OR 1.01 95% CI 1.01-1.02) and a 6%

increase in odds of mortality (OR 1.06 95% CI 1.05-1.06) if a patient was compared with a matched patient one year younger.

The increase in mortality with age has been shown to be independent of the presence of co-morbidities in a prospective cohort study by Hamel and colleagues *(24)*which looked at 26 648 patients aged 80 and over enrolled in the Veterans Affairs NSQIP who underwent major non-cardiac surgery. After adjustment for comorbidities and characteristics of surgery the adjusted odds ratio for mortality was 1.05 for each additional year above 80. This is a cumulative risk with each added year conferring further risk, therefore a 90 year old will be at 50% greater risk of mortality at 30 days compared to an 80 year old undergoing the same surgery, suffering from the same co-morbidities.

However, there are limitations to using age as an absolute indicator of high risk. Del Guercio and colleagues(19) showed that elderly patients do not form a uniform group when it comes to post-operative outcome. In a study of 148 patients aged over 65 years of age (mean age 68 years) they identified that variations in physiology existed between patients associated with making them at higher and lower risk for having major surgery with significant differences in mortality depending on severity of cardiorespiratory dysfunction identified on pulmonary artery catheterisation. Of this group approximately 15% had normal values and no peri-operative mortality was recorded, but over 20% of patients who were cleared as fit for surgery had such severe cardiorespiratory disease that post operative mortality was 100%.

It is not chronological age that is predictive of outcome but the presence of impaired cardiovascular function which may or may not be present with ageing, hence using age as a sole indicator of risk is not helpful.

Co-morbidities

Surgical patients, particularly the elderly, commonly have multiple co-morbidities that include amongst others hypertension, ischaemic heart disease, heart failure, chronic obstructive pulmonary disease (COPD) and diabetes mellitus.

The importance of co-morbidities and their impact on peri-operative outcomes is reflected by their inclusion in most scoring systems that attempt to predict post-operative outcomes. The cumulative number and severity of co-morbidities present has been shown to be an independent variable in predicting postoperative mortality(25) (26), therefore it is important to take them into account when assessing a patient prior to surgery.

Retrospective data from the Netherlands (26) shows the impact of co-morbidity on mortality following oesophageal cancer resections. The presence of a single co-morbidity increased mortality from 3.6% to 8.6%, with mortality rates being highest in those with 2 or more co-morbidities at 11.2% ($p=0.015$). With regards to colorectal surgery, the presence of cardiorespiratory co-morbidity was shown to increase the risk of developing post-operative morbidity (RR 1.50) in a study of French patients (13).

Ischaemic heart disease has commonly be associated with increased peri-operative risk, hence its inclusion in many scoring systems. However, this may no longer be an accurate reflection of the impact of this disease state. Hernandez and colleagues (18) showed that it is heart failure that significantly increases post-operative mortality, whilst ischaemic heart disease had no effect on post-operative outcome. This observation is important as heart failure may be present in almost one fifth of elderly patients undergoing major non-cardiac surgery(27). In this study 1532 patients with previously diagnosed heart failure undergoing surgery were compared with 1757 patients with ischaemic heart disease and 44512 controls who had neither co-morbidity. Risk adjusted 30 day operative mortality was significantly higher in the heart failure cohort compared to patients with ischaemic heart disease (11.7% v 6.6% p= 0.001) and there was no significant difference in mortality between the ischaemic heart disease patients and control group (6.6 v 6.2% p= 0.518). In addition there was no difference in mortality when the presence of heart disease was included into those with a diagnosis of heart failure further suggesting that ischaemic heart disease has limited impact on peri-operative outcomes. In addition to increased risk of peri-operative death, heart failure patients had increased critical care usage and hospital length of stay, and readmission rates were almost double in heart failure patients compared to controls (20.0% v 11.0% P<0.001). The only outcome difference in patients with ischaemic heart disease compared to controls was in readmission rates (14.2% v 11.0% p<0.001). This data suggests that patients with a history of ischaemic heart disease who have been adequately treated do not have increased post-operative risk and therefore it should not be automatically

stratified into a high- risk group. It is those who develop cardiac dysfunction and decompensation who have the highest risk of poor post-operative outcome.

This observation is further strengthened in a cohort of over 10 000 patients undergoing colorectal cancer resections (27). Mortality within 30 days of procedure was shown to be significantly higher in patients with heart failure compared to those with ischaemic heart disease or controls who had neither (18% v 13.2% v 10.5, $p<0.001$). This effect was not limited to colorectal resections but seen across all types of non-cardiac surgery examined in this study, ranging from laparoscopic cholecystectomies to major vascular surgery, with patients with heart failure having an overall adjusted hazard ratio of mortality of 1.63 (95% CI 1.52-1.74) compared to controls or 1.51 (95%CI 1.41- 1.61) compared to patients with ischaemic heart disease. No further risk was conferred by ischaemic heart disease in the presence of heart failure with no significant difference in adjusted hazard ratio for mortality between heart failure patients with or without ischaemic heart disease (1.60 v 1.74 $p=0.11$).

Extremes of body mass index are encountered in patients undergoing colorectal surgery. Weight loss may result from the malignant processes that results in the patient presenting for surgery but also increasingly likely is obesity, which is an increasingly prevalent issue in the developed world. Many patients presenting for surgery are obese of varying magnitudes. Morbid obesity is associated with the development of co morbidities which include hypertension, ischaemic heart disease and diabetes mellitus and these may result in reduced life-expectancy (28). Counter-

intuitively however, mild obesity may be protective with regards to peri-operative outcomes in what is referred to as the 'obesity paradox'. The risk of post-operative mortality is reduced in overweight and mildly obese patients whilst it is increased in those that are underweight.

Retrospective data from NSQIP (29) on intra-abdominal cancer surgery (oesophagectomy, gastrectomy, hepatectomy, pancreatectomy, low anterior resection and proctectomy) revealed that underweight patients (BMI ≤18.5) were at the highest risk of 30 day mortality when compared with patients of normal or high BMI (Table 6).

Class	**BMI (kg/m^2)**	**Odds Ratios (95% CI)**	
		Morbidity	**Mortality**
Underweight	≤18.5	0.941 (0.47-1.85)	5.24 (1.70-16.2)
Normal weight	18.6 - 25.0	1.0	1.0
Overweight	25.1 - 30.0	1.22 (0.97-1.54)	1.06 (0.52-2.19)
Obese I	31.5 - 35.0	1.42 (1.06-1.90)	0.61 (0.17- 2.15)
Obese II	35.1 - 40	1.50 (0.99-2.26)	0.45 (0.06 – 3.75)
Obese III	>40	1.53 (0.91 – 2.57)	1.67 (0.33 – 8.6)

Table 6 Variation in mortality and morbidity according to BMI class adapted from Mullen and colleagues (29)

In a larger prospective cohort study (30) of 118707 general surgical patients undergoing non-bariatric surgical procedures underweight patients again had the highest mortality risk with an odds ratio of 1.35 (95% CI 1.07-1.70). However, overweight patients (BMI 25.1 – 30.0 kg/m^2) were found to have a lower mortality

risk than patients of normal weight (OR 0.85, 95%CI 0.74-0.99). This 'paradox' has also been shown in a further study by Glance and colleagues (31) of over 310 208 patients undergoing general, orthopaedic and vascular surgery where overweight (BMI 25-29.9 kg/m^2) or obese (BMI 30-30.9 kg/m^2) patients were noted to have reduced risk of 30 day mortality compared to normal weight patients (adjusted OR overweight 0.85, 95% CI 0.78-0.92, OR obese 0.90 (0.81 -1.00). There was no significant increase in 30 day mortality in morbid or super-morbid obesity except in patients with BMI ≥ 50 in the presence of metabolic syndrome who were almost twice as likely to die (adjusted OR 1.99, 95%CI 1.41-2.80).

With increasing body mass index there has been shown to be a significant increased risk of morbidity (Table 6 and 7), however, this is largely related to an increase in wound infection rates (29, 30), which may be why it is not reflected in increased mortality.

Body Mass Index (kg/m^2)	**Morbidity** **Adjusted OR (95% CI)**
≤18.5	1.07 (0.96 – 1.20)
18.6 – 25.0	1
25.1 – 30.0	1.12 (1.06 – 1.18)
30.1 – 35.0	1.25 (1.17 – 1.33)
35.1 – 40.0	1.40 (1.29 – 1.51)
>40.0	1.55 (1.42 – 1.68)

Table 7 Variation in morbidity according to BMI class adapted from Mullen and colleagues (30)

Whilst co-morbidity impacts on post-operative outcome, research over the past few decades has shown that traditionally held thoughts regarding the impact of co-morbidity may be flawed, therefore stratification based on co-morbidity needs to be carefully applied, with attention needing to be paid to factors such as heart failure and low body weight. Further, the impact of optimally treated co-morbidities is difficult to gauge. Finally patients are commonly like to present with multiple co-morbidities, risk stratification based on history alone may be difficult due to the interaction between co-morbidities.

1.2.3 Scoring Systems

Observation and investigation of the impact of co-morbidity on post-operative outcome has led to the development of scoring systems taking these variables into account and their use in anaesthetic practice. Some scoring systems are predictive of general risk (ASA, Charlson), whilst others may be organ specific in predicting for complications (LRCRI) or specific to the type of surgery (CR-POSSUM).

General Scoring Systems

The American Association of Anaesthesiologists classification of physical status is one of the commonest used scoring systems in peri-operative medicine. It was developed in 1941(32) and further modified in 1962(33). Derived initially as a standardised method to collect and tabulate statistical data in anaesthesia; a five

class system (Table 8) classifies a patient's pre-operative physical status, and has been shown to be a predictor of peri-operative morbidity and mortality (34) (35)

ASA Grade	Classification	Mortality (%)
I	A normal healthy patient	0.1
II	A patient with mild systemic disease	0.7
III	A patient with a severe systemic disease that limits activity but is not incapacitating	3.5
IV	A patient with an incapacitating systemic disease that is a constant threat to life	18.3
V	A moribund patient not expected to survive 24 hours with or without operation	
For emergency operations the number should be preceded by an E		

Table 8 ASA classification and associated mortality rates adapted from New Classification of Physical Status(33) and Wolters and colleagues(35)

A study of 6301 surgical patients by Wolters and colleagues(35) compared post-operative complication rates between ASA grades and showed an increased incidence of pulmonary, cardiac, wound complications with increasing ASA grade, and a 5 to 7 fold stepwise increase in in-hospital mortality (Table 8).

However, a significant drawback of the ASA grading system is inter-observer variation on assigning ASA grades. Haynes and colleague (36) examined responses by 97 anaesthetists from Northern England who were asked to assign grades to 10 hypothetical patients. In none of the cases was there complete agreement on a

grade. Whilst in each case there was a majority viewpoint the responses to each case varied between two and five different grades. Further weakness arises from the omission of adjustment for surgical procedure related factors and the omission of grading for age and weight. Whilst there is gradation within the scale for the severity of co-morbidity of disease in terms of impact on physical capacity, the categories are broad and there is a vast difference between the extent of a co-morbidity that "*is not incapacitating*' and one that is a '*constant threat to life*'.

The Charlson "Weighted Index of Co-morbidity (Table 9) (37) is a weighted index which takes into account the number and seriousness of various co-morbidities in an attempt to predict post operative mortality. It was derived from a cohort of 559 medical patients who were followed up over one year, and was shown to be a significant predictor of survival. This index was then further validated in cohort of 685 breast cancer patients followed up over a 10 years period, which also showed that over this longer time period, age was also a significant predictor of death with each decade of age adding a similar risk to an increase of 1 in the comorbidity index, hence its incorporation into the score.

A further study of 218 elective general surgical patients (25) followed up for between 3 to 5 years post-operatively showed that relative risk of death for each co-morbidity rank was 1.46 (99% CI 1.22-1.74). This is supported by multivariate analysis of patients undergoing colorectal cancer surgery (38) showing an increased odds of death with an increasing Charlson score. Odds of mortality was more than

four times greater (OR 4.51 [95%CI 4.06-5.01]) in patients with a Charlson score of greater than 3 compared to those with a Charlson score of zero.

Assigned Weights for disease	**Condition**
1	Myocardial Infarction
	Congestive cardiac failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic Pulmonary Disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumour
	Leukaemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic Solid Tumour
	AIDS

Table 9 Charlson Weighted index of Co-morbidity (37)

The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) was originally developed to compare risk-adjusted outcomes between different surgeons and institutions (39), and consists of preoperative physiological (Table 10.1) and operative variables (Table 10.2) which when combined estimate the risk of post operative mortality and morbidity.

	Physiological Score			
	1	**2**	**3**	**4**
Age	≤60	61-70	≥71	
Cardiac Signs	No failure	On diuretic, digoxin, antianginal, anti - hypertensive therapy	Peripheral oedema, on warfarin therapy	Raised jugular venous pressure
Chest radiograph			Borderline Cardiomegaly	Cardiomegaly
Respiratory History	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea	Dyspnoea at rest (rate ≥30)
Chest radiograph		Mild evidence of COPD	Moderate evidence of COPD	Fibrosis or consolidation present
Systolic Blood Pressure (mmHg)	110-130	131-170 100-109	≥171 90-99	≤89
Pulse (beats/min)	50-80	81-100 40-49	101-120	≥121 ≤39
Glasgow Coma Score	15	12-14	9-11	≤8
Haemoglobin (g/100ml)	13-16	11.5-12,9 16.1- 17.0	10.0 – 11.4 17.1 – 18.0	≤9.9 ≥18.1
White cell count (x 10^{12}/1)	4-10	10.1-20.0 3.1-4.0	≥20.1 ≤3.0	
Urea (mmol/l)	≤7.5	7.6-10.0	10.1-15.0	≥15.1
Sodium (mmol/l)	≥136	131- 135	126-130	≤125
Potassium (mmol/l)	3.5 – 5.0	3.2 – 3.4 5.1- 5.3	2.9-3.1 5.4-5.9	≤2.8 ≥6.0
Electrocardiogram	Normal		Atrial Fibrillation (rate 60-90)	Any other abnormal rhythm ≥5 ectopics/min Q waves present ST/T wave changes

Table 10.1 Physiological components of POSSUM (39)

	Operative Score			
	1	**2**	**4**	**8**
Operative severity *	Minor	Moderate	Major	Major +
Multiple procedures	1		2	>2
Total blood loss (ml)	≤100	101-500	501-999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation of >2 hours possible with operation <24 hours after admission	Emergency (immediate surgery <2 hours required)

*** Moderate severity includes appendicectomy, choleystectomy, mastectomy, transurethral resection of prostate. Major surgery includes any laparotomy, bowel resection, cholecystectomy with choledochotomy, peripheral vascular procedure or major amputation. Major + surgery includes any aortic procedure, abdominoperineal resection, pancreatic or liver resection, oesophagogastrectomy.**

Table 10.2 Operative components of POSSUM (39)

POSSUM was derived by Copeland and colleagues(39) from a cohort of 1372 patients undergoing vascular, gastrointestinal, hepatobiliary and urological surgery. Twelve variables were identified that were predictive of the risk of morbidity and mortality

however, intergroup variability was present dependent upon the nature of the surgical procedure. To adjust for this the operative score from 6 variables was developed through logistic regression. Both the physiological and operative scores are graded exponentially and are then inserted into a formula.

POSSUM, however, has been shown to over-predict mortality data. Whiteley and colleagues(40) showed a significant difference between predicted and observed mortality (n= 90 v 37 $p<0.0001$) when examining 1485 POSSUM data sets, with performance being worst in low risk patients. Following further logistic regression of this data the Portsmouth Predictor Equation for mortality was derived (P-POSSUM) which uses the same parameters as POSSUM but instead utilising an alternative equation.

P-POSSUM has been validated in a prospective cohort of 7500 general surgical patients (41) where there was close agreement between predicted and observed mortality rates. Comparison of POSSUM and P-POSSUM in colorectal patients by Tekkis and colleagues(42) showed that in elective colorectal surgery patients P-POSSUM predicted mortality (3.8%) was closer to observed (3.2%) mortality than POSSUM predicted mortality (4.6%). Both scoring systems however, over-predicted mortality in the young, and significantly underpredicted deaths in the elderly.

A dedicated colorectal specific version of POSSUM (CR-POSSUM) has been developed by Tekkis and colleagues(43) with six physiological factors and four operative factors again with exponential scoring to indicate severity (Table 11).

Comparison of CR-POSSUM with P-POSSUM showed both performed similarly in this patient group despite CR-POSSUM requiring less data to calculate predicted risk (44).

	Physiological Score				
	1	**2**	**3**	**4**	**8**
Age (years)	≤60		61-70	71-80	≥81
Cardiac failure	None or mild	Moderate	Severe		
Systolic Blood Pressure (mmHg)	100-170	>170 90-99	<90		
Heart rate (beats/min)	40-100	101-120	>120 or <40		
Urea (mmol/l)	≤10	10.1 – 15.0	>15.0		
Haemoglobin (g/dl)	13-16	10 – 12.9 16.1 - 18	<10 >18		
	Operative Severity Score				
	1	**2**	**3**	**4**	**8**
Operative Severity	Minor		Intermediate	Major	Complex major
Peritoneal Soiling	None Serous fluid	Local pus	Free pus Faeces		
Operative urgency	Elective			Urgent	Emergency
Cancer staging	No Cancer Dukes' A-B	Dukes' C	Dukes' D		

Table 11 Colorectal POSSUM Scoring System adapted from Tekkis and colleagues (43)

The tendency of POSSUM bases systems to over predict mortality especially in lower risk groups could be due to the minimum possible risk of death being 1.1% by POSSUM and 0.2% by P-POSSUM, which is higher than one would expect in the lowest risk group of patients. Therefore whilst POSSUM systems have been extensively used for risk prediction it is not the perfect tool in the low-risk patient group.

Cardiac Specific Scoring Systems

Major cardiac complications (MACE) occur in around 2% of patients following non-cardiac surgery (45). Patients with risk factors for ischaemic heart disease are likely to be at higher risk as evidenced by the 6.9% rate of MACE in the placebo control group of the POISE study (46) that recruited patients with or at risk of atherosclerotic disease. There are a number of multi-factorial scoring systems that have been developed to predict the risk of major cardiac complications using both patient history and clinical findings. These can be used not only for risk stratification of patients, but also to help guide pre operative investigations, or to aid pre-operative management. The most commonly used scoring system is that developed by by Lee and colleagues(45). This simple to use system uses identifies six risk factors (Table 12) with equal weight for peri-operative cardiac complications, with risk increasing with the number of risk factors present (Table 13)

High risk surgery
Ischaemic Heart Disease
History of Congestive heart failure
History of cerebrovascular disease
Insulin therapy for diabetes
Pre-operative serum creatinine >2.0mg/dl

Table 12 Factors predictive of cardiac risk utilised in Lee's Revised Cardiac Risk Index (45)

Number of Variables present	**Rate of major cardiac complications in validation cohort (n=1422)**
0	0.4%
1	1.0%
2	7%
Greater than 2	11%

Table 13 Risk of cardiac morbidity and mortality based on classification by Lee's Revised Cardiac Risk Index (45)

Derived from a study of 2893 patients undergoing elective non-cardiac procedures the revised cardiac risk index was then validated in a further cohort of 1422 patients. In the derivation cohort 6 variables were identified using logistic regression to have independent correlation with major complications, these were then used to construct the revised cardiac risk index (RCRI).

Risk of mortality was shown to be significantly higher in patients with 2 or more risk factors present (Table 13) therefore Lee's Revised Risk Index can be used to stratify patients into a low risk group (with less than 2 variables present) and a higher risk group (2 or more variables).

ROC analysis within the validation cohort (45) showed superior diagnostic performance compared to the previous indices of Goldman (47) and Detsky (48)($P<0.01$). A weakness of the RCRI is that in the validation cohort insulin therapy for diabetes and raised serum creatinine were not independent correlates for cardiac complications. However, despite this a recent a meta-analysis (49) has shown that RCRI is still a moderate predictor of cardiac complications, with the ability to discriminate between low and high risk patients for post-operative cardiac morbidity and mortality.

The RCRI has been integrated into the 2007 ACC/AHA guidelines for peri-operative cardiac evaluation for non-cardiac surgery. According to these guidelines patients with stable cardiac disease should proceed straight to planned surgery if they have good functional capacity, if they have poor functional capacity it is considered appropriate for them to proceed to surgery if none of Lee's risk factors are present, without the need for further investigation or consideration of beta blockade.

Ackland and colleagues (50) showed that patients with a lower RCRI Score had reduced post-operative morbidity. The incidence of pulmonary, infectious, cardiovascular, renal, wound and neurological morbidities were all less likely to

occur in patients with a lower RCRI. Whilst LRCRI primarily stratifies for cardiac risk it may be possible to adapt it for use in predicting risk for events of morbidity; however, this use has not been validated. Further, a low score is not an indicator of the absence of risk as shown by Wilson and colleagues (51) with some patients having significant risk of mortality (RR 10, 95%CI 1.7-61.0) despite absence of Lee's risk factors.

1.2.4 Perioperative Investigations

The aim of pre-operative investigations is to obtain information that will either allow an estimation of the patient's risk or alter their perioperative management. Various investigations can be performed ranging from simple blood tests, to biomarkers and more advanced cardiac investigations.

Biomarkers

Simple investigations that offer information to help evaluate risk can be in the form of blood tests that can be carried out at a pre-operative assessment clinic. Recommendations from the National Institute for Clinical Excellence (52) suggest that all adult patients undergoing major colorectal surgery have pre-operative testing of their full blood count and renal function. However, these are not predictive of peri-operative risk as shown in a study by Dzankic and colleagues(53) which examined the predictive value of various pre-operative laboratory tests in patients over the age of 70 undergoing non cardiac surgery. Of the 2462 laboratory

tests that were performed 6.8% had abnormal results. No pre-operative test, including that for hyperglycaemia, anaemia, abnormal potassium levels, hyponatraemia and thrombocytopaenia had an association with adverse post-operative outcomes following multivariate logistic regression. However, whilst the presence of abnormal tests in this study did not affect post-operative outcomes, this may reflect that these abnormal values were corrected prior to surgery. Hence whilst they are a poor predictor of outcome, they still have an important role in pre-assessment in order that correctible abnormalities can be addressed, and they also act as a baseline for post-operative comparison.

Several biomarkers have been identified as potential risk markers for poor peri-operative outcome, including b-type natriuretic peptide, n-terminal pro-brain natriuretic peptide, and highly sensitive c-reactive protein (54).

B-type natriuretic peptide (BNP) is a cardiac hormone produced by the ventricular myocytes in response to increased myocardial wall tension, and plays a role in regulation of blood pressure, sodium balance and diuresis. Measurement of BNP and its biologically inactive precursor N-terminal pro-brain natriuretic peptide (NT-proBNP) have been shown to be predictors of mortality and cardiac events in patients with heart failure(55).

A meta-analysis by Ryding and colleagues (56) showed that elevated BNP levels were associated with increased risk of both all cause short term (up to 42 days) mortality (OR 9.28, 95% CI 3.51-24.56) and longer term (> 6 months) mortality (OR 4.72, 95%

CI 2.99 – 7.46). MACE was associated with higher BNP (OR 25.41, 95% CI 12.46-51.97) and NT ProBNP (OR 15.65 95% CI 10.39 – 25.37) levels. This meta-analysis further showed that the negative predictive value for BNP was high with no deaths in patients with normal BNP; in addition there is a negative predictive value of at least 95% for MACE. The predictive ability for pre-operative NT-pro BNP levels for post-operative cardiac events in vascular surgery has been shown to be independent of clinical history, wall motion abnormalities at rest and stress induced myocardial ischaemia (57). A cut off level of 319ng/l has been identified as a predictor of 6 month mortality and the occurrence of major adverse cardiac events (MACE) following vascular surgery, with a hazard ratio of 4.0 (95% CI 1.8 – 8.9) for mortality and 10.9 (95% CI 4.1 – 27.9) for MACE in patients with NT-proBNP ≥319ng/l (58). ROC curve analysis of 6 month mortality in this same study suggests that NT-proBNP is a superior long-term marker of risk compared to the Revised Cardiac Risk Index and Dobutamine stress echocardiography.

The clinical utility of BNP measurements likely lie in its high negative predictive value where normal values would rule-out the need for further investigation, as they signify low risk of poor peri-operative outcome. However, a recent pilot study by James and colleagues(59) showed that whilst BNP had a fair predictive ability for MACE (89 v 28 pg/ml, p=0.0001), its predictive ability for overall complications was poor ROC curve AUC 0.60 (95%CI 0.48-0.73). In comparison cardiopulmonary exercise testing was a better predictor of MACE than BNP on ROC curve analysis (AUC 0.83 (95% CI 0.69-0.96) v 0.75(95%CI 0.59- 0.92).

Most of the data on BNP and NT-ProBNP and its association with post-operative outcome are derived from vascular patients, with the exception of one study (56) which included 84 patients undergoing elective, non-specified major abdominal surgery. The pathophysiology of the vascular population could lead to a disparate group of patients with regards to cardiac complications when compared to patients undergoing colorectal surgery. A further weakness in the evidence for the use of BNP and NT-ProBNP in predicting risk is the variation between studies regarding the optimal cut-off between low and high risk patients (56) Further work is needed before these biomarkers become established as standard investigations in the pre-operative assessment of patients in order to improve clinical outcome.

Cardiac Investigations

Cardiac investigations that can be carried out in the pre-operative patient range from a simple 12 lead electrocardiograph (ECG) to exercise or pharmacological stress testing to invasive imaging of the coronary arteries.

The 2014 ACC/AHA guidelines for perioperative cardiovascular evaluation prior to non-cardiac surgery (60) recommends routine recording of an electrocardiograph (ECG) unless the patient is undergoing low-risk surgery. Further investigations depend on the physician's assessment of patient's risk and functional capacity. Patients considered at elevated risk with poor functional capacity are recommended to have non-invasive stress testing if it would change management leading either to

the patient having coronary revascularisation or the original surgical procedure being cancelled.

Analysis of 108 593 Dutch patients undergoing non cardiac surgery by Noordzij and colleagues (61), showed patients with abnormal ECG results had a higher incidence of cardiovascular death than those with normal results (OR 5.1 95% CI 3.9-6.9), and adding ECG data to information on cardiovascular co-morbidities and type of surgery improved prediction of cardiovascular mortality. However, this was more pronounced in patients under-going intermediate or high risk surgery compared to those undergoing low risk surgery. However, as with routine testing of electrolytes and renal function its true value is likely to lie as a pre-operative baseline comparator, in case of post-operative cardiac morbidity.

Assessment of cardiac function can be aided by static or dynamic imaging. Resting echocardiography is easily accessible in most UK hospitals compared to dynamic scans. However, a study by Halm *and colleagues(62)* showed that whilst echocardiographic measurement of ejection fraction or wall motion did predict post-operative congestive heart failure and episodes of ventricular tachycardia, it did not add any significant predictive value to a clinical model.

Dynamic cardiac imaging can be used to test the myocardium's response to stress. Dynamic perfusion scans use radionucleotides such as technecium or thallium, to evaluate perfusion at rest or following dipyridamole driven vasodilation. Dobutamine can also be used to increase myocardial oxygen demand which is then

evaluated using echocardiography to look for wall motion abnormality representative of ischaemia.

A meta-analysis of 10 studies in vascular patients by Shaw and colleagues (63) showed cardiac event rates of 3, 11 and 18% in the presence of normal scans, fixed and reversible defects respectively (p=0.0001). Multivariate logisitic regression analysis showed the greatest independent predictor of post-operative death or myocardial infarction was the presence of a reversible perfusion defect (p=0.0001, OR 2.9), the predictive value of which was greater than the presence of congestive heart failure or a fixed perfusion defect on scanning. A further meta-analysis by Etchells and colleagues(64) of dipyridamole myocardial perfusion scans showed that patients who had reversible defects in up to 20% of myocardial segments did not have any increased risk of peri-operative complications. However with increasing percentage of segments affected there was an increasing likelihood of adverse cardiac events.

In Dobutamine stress echocardiography (DSE), echocardiographic examination is carried out at rest, and then following an administration of dobutamine sometimes in combination with atropine in order to achieve at least 85% of maximal predicted heart rate. Ventricular wall motion is then assessed by continuous echocardiography to detect any abnormalities. A study of 134 elective vascular patients by Poldermans (65) showed that patients with a positive DSE were 95 (95% CI 11-823) times more likely to suffer a peri-operative cardiac event than those with a negative echo, with a positive predictive value of 42% and a negative predictive value of 100%. In a non-

vascular surgical population the value of DSE was investigated by Das (66) in 530 patients with known or suspected coronary artery disease. DSE could be used to identify patients at low, intermediate or high risk for post-operative cardiac events. No events occurred in patients with a negative DSE. Nine percent of patients who had an ischemic threshold at 60% or more of predicted heart rate had cardiac events, while 43% of patients who had an ischaemic threshold at less than 60% had post-operative cardiac events.

Comparison of dynamic perfusion scanning in the form of thallium imaging with dobutamine stress echocardiography in a meta analysis of 25 studies by Beattie and colleagues (67) showed that DSE was 2 times more predictive than a positive thallium imaging scan in predicting a postoperative cardiac event. In addition a negative stress echo was a better predictor of an uneventful post-operative period than a negative thallium imaging scan. This is supported by a further meta-analysis by Kertai and colleagues (68) which showed that dobutamine stress echocardiography was significantly better at predicting peri-operative cardiac death or myocardial infarction than myocardial perfusion scintigraphy.

However, the information gained by such tests should be balanced against the urgency of surgery. A study by Poldermans and colleagues(69) showed that in a group of vascular patients at intermediate risk (RCRI Score 1-2) who had adequate beta blockade, there was no difference in cardiovascular outcome whether the patients underwent stress echocardiography or not, but the non tested group received earlier surgery by approximately 3 weeks . Therefore in a situation such as

colorectal resections for cancer where immediacy of surgery is a factor, the patients may benefit more from earlier surgery rather than from waiting for cardiac imaging.

For risk stratification of patients these investigations maybe suitable for the identification of patients at low risk of poor cardiac outcome, due to the high negative predictive value of finding no wall motion abnormality. However, the cost must be taken into account, not just in terms of financial expense but also due to the additional risk posed to patients whilst undertaking these tests. Further it is important that time-critical cancer surgery is not delayed whilst waiting for results from these investigations, which have not been shown to improve post-operative outcome.

1.2.5 Investigation of Functional Capacity

Functional capacity is an important factor in pre-assessment both as a marker of severity of co-morbid disease but also in the assessment of cardiopulmonary reserve, with the maximal oxygen consumption achievable having a significant effect on post-operative outcome. Tests of functional capacity can be subjective, estimating oxygen consumption based on the patients' recall of daily activities or an objective measurement through direct or indirect measurement of oxygen consumption.

Self-reported Exercise Tolerance

Self-reported exercise tolerance can be used to predict in-hospital peri-operative risk. A study of 600 patients undergoing non-cardiac surgery by Reilly and colleagues(70) showed that the likelihood of a serious complication developing in a patient was inversely related to the number of blocks (0-4) that they reported they could walk, or flights of stairs (0-4) that could be climbed.

Metabolic equivalents (MET) are often used to quantify levels of self-reported physical activity. The origins of the development of the unit MET are unclear, but it is accepted in the published literature as being a multiple of resting metabolic rate and that 1 MET is equal to consumption of 3.5 ml O_2/kg/min (71). The ACC/AHA guidelines (60) consider that patients capable of completing activity that require more than 4 METS (such as climbing a flight of stairs or walking up a hill) are low risk and therefore should proceed with surgery without further investigation.

METS are also used to calculate the Duke Activity Status Index (DASI). The DASI was designed as a self-administered questionnaire to determine functional capacity based on activities that patients can undertake (72). It was developed using data from 50 patients who underwent exercise testing on a cycle ergometer to determine their peak oxygen consumption. These patients then were interviewed to determine their ability to undertake a range of daily activities. Regression analysis was used to identify activities which provided independent information regarding peak oxygen uptake which was then used to produce a 12 point questionnaire with weighted items based on the metabolic cost of each activity in METS (Table 14). The cumulative score showed a significant correlation with peak oxygen uptake

(Spearman correlation 0.58 P<0.0001) in a separate validation cohort of 40 subjects, and can be used to calculate VO_2 (VO_2 = 0.43 x DASI +9.6).

Scoring by the DASI allows a cost-effective, non-investigator reliant measurement of functional capacity. However in patients with poor functional capacity represented by a score < 5METs, there was a poor correlation with measured exercise capacity (72). This may be due to individual variation in oxygen consumption per MET. It is thought that the value on which 1 MET was calculated upon the resting oxygen consumption of a single 40 year old male who weighed 70 kg (71). Byrne and colleagues (71) have shown that resting oxygen consumption varies with age, gender, BMI and body fat mass, with an mean resting metabolic rate of 2.6ml O_2/kg/min in their cohort of 593 patients, which suggests that the conventionally used value of 3.5 ml O_2/kg/min may over-estimates metabolic rate at rest in some subjects. This is supported by evidence (73) which shows the subjective DASI to have weaker correlation with peak oxygen consumption compared to objective measures of functional capacity.

Activity which patient can achieve	**Index Weight (MET)**
Eat, dress, bathe, toilet	2.75
Walk indoors e.g. around the house	1.75
Walk 200 yards on level ground	2.75
Climb flight of stairs or walk up a hill	5.50
Run a short distance	8.00
Light work around the house e.g. dusting, washing dishes	2.70
Moderate work around the house e.g. vacuuming, sweeping floors, carrying groceries	3.50

Heavy work around the house e.g. scrubbing floors, moving heavy furniture	8.00
Yard work e.g. raking leaves, weeding, pushing a lawn mower	4.50
Sexual relations	5.25
Moderate recreational activities e.g. golf, bowling, dancing, doubles tennis, throwing a ball	6.00
Strenuous sports e.g. swimming, singles tennis, football, basketball, skiing	7.50

Table 14 Duke Activity Status Index adapted from Hlatky and colleagues(72)

As self-reported assessment of functional capacity is subjective, relying on the patient's own views of their abilities to estimate maximal oxygen consumption, this reduces the reliability of the test. Whilst the DASI may identify low risk patients by virtue of their ability to undertake strenuous activity further investigation is required into this easy to use tool to examine whether is it is a reliable predictor of post-operative outcome.

Incremental Shuttle Walk Testing

Originally developed as a standardised test of disability in patients with chronic obstructive pulmonary disease(74), the incremental shuttle walk test (ISWT) requires the patient to walk up and down a course of set length to a speed dictated by an audio signal. The test is incremental with the time allowed to complete the course decreasing as the test progresses until the patient reaches maximal exertion. The total distance walked offers an objective estimate of functional capacity. In a study of 46 heart failure patients Morales *and colleagues*(75) showed a correlation

between distance walked and peak VO2; a distance of <450m predicted a peak VO2 of <14ml/kg/min on cardiopulmonary exercise testing with a sensitivity of 100% and a specificity of 89%.

This principle has been applied to pre-operative assessment of surgical patients. It utilises a familiar activity for the patient without the need for additional equipment. Murray and colleagues (76) examined the value of incremental shuttle walk testing in predicting outcome after oesophagectomy, showing an increased risk of 30-day mortality in patients with a shuttle walk distance of less than 340m. Patients with better post-operative outcomes achieved longer distances with patients discharged home before 30 days achieving a mean distance of 540m, compared to the shorter mean distance of 300m in those who died (n=8). A larger more robust prospective trial by Nutt and colleagues (77) of 121 consecutive patients undergoing major colorectal surgery demonstrated decreasing complication rates with increasing distance achieved on ISWT. Patients who did not develop complications had a significantly higher mean ISWT distance compared to those who did (389.6m v 276.6m, p<0.001), with those developing a major complication having an even lower mean ISWT distance (256.8m). An ISWT distance less than 250m was noted in 80% of patients who developed a complication, which was the optimum cut-off on ROC analysis. In this group the hospital length of stay was significantly longer (14 days v 8 days, P<0.0001).

Comparing the ISWT with DASI, Struthers and colleagues (73) showed that ISWT distance had a stronger correlation with peak oxygen consumption found on

cardiopulmonary exercise testing (CPET) (R^2 = 0.57, p<0.0001) than DASI R^2 = 0.45, p<0.0001). Adding DASI to ISWT distance did not improve prediction of VO_2 peak. However, this study also showed that ISWT distance was likely to miss a proportion o f patients that would be classified as low risk on CPET using the cut off of 360m which corresponded with an anaerobic threshold of 11ml/kg/min therefore these patients would be considered high risk and receive unnecessary interventions.

Stair Climbing

As with the incremental shuttle walk test, stair climbing offers patients a familiar task, which can be used to estimate functional capacity without the need for complex equipment. This can either be achieved through self-reported assessment, or by carrying out a physician supervised test where functional capacity can be assessed by recording step height, the number of steps in a flight, and the speed of ascent.

As previously described, a study by Reilly *and colleagues*(70) examined self-reported ability to climb flights of stairs as one of several measures of exercise tolerance. The frequency of serious post-operative complications was inversely related to the number of flights of stairs that could be climbed. Inability to walk 4 blocks and climb 2 flights of stairs had a sensitivity of 0.71 and a specificity of 0.47 for predicting serious post-operative complications.

Amongst lung resection patients studied by Brunelli *and colleagues(78)* as ability to climb stairs decreased, post operative complications increased. Patients who developed cardiopulmonary complications achieved a significantly lower vertical height of ascent (14.96m v 20.6m $p<0.0001$). Conversely a sub-set of patients who ascended greater than 14m in vertical height had significantly lower complication rates at 6.5% compared to 29.2% in those achieving 12-14m and 50 % in those unable to reach 12m ($p=0.003$).

Girish and colleagues (79) conducted a prospective study of stair climbing in 83 patients undergoing major thoracic or upper abdominal surgery (including 23 colectomies). Inability to climb 2 flights of stairs was associated with a positive predictive value of 80% of developing a post-operative complication, with a sensitivity of 32%. Patients who were able to climb five or more flights had a low likelihood of developing post-operative complications (sensitivity 95%, specificity 32%). There was a negative correlation between increased ability to climb stairs and length of stay.

Further studies are needed to validate the technique as the majority of studies looking at stair climbing have been in patients undergoing thoracic surgery. These patients are likely to have serious lung pathology due to the common risk that smoking poses for lung cancer and chronic obstructive pulmonary disease. Colorectal patients form a separate population, less likely to have pulmonary co-morbidities, whilst functional capacity impacts on post-operative outcomes in both groups, further work is required in patients undergoing non-thoracic procedures to

see the reliability of this technique in predicting risk with different co-morbid states affecting functional status.

The previously mentioned tests whether subjective or objective are all indirect measures of maximal oxygen consumption. Cardiopulmonary exercise testing in contrast offers a direct measure of oxygen consumption.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is the currently considered the gold-standard for assessment of functional capacity in pre-operative patients. Estimated to be available in approximately 40% of hospitals in the United Kingdom (17), it provides an objective measurement of oxygen consumption compared to the inferred estimates derived in the tests described above.

CPET uses incremental exercise to assess the functional capacity of the body. Measurement of oxygen consumption, CO_2 production and minute ventilation during this incremental exercise allows the evaluation of the body's ability to utilise oxygen. A large number of variables are measured during the test. However 3 of these variables are commonly used in terms of predicting post operative risk; namely anaerobic threshold, peak oxygen consumption, and ventilatory equivalents.

Anaerobic threshold.

Metabolic demand for oxygen rises with exercise, if the supply of oxygen cannot match this rise in demand then anaerobic respiration ensues, leading to the production of lactate. Lactate is buffered by bicarbonate to CO_2, which is then excreted through the lungs. The rise in CO_2 production is accompanied by an increase in minute ventilation (VE) in order to maintain normocapnia.

Anaerobic threshold describes the point at which oxygen delivery to the tissues becomes inadequate to meet the oxygen demand, and hence anaerobic metabolism ensues in order to meet this energy deficit. The most commonly used method to detect anaerobic threshold is the modified v-slope method (see figure 1), where carbon dioxide production (VCO_2) is plotted against oxygen production (VO_2). The anaerobic threshold occurs at the inflection point where VCO2 begins to rise out of proportion to VO2, and is reported as the oxygen consumption at the onset of anaerobic respiration (AT) with the units of ml/kg/min. The AT can also be identified using a plot of VE/VO_2 at the point where VE/VO2 increases without an increase in the corresponding values for carbon dioxide.

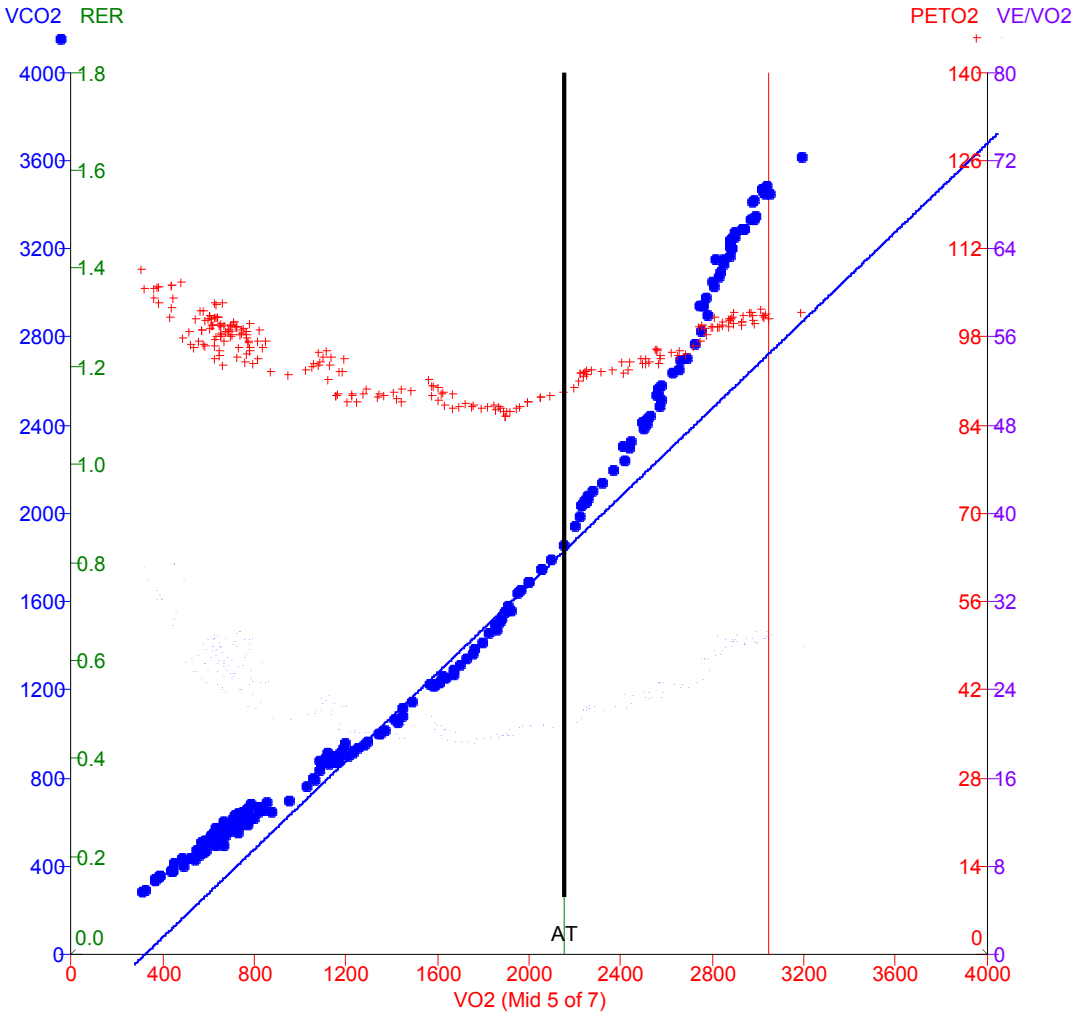

Figure 1 Modified V-Slope method of detecting anaerobic threshold on CPET

Peak oxygen consumption.

VO_2 peak is the maximum oxygen consumption obtained by a patient during an exercise test.

Ventilatory equivalent for carbon dioxide (VE/VCO_2).

This unit-less entity describes the ratio of minute ventilation (VE) to the volume of CO_2 produced (VCO_2) and is a measure of ventilatory efficiency, hence reflecting ventilation/perfusion mismatch. Whilst VE/VCO_2 has historically been reported as

the gradient of the VE/VCO_2 slope, VE/VCO_2 is conventionally reported as the value at AT for the purposes of pre-operative risk stratification.

Clinical Application of Cardiopulmonary Exercise Testing

CPET was first used in the evaluation of patients with cardiac failure, and offered a quantitative approach to evaluating the severity of impairment of a subject's functional capacity. In 1982 Weber and colleagues(80) published a study looking at 62 patients with chronic stable heart failure. They measured the maximum oxygen uptake achieved (VO_2 max) and anaerobic threshold achieved on graded exercise using a treadmill, where the patients exercised to a point of exhaustion. In addition, the cardiac output, systemic O2 extraction and lactate production during exercise was measured directly using a pulmonary artery occlusion catheter in 40 patients. When the patients were divided into groups A-D depending on their decreasing VO2 max (Table 15), it was noted that there was a significant corresponding decrease in cardiac index in patients in classes B-D both at rest and maximal exercise ($p<0.01$), with resting oxygen extraction greatest in group D ($p<0.02$) – reflecting the poorest oxygen delivery. Patients in group D showed no significant rise in stroke volume with exercise (SVI rest 22 v maximal exercise 26 ml/m^2) suggesting that the cardiac output response to exercise was entirely reliant on heart rate response.

Group	VO_2 Max (ml/kg/min)	Mean Cardiac Index (l/min/m^2) (SD)		Mean Oxygen Extraction (%) (SD)	
		Rest	Maximal Exercise	Rest	Maximal Exercise
A	**>20**	Not measured			
B	**16-20**	2.23 (0.24)	7.81 (0.95)	33 (8)	75 (2)
C	**10-15**	2.01 (0.41)	4.68 (1.1)	39 (9)	71 (5)
D	**<10**	1.81 (0.51)	3.04 (0.48)	48 (10)	75 (8)

Table 15 Variation in Cardiac index and Oxygen Extraction adapted from Weber and Colleagues (80)

Gitt and colleagues (81) prospectively studied 223 patients with congestive cardiac failure comparing the predictive value of AT, Peak VO2 and VE/VCO2 on long term survival. Peak VO2 ≤ 14, AT < 11 and VE/VCO2 >34 elucidated from cycle ergometry were all shown to be significant predictors of six month mortality (Table 16), with patients who had a combination of AT < 11 and VE/VCO2 >34 having the highest risk of mortality at six months.

CPET parameter	Relative risk	95% CI
Peak VO_2 ≤14 (ml/kg/min)	2.9	(1.5-5.4)
AT <11 (ml/kg/min)	2.7	(1.3-5.6)
VE/VCO_2 slope >34	2.7	(1.5-5.1)
Peak VO_2 ≤14 (ml/kg/min) and AT <11 (ml/kg/min)	3.2	(1.5-6.7)
Peak VO_2 ≤14 (ml/kg/min) and VE/VCO_2 slope >34	4.5	(2.1-10.0)
AT <11 (ml/kg/min) and VE/VCO_2 slope >34	5.1	(2.0-12.7)

Table 16 CPET parameters and prediction of six-month mortality adapted from Gitt and colleagues (81)

The association of poor peri-operative outcome in patients with heart failure (18), (27) and the predictive value of CPET in this population has lead to the development of the use of CPET to predict peri-operative outcome.

A study by Older and colleagues (82) applied cardiopulmonary testing to the pre-operative population and identified an oxygen consumption at AT of <11 ml/kg/min as a marker for increased risk of post-operative mortality. 187 patients over 60 years of age undergoing major abdominal surgery underwent pre-operative cardiopulmonary exercise testing. Overall 5.9% of patients died from non-surgical causes. A significant increase in post-operative non-surgical related mortality was shown in patients with an anaerobic threshold < 11 ml/kg/min compared to those with an AT >11 ml/kg/min (18% vs. 0.8%, $p<0.001$). The presence of pre-operative ischaemia increased mortality risk in both these groups with rates being 4% and 42% in the high and low AT groups respectively.

Older expanded on this study (83) where he used CPET to determine post-operative management in patients undergoing major surgery who were over 60 years of age, or had a history of myocardial infarction or heart failure. Patients (n=548) were admitted to ICU, HDU or a ward based on their AT, presence of myocardial ischaemia type, VE/VO2 and the type of surgery. Despite triaging of patients to intensive care patients with an AT<11 ml/kg/min had the highest cardiovascular mortality at 4.6%, compared to patients triaged to HDU (AT≥11 ml/kg/min and myocardial ischaemia or VE/VO2>35) who had a mortality of 1.7%, or the ward (AT≥11 ml/kg/min, no myocardial ischaemia and VE/VO2 ≤34) with a mortality of 0%. Therefore whilst

CPET identifies patients at risk of poor post-operative outcome and can stratify that risk, post-operative management alone cannot nullify the difference in outcome between high and low risk groups.

A large retrospective study of patients over 55 years undergoing major colorectal or urological surgery by Wilson and colleagues (51) showed an increased relative risk for all cause in-hospital mortality in patients who had AT of ≤ 10.9ml/kg/min (RR 6.8, 95%CI 1.6-29.5), a VE/VCO2 of ≥ 34 (RR 4.6, 95% CI 1.4-14.8) or a history of Ischaemic Heart Disease (RR 3.1, 95% CI 1.3-7.7).

Survival at 90 days was significantly better in lower risk patients with an AT≥11 ml/kg/min (p=0.034), VE/VCO2 <34 (p=0.021) and in those with no history of ischaemic heart disease (p=0.02). In addition median inpatient stay was significantly lower in patients with AT≥11 (8 vs.9 days p=<0.001).

Snowden and colleagues (84) showed a higher frequency of post-operative complications in patients who had a reduced cardio-respiratory reserve predicted by CPET testing. The post-operative morbidity survey was used to follow-up of 123 elective patients who underwent major vascular surgery, liver resection or pancreatectomy. Patients with more than one complication at post-operative day 7 had a lower mean AT compared those who had one or less complication (AT = 9.1 v 11.9 ml/kg/min).

The conventional cut-off for anaerobic threshold and prediction of low risk of complications has been greater than or equal to 11ml/kg/min based upon Older's original data. This value is supported in work by Wilson and colleagues (51) where ROC analysis showed that an AT ≤ 10.9 ml/kg/min had a sensitivity of 88% and specificity of 47% for post-operative mortality. For prediction of post-operative morbidity Snowden *and colleagues(84)* showed that a cut off of < 10.1 ml/kg/min had a sensitivity of 88% and a specificity of 79% for predicting complications at day 7, and this is supported by a recent publication by West and colleagues (85) which also showed an optimal cut-off of 10.1 ml/kg/min for predicting post-operative morbidity this time at day 5, albeit with a lower sensitivity (68%). The strength of this study is that the intra-operative team were blinded to the CPET results, and hence these values were not used to alter perioperative management, which is a confounding factor of other cited studies, where the results were used to influence management.

Whilst AT is the most commonly used variable, it is not clear if there is a single CPET variable which is superior at prognosticating outcome following all types of surgery. In bariatric surgery, for example, peak VO_2 >15.8 ml/kg/min has been shown to identify a subset of patients less likely to develop complications following surgery (86). However there was no significant difference in complication rates between patients with high or low AT. A study of 108 patients undergoing oesophageal resections (87) showed similar AUC for patients on ROC curve analysis of the predictive power of AT and VO_2 peak for cardiopulmonary complications (AUC AT 0.62, 95% CI 0.5-0.4, VO_2 peak 0.60, 95% CI 0.48-0.72).

Comparison of results from the Duke Activity Status Index (DASI), incremental shuttle walk test (ISWT) and cardiopulmonary exercise testing in a prospective cohort of 50 patients undergoing intra-abdominal surgery (73) showed that all patients who walked 360m or who had a DASI of 46 or over had an AT>11 ml/kg/min. There was no significant difference on ROC analysis of ISWT and DASI on predicting AT ≥ 11 ml/kg/min. However, 19 patients who were not able to achieve 360m on the ISWT and 23 patients with a DASI less than 46 also achieved an AT>11 ml/kg/min, and would not have been identified as low risk by these methods. Therefore these techniques are not as reliable as CPET at identifying low risk patients.

Though as described above CPET testing has been shown to be a tool with significant value in predicting both cardiovascular and all-cause mortality in addition to an increased frequency of complications and hospital length of stay, the exact mechanism by which poor functional capacity is associated with poor post-operative outcome remains unclear. Subgroup analysis by Wilson *and colleagues*(51) showed that patients who had the worst survival were those with AT<11 ml/kg/min with none of Lee's cardiac risk factors present except that they were undergoing major abdominal surgery (RR 10.0, 95% CI 1.7-61.0). In this study 54% of patients had an AT <11ml/kg/min, but only 3% had a previously made diagnosis of heart failure. Therefore does CPET detect asymptomatic heart failure which is stable at rest and in the patients day to day activities or rather does low AT identify patients (including

those with heart failure) who are unable to meet the body's increased metabolic demands after surgery, which is simulated by exercise?

Cardiopulmonary exercise testing remains the gold-standard tool for stratification of pre-operative patients into high and low risk groups. Whilst there are limitations to the evidence available supporting its use, it is currently the only direct measure of functional capacity available for pre-operative assessment of surgical patients.

1.3 Fluid therapy and optimisation of the surgical patient

Fluid therapy has a significant role in the peri-operative management of the surgical patient by allowing the clinicians to optimise the patient's circulating volume in order to achieve an optimal cardiac output, and hence improve oxygen delivery to the tissues. Many studies have investigated peri-operative fluid and vasopressor regimens designed to improve post-operative outcomes. Whilst hypovolaemia may result in poor cardiac output and oxygen delivery to the tissues, over administration of intra-venous fluids can be harmful too, as shown in some investigations leading to debate on the so called 'liberal' versus 'restrictive' perioperative fluid regimens (88).

A meta-analysis of 3861 patients undergoing major surgery (89)showed that patients receiving fluids according to non-targeted liberal regimens were more likely to develop pneumonia (RR 3, 95% CI 1.8-4.8), have a longer length of stay (4 days difference, 95% CI 3.4-4.4) and to have a longer time until first bowel movement (2 days difference, 95% CI 1.3-2.3) compared to patients who received goal directed fluid therapy. Whilst patients in both liberal and goal directed fluid arms of studies received significantly greater volumes of fluid than their respective control arms, patients receiving goal directed fluid therapy had better outcomes, suggesting that patients benefited from having set haemodynamic goals.

In goal directed fluid therapy cardiac output monitoring is used to optimise haemodynamic status using strategies that target various cardiovascular end-points

at different points during the peri-operative period. These have been shown to improve post-operative outcome (90, 91).

Standard intra operative monitoring including heart rate, mean arterial pressure (MAP) and central venous pressure (CVP) are poor predictors of fluid responsiveness and also of post-operative outcome. Comparison by Shoemaker and colleagues (92) of survivors and non-survivors of post-operative shock showed that heart rate and central venous pressure were amongst the worst cardiorespiratory variables at correctly predicting post-operative outcome (survival or death), whilst MAP was a good predictor in late stages of shock it performed poorly in earlier stages, in contrast efficiency of tissue oxygen extraction, oxygen delivery and cardiac index performed well in most stages. Data from a study by Bundgaard-Neilson *and colleagues*(93) showed that MAP did not significantly change in respond stroke volume maximisation (mean MAP pre 73 v post 70mmHg $p>0.05$)) and therefore was a poor predictor of intravascular volume. Central venous pressure is the amongst the most commonly used targets for haemodynamic optimisation amongst European (83.6%) and American (72.6%) anaesthetists (94). However, it is a poor predictor of fluid responsiveness as shown in a meta-analysis by Marik *and colleagues*(95) using data from 830 patients where there was no significant difference in mean CVP between patients who responded to a fluid challenge compared to those who did not (8.7 v 9.7 $p=0.30$). Therefore commonly used protocols for goal-directed fluid therapy have been developed using additional monitoring that allows measurement of haemodynamic values that reflect cardiac output.

The 2011 report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) into peri-operative care of surgical patients showed that cardiac output monitoring was only used in 4.7% of high risk cases (17), and they considered that it should have been used in a further 12% of cases who were considered at high risk and had poor post-operative outcome. In a survey by Cannesson and colleagues (94) 48.4% of American and 26.8% of European non-users of cardiac output monitoring described the available technologies for cardiac output monitoring as being too invasive, suggesting that non- invasive technologies may be more palatable to anaesthetists for use in lower risk patients.

Adoption of targeted fluid therapy using cardiac output monitoring technology such as the Oesophageal Doppler in major or high risk surgery is forecasted to save the NHS over £400 million according to the National Institute of Clinical Excellence (NICE). It has been included as a "High Impact Change in Innovation Health and Wealth"(96) as published by the Department of Health in 2012 and has become a qualification requirement for Commissioning for Quality and Innovation (CQUIN) payments.

1.3.1 Goal Directed Therapy

Goal directed therapy has been shown to reduce post-operative risk by improving oxygen delivery to the tissues allowing them to meet the increased metabolic

demands of surgery. This can be achieved by administering fluid and inotropes in order to improve cardiac output and hence oxygen delivery.

A constant supply of oxygen is required in order to act as a substrate for aerobic metabolism. The cardiovascular system needs to match tissue oxygen consumption with supply in order to avoid tissue hypoxia. Tissue hypoxia leads to increased production of inflammatory markers and endothelial activation factors which lead to inflammation, capillary leak, vasoconstriction, intravascular coagulation and failure of local microcirculation all of which contribute to organ dysfunction(97). This is particularly pertinent in colorectal surgery where poor perfusion of the bowel may lead to ischaemia and anastomotic breakdown.

Oxygen delivery (DO_2) is related to the cardiac output and the oxygen content of arterial blood (CaO_2) by the following equation.

DO_2 (ml/min) = Cardiac Output (L/min) x CaO_2 (ml)

In health oxygen, delivery exceeds tissue oxygen consumption. As oxygen demand rises an inadequate supply means that anaerobic metabolism occurs. An inadequate supply is demonstrated by an increase in the oxygen extraction which is reflected by a reduction in mixed venous oxygen saturation to <70%(98).

Observational research from Schoemaker and colleagues (99) looking at post-operative patients with hypovolaemic shock showed that patients who survived had a significantly greater cardiac index and oxygen availability than patients who did

not. In contrast factors such as arterial and central venous pressure did act as good predictors of survival.

Major abdominal surgery has been shown to increase oxygen consumption significantly. In an observational study of 100 patients by Older *and colleagues*(100) mean oxygen consumption increased 44% from 121 ml/min/m^2 pre-operatively to 174 ml/min/m^2 post-operatively.

In a further study by Shoemaker and colleagues (101) of high risk surgical patients, survivors were noted to have a greater increase in cardiac index, DO_2 and VO_2 when compared to non-survivors, even if they started with normal cardiac index.

Therefore it is important that post-operatively patients can increase oxygen delivery to meet this increased demand. This can be achieved by increasing cardiac output assisted by increasing the oxygen content of arterial blood (by optimising haemoglobin content of blood and the inspired fraction of oxygen). If a patient has poor cardiac reserve with an impaired ability to increase cardiac output, this can lead to increased mortality.

These findings led to the development of interventions for haemodynamic optimisation. Earlier trials focused on the concept of pre-optimisation. Over subsequent decades strategies have changed and current practice is for intra-operative optimisation.

Currently available methods of cardiac output monitoring can be divided into invasive, minimally-invasive and non-invasive monitoring. Protocols have been developed to utilise these technologies in the pre-operative, intra-operative and post-operative periods.

1.3.2 Invasive Monitoring

Initial studies of goal-directed therapy used invasive monitoring through pulmonary artery catheters in the pre-operative period in order to target fluid and inotropes. Subsequent studies moved optimisation into the intra-operative setting, which is where current practice of goal-directed therapy is focused.

Pulmonary Artery Catheterisation

Pulmonary artery catheterization (PAC) as currently used for cardiac output monitoring was first described by Swan and Ganz in 1970 (102). It involves the insertion of a balloon tipped catheter using a central vein, which is then passed through the right atrium from where the balloon is deployed and it is flow guided into the right ventricle, and then the pulmonary artery. The catheter is then further advanced until it occludes a pulmonary vessel ideally in West Zone 3 at which point the Pulmonary Capillary Wedge Pressure (PCWP) is displayed. This is also known as the Pulmonary Artery Occlusion Pressure (PAOP) and can be used as a surrogate for left ventricular pre-load as at the end of diastole when the mitral valve is open, there is an uninterrupted column of blood between the left ventricle and the PAC

transducer. However, measurement may be inaccurate where the assumption of an uninterrupted column of blood is flawed such as in patients with mitral valve disease or pulmonary vessel disease or if there is decreased left ventricular compliance which would not be reflected in the PAOP.

Thermodilution using the PAC can be used to calculate cardiac output. It involves the injection of a known volume of cold fluid through the proximal port of the PAC into the superior vena cava. A thermistor at the distal port detects the change in temperature in the pulmonary artery. The cardiac output of the right heart can be calculated by calculating the area under a curve of temperature against time, this is assumed to be equal to that of the left heart(103).

Pre-optimisation

Improved oxygen delivery guided by the pulmonary artery catheter (PAC) has been shown to improve post-operative mortality in a series of 159 high-risk patients (104). Subjects were randomised pre-operatively to receive a protocol to achieve a supra-normal oxygen delivery of >600ml/min/m^2. This target was derived from the median values of survivors of critical surgical illness from previous studies (99) (105) or standard care. The therapeutic goals for the protocol group were a cardiac output >4.5l/min, DO_2 >600ml/min m^2 and VO_2 >170 ml/min m^2 and this was achieved using a combination of fluids, packed red blood cells, inotropes, and vasopressors. Control group care consisted of standard therapy to maintain arterial and venous pressures.

There was a significant reduction in mortality in patients who received the intervention using the study protocol compared to standard therapy (4% v 28% P<0.02). In addition there was a reduction in complications in patients in the protocol group, with both the proportion of and mean number of complications being lowest in the PA-protocol group (p<0.05).

Increasing oxygen delivery using dopexamine (a dopamine analogue) has been shown to reduce mortality and complications *(106)*. Dopexamine acts at beta 2 and DA_1 receptors to produce a peripheral vasodilation and an increased cardiac index but does not increase myocardial oxygen consumption significantly. In this study 81 patients were recruited pre-operatively, all of these patients received pre-operative cardiac output optimisation with colloid guided using a pulmonary artery catheter, however the intervention group had oxygen delivery maintained at 600ml/min/m2 using an infusion of dopexamine started pre-operatively, and continued post-operatively until serum lactate was <1.5mmol/l. There was a significant reduction in mortality in the intervention group (7 vs. 23.7% p=0.041), and a reduction in the number of complications was also seen (mean complications per patient 0.70 v 1.45 p=0.009).

A study by Wilson *and colleagues*(107) in 138 patients undergoing major abdominal surgery compared pre-optimisation of oxygen delivery using adrenaline and dopexamine to standard care. Patients were randomised into 3 groups: a control group and 2 intervention arms for a protocol of pre-operative optimisation using a dopexamine or adrenaline infusion to a targeted DO_2. Patients in the intervention

groups were admitted pre-operatively to intensive care or high dependency and a PAC was inserted. Subjects received 1 litre of Hartman's solution followed by 4.5% human albumin solution, which was infused until PAOP was 12mmHg, following which an infusion of adrenaline or dopexamine was commenced with the rate increased until a target DO_2 of 600ml/min/m^2 was achieved. Pre-optimisation significantly improved mortality in the optimisation groups compared to control care (3% v 17% p= 0.07). There was also a significant decrease in morbidity in subjects who received dopexamine group (OR dopexamine v adrenaline 0.30, 95% CI 0.11-0.50, dopexamine v controls 0.21, 95% CI 0.02- 0.41), but there was no significant difference in morbidity between the adrenaline group and the controls (OR 0.09, 95% CI -0.11 – 0.28). In addition length of hospital stay was significantly lower in the dopexamine group (mean bed days per patient dopexamine 13 v adrenaline 19, p= 0.02 v control 22, p=0.001). However, it is to be noted that 16 patients in the control group were admitted directly to the ward post-operatively compared to only one adrenaline group patient (who had an inoperable lesion), and none in the dopexamine group. Therefore standards of post-operative care may be a confounding factor. In addition there was no true blinding between the control and intervention groups, even though blinding occurred between the adrenaline and dopexamine groups.

In contrast to the above mentioned studies a larger later study by Sandham and colleagues (108) of 1994 patients showed no benefit of using a pulmonary artery catheter to optimise oxygen delivery . In this study patients were randomised patients to receive standard care without a PAC or to an intervention arm where

they received fluid, inotropes, vasodilators or vasopressors and blood to maintain oxygen delivery 550 – 600 ml/m^2, cardiac index 3.5-4.5ml/min/m^2, MAP 70mmHg, PAOP 18mmHg, HR <120bmp and haematocrit>27%. There was no difference in in-hospital mortality (PAC 7.8 v standard 7.7% p=0.93) and there was similar one-year survival (RR 1.1 CI 0.9-1.4). Morbidity was similar in both groups except for the incidence of pulmonary embolus which was 0.8% in the intervention group compared to 0% events in the controls (p=0.004). However, although this is a large multi-centre study its results are confounded by poor adherence to protocol with goals (Table 17) for cardiac index and oxygen delivery not met in a large proportion of patients. Further the study was carried out over a period of 9 years a factor that could have introduced bias by a Hawthorne effect.

Target	% target met pre-operatively	% target met post-operatively
Cardiac index	18.6	79.0
Oxygen Delivery	21.0	62.9

Table 17 Proportion of patients where targets for PAC directed goals met, data from Sandham and colleagues (108)

Berlauk *and colleagues*(109) in a study of vascular patients used a combination of inotropes, vasodilators and fluids to achieve haemodynamic endpoints of a pulmonary artery wedge pressure of 8-14mmHg, CI ≥ 2.8l/min/m^2 and a SVR ≤1100 dyne-sec/cm^{-5}, in two groups who received the intervention either 12 or 3 hours prior to surgery. These groups were compared against a control group who did not receive a pre-operative PAC. Mortality was significantly improved in the

intervention groups compared to the controls (1.5% v 9.5% p=0.08), and there were significantly less complications (16.2% v 42.9%). A similar protocol used by Bender *and colleagues*(110) to achieve the same haemodynamic targets showed no difference in mortality (1 death in each group) or post-operative complications (7 in each group) in a study of 104 vascular patients. However the very low mortality rates in the later study compared to 9.5% in the control group of the Berlauk's study(109) suggest that a disparate population was studied and raises the question whether Bender's (110)population had a lower risk profile.

Intraoperative optimisation

An intra-operative protocol for goal-directed therapy using the pulmonary artery catheter was studied by Lobo *and colleagues*(111) which randomised patients to supra-normal DO_2 >600ml/min/m2 with a CI >4.5l/min, compared to a control group for whom DO_2 was targeted between 520-600ml/min/m2. There was a significant reduction in 60 day mortality between control and intervention groups (50% v 15.7% RR 0.32, 95%CI 0.101-0.984) leading to the study being terminated early, however, their difference in mortality at 28 days was not significant (33% v 15% RR 0.47, 95% CI 0.139-1.616). Control group mortality was higher than that seen in other similar studies, 35% of patients did not achieve their targets and there was no significant difference in amount of fluid administered intra-operatively, which makes the positive result seem less conclusive compared to pre-operative PAC studies, however this has contributed to the lack of consensus on the usefulness of invasive PAC derived targets for optimisation.

Whilst some protocols using the PAC to target oxygen delivery successfully showed a decrease in mortality in patients undergoing major abdominal surgery, in recent years there has been a decline in its use both due to the development of less invasive methods of cardiac output monitoring and controversy over complication rates related to use this highly invasive technique. A 1996 observational cohort study by Connors and colleagues (112) in critically ill patients showed that in 1008 matched pairs there was an increased mortality and length of critical care stay in patients who had undergone right heart catheterisation (RHC) in the first 24 hours of admission to intensive care, compared to those who had not (Table 18). However, although this study was risk adjusted, with propensity scores used to match patients with regard to how unwell the patients were, it was not randomised and there was no observer blinding.

Survival Interval	**OR (95%CI)**
30 days	1.24 (1.03-1.49)
60 days	1.26 (1.05-1.52)
180 days	1.27 (1.06-1.52)

Table 18 Risk of death in patients who had RHC compared to those who did not adapted from Connors and colleagues (112)

However, the subsequent 2005 PAC-MAN trial (113) showed no increase in mortality in ICU patients randomised to undergo pulmonary artery catheterisation. This large study of 1041 intensive care patients showed no significant difference in in-hospital mortality (68% v 66% p=0.39) or 28 day mortality (62% v 60% p=0.52), further, no

difference in ICU or hospital length of stay or in days of organ support. However, it should be noted that the critically ill population are a different population from those undergoing elective surgery and outcomes may not be generalisable between the two. It is important to note that within this study there was a 10% rate of insertion-related complications – mainly related to gaining central venous access, which could occur in the elective surgical patient. The incidence of complications as experienced in this study (Table 19) make it desirable to use less invasive forms of monitoring in low risk patients, especially in the context of evidence other studies (108, 110) which showed no mortality benefit in patients who underwent PAC guided pre-optimisation.

Complication related to PAC insertion	**Number** **(% of total insertions)**
Haematoma at insertion site	17 (4)
Arterial puncture	16 (3)
Arrhythmias needing treatment within 1hour of insertion	16 (3) Including 1 cardiac arrest
Pneumothorax	2
Haemothorax	1
Lost guide-wire needing retrieval	2

Table 19 Complications related to PAC insertion adapted from Harvey and colleagues (113)

1.3.3 Minimally -invasive monitoring

Less invasive methods of monitoring cardiac output have been developed for use in patients where PAC insertion has not been clinically indicated. These include

oesophageal Doppler and arterial waveform analysis methods. The use of these devices in the delivery of goal directed fluid therapy have been widely studied in the intra-operative period.

Oesophageal Doppler

Less invasive than the pulmonary artery catheter, the technique of Oesophageal Doppler Monitoring (ODM) is based on the Doppler effect where ultrasound waves emitted by a transducer are reflected by moving red blood cells with a change in frequency proportional to the velocity of flow towards the detector. The oesophageal Doppler monitor uses this signal to display a waveform representing the flow of blood in the descending thoracic aorta. The probe is used to obtain a velocity-time waveform, and the area under the curve of this velocity-time waveform is called the stroke distance, that is the distance blood in the aorta will travel with each contraction of the left ventricle. The cross-sectional area of the aorta is estimated using a normogram based on the patient's age, sex, height and weight. When stroke distance and the cross-sectional area are multiplied this gives a measure of stroke volume (114).

A strength of oesophageal Doppler is that unlike some other minimally invasive monitors it measures a number of different parameters. In addition to stroke distance measurements of peak velocity and flow time are also calculated .The flow time is the duration that blood flows forward in the aorta, and needs to be corrected for heart rate to give the corrected flow time (FTc), which is an indicator of systemic

vascular resistance. The normal range for FTc is 330-360ms, and a value below this range is often used as an indicator of hypovolaemia (115).

ODM is limited by the assumption of a fixed blood flow distributed between the upper and lower body, with a split of 70% to the descending aorta. Changes in haemodynamic distribution such as due to the presence of epidural anaesthesia (116), or cross clamping of the aorta (117) lead to under or over-estimation of cardiac output. Further, the normogram assumes that aortic cross-sectional area is constant rather than dynamic whereas it has been shown that cross-sectional area can vary with the cardiac cycle with fluctuations of up to 1.2mm (114). One version of the oesophageal Doppler Monitor (Hemisonic 100) utilises M-mode ultrasound to directly measure aortic diameter instead of using the normogram, however concerns exist on the accuracy as a discrepancy of 2mm on measurement could introduce a 16% variation in cross-sectional area(114). Finally limitations exist due to inter-user variations in placement of the Doppler probe as shown in a study by Valtier and colleagues (118) where there was an 8% variation in cardiac output measured. Further a degree of operator training is required in order to reliably produce a clear Doppler waveform with a cardiac output within 15% of that elucidated from trans-thoracic Doppler (119).

A systematic review by Dark and Singer (120) looked at 11 papers involving a total of 314 patients cardiac output data from oesophageal Doppler monitoring, and compared this to simultaneous measurements of cardiac output derived from the pulmonary artery catheterisation thermodilution. On review of paired

measurements from PAC or ODM, the percentage of values within the limits of 15% of mean bias were used to calculate percentage of clinical agreement (PCA). On comparison of PAC thermodilution compared to cardiac output from ODM the median PCA was 52% (IQR 42-69%). However, if trend monitoring was used instead of absolute values, then agreement was higher with a mean PCA of 86% (IQR 55-93%), suggesting cardiac output values derived from ODM are more useful in following trends rather than as an absolute indicator of cardiac output.

Goal directed fluid therapy using the oesophageal Doppler has been endorsed by National Institute for Health and Clinical Excellence (NICE) for fluid optimisation (121), and is the most commonly used technology in the delivery of goal directed fluid therapy in the UK (122). The oesophageal Doppler allows continuous monitoring of trends in cardiac output, and allows real-time assessment of the effect of fluid therapy on stroke volume.

Following an initial study showing improved post-operative outcomes in orthopaedic patients where oesophageal Doppler was used to target fluid therapy (123) there have been many studies investigating its use in major abdominal surgery.

A study by Gan (124) looking at 100 relatively low risk (majority ASA 1 or 2, mean age <60 years) patients undergoing elective general, urological or gynaecological surgery, randomised patients into a control group which received fluids targeted on variation in heart rate, systolic blood pressure, central venous pressure and urine output, and an intervention group which received boluses of hydroxyethyl starch targeted to maximise stroke volume within limits maintained by corrected flow time,

patients then received further boluses if stroke volume fell by greater than10% or FTC decreased below 0.35 seconds . Patients in the intervention group received significantly more colloid (847 ml v 282 ml, P<0.01) but similar volumes of crystalloid infusion (4406 v 4375ml). Patients in the intervention group had a significantly shorter length of stay (mean 5 v 7 days P<0.003), and a shorter time to return to oral diet (mean 3 v 5 days p<0.01). There was however, no significant difference in complications except for a reduction in the occurrence of post-operative nausea and vomiting (7 v 18 cases p<0.05). However, it is noted that the majority of patients (69%) were from a gynaecological or urological background rather than general surgical, and further there was no indication of how many of the general surgical patients were colorectal cases.

Additional studies have shown improved post-operative gastrointestinal function in patients who received intra-operative fluid optimisation using the oesophageal Doppler. Wakeling (125) in a trial of 128 elective colorectal patients showed a reduction in gastrointestinal complications in patients who received goal directed fluid therapy targeted using stroke volume and central venous pressure, compared to patients who received fluid targeted to standard cardiovascular and central venous pressure parameters (45.3% v 14.1% p<0.001). An associated reduction in time that patients took to open bowel (median 4 v 5 days p=0.014), and resume full diet (median 6 v 7 days p<0.001) was also reported.

The improvement in complication rates and earlier return to gastric function in patients who are fluid optimised is reinforced in work by Conway and colleagues (126). Fifty seven patients undergoing bowel surgery received fluid therapy at the discretion of the anaesthetist, in addition patients in the intervention group received initial stroke volume maximisation through IV colloid administration, followed by colloid boluses of 3ml/kg if stroke volume decreased by 10% or if FTC <0.35 secs. This study showed a reduction in critical care admissions in the intervention group (0 v 5 p=0.02), however the difference in post-operative complications, hospital length of stay and return to oral diet did not reach statistical significance. It is to be noted however, although the patients in the intervention group did receive significantly more colloid than the control group (28 v 19.4 ml/kg p=0.02), the difference in the total volume of fluid infused did not reach statistical significance (55.2 v 64.6 ml/kg).

In contrast a larger study by Noblett (14) of 108 elective colorectal patients using an algorithm similar to that used by Gan *and colleagues(124)* where stroke volume and corrected flow time were used to target fluid therapy, did show a reduction in length of stay (7 v 9 days p=0.005), faster return to tolerating oral diet (2 v 4 days p=0.029) and reduced complications (2% v 15% p=0.043) in the intervention group. This suggests that the Conway study may have possibly been underpowered. Benefits of using Doppler guided fluid therapy on reducing the inflammatory response experienced in the peri-operative period were shown, with post-operative interleukin-6 levels being significantly lower in the intervention group (mean 673.1 v 369.4 pg/ml, p=0.039), which could reflect that less patients required vasopressor support in the intervention group (14 v 26 patients p=0.015). Interestingly there was

no significant difference in fluid volumes administered (crystalloid 1209 v 1340 ml, p=0.397, colloid 2625 v 2298ml, p=0.077), suggesting that the outcome benefit may lie in timing of fluid administration rather than absolute volume as more than 50% of trial fluid was administered in the first quarter of the operation.

Challand and colleagues (127) used an algorithm targeting percentage change in stroke volume with boluses of colloid in patients randomised to the intervention group. Both groups received maintenance fluid of 10ml/kg/hour Hartman's solution. This algorithm, an updated one, as recommended by the manufacturers of the ODM, Deltex medical (115), did not include FTc in contrast to previous studies described above. Whilst the study included both high and low risk patients, there was separate subgroup analysis of a cohort of 121 low risk patients with anaerobic threshold >11 ml/kg/min and therefore considered low risk. Analysis of this subgroup showed a significantly longer hospital length of stay in the intervention group (7.0 v 4.7 days p=0.01) suggesting that oesophageal Doppler targeted goal directed therapy could be deleterious in aerobically fit individuals. However, it is to be noted that there was no significant difference in time taken to tolerate oral diet (1.7 v 1.6 days p=0.41) or the number of serious post-operative complications (6 v 6 p=0.32). Of importance, is that the total volume of IV fluid administered (mean 5309 ml) was considerably higher than in other studies, with patients in the intervention group receiving a mean 1360mls administered in protocol driven boluses in addition to the maintenance fluid received as with the control group and this could have caused occult fluid overload in this fit group of patients contributing to the increased length of stay. In previous studies described above, a high FTC would indicate a longer time

period to eject blood, indicating a well-filled patient, this newer algorithm, does not include this indicator, which would prevent stroke volume maximisation from reaching a deleterious level where overstretching of myocytes (to the right of the starling curve) leads to a reduced cardiac output and increasing risk of fluid overload, thereby increasing their risk of peri-operative morbidity as described in the 'J-shaped curve' postulated by Bellamy (128). This study also raises the question, whether standard care for low risk patients was good enough to minimise the benefits of goal directed therapy, however, this may be institution specific, as non high-risk patients have been shown to benefit from goal directed fluid therapy as shown by a lower incidence of post-operative complications in a recent systematic review (129).

A study of 64 patients of mixed risk status by Sennagore and colleagues (130) using a similar protocol to Challand (127) also showed a longer length of stay amongst patients who received goal directed therapy compared to patients receiving standard care.

Therefore despite its endorsement by NICE, there is a lack of consensus on how oesophageal Doppler should be used to target goal directed therapy in the population of low-risk colorectal patients. Protocols without an inbuilt stop signal to indicate a well-filled patient may in fact prove to be detrimental to post-operative recovery, due to overfilling. Other minimally invasive technologies with less complex protocols may prove more beneficial in this particular population.

Pulse Contour and Pulse Power Analysis

Devices that analyse the arterial waveform can be used to determine cardiac output based on the physiological concept that the arterial pressure waveform is dependent on stroke volume.

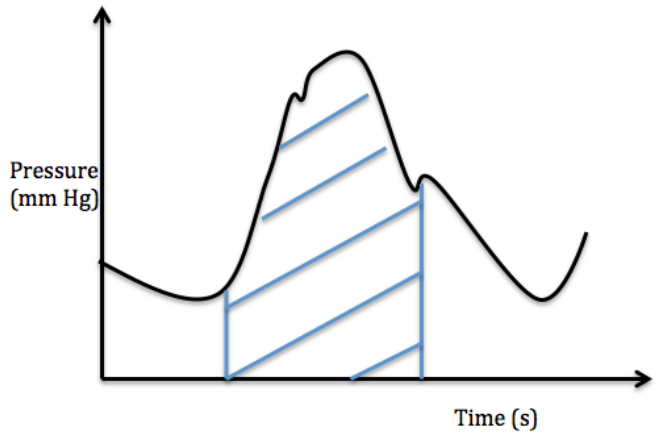

Figure 2 Arterial waveform, with area under curve used to determine stroke volume

In pulse contour analysis integration of the area under the curve of a pressure-time curve (figure 2) can be used to determine stroke volume and thereby cardiac output, however, as this is also affected by arterial compliance and tone correction is required either through external calibration (using thermodilution or lithium dilution) or by the use of a normogram. Pulse power analysis estimates cardiac output using an algorithm based on the law of conservation of mass, where the net power change in the system is the difference between the amount of blood entering the systemic circulation (SV) and the amount leaving peripherally. Use of a standard algorithm means that in vasodilated states stroke volume calculations may be

inaccurate as it does not compensate for changes in vascular tone as a result of inflammatory markers or epidural related sympathetic blockade.

There are three commonly used systems using algorithms based on pulse contour or power analysis, the PiCCO (Pulsion, Munich, Germany), the Flotrac/Vigileo (Edwards Lifesciences, Irvine, USA), and the LiDCO (LiDCO, Cambridge, UK).

Clinical use of these monitors in assessing fluid responsiveness uses variation in stroke volume, changes in the left ventricular stroke volume occurring with the respiratory cycle allow these monitors to indicate fluid responsiveness without using a fluid challenge. As shown by Jardin and colleagues (131) in patients ventilated mechanically with intermittent positive pressure there is a transient increase in left ventricular stroke volume output during lung inflation followed by a fall during expiration. This is because of the rise in pleural pressure and transpulmonary pressure on inspiration with a positive pressure breath (figure 3). These lead to a decreased right ventricular (RV) preload and increased RV afterload, resulting in a reduced right ventricular stroke volume. This leads to a reduced left ventricular (LV) preload resulting in a decreased LV stroke volume, however, this occurs in the expiratory phase due to the time taken for blood to transit through the pulmonary circulation (2-3 heart beats). In the inspiratory phase there is in fact an increased LV stroke volume due to raised pleural and transpulmonary pressures causing an increased LV preload and decreased LV afterload. Therefore LV stroke volume is maximal at the end of the inspiratory phase and least during the expiratory phase (132). The difference between the maximal stroke volume at the end of inspiration

and the minimal at the end of expiration is called stroke volume variation and is a predictor of fluid responsiveness – with each breath acting effectively as a fluid challenge. These cyclical variations in stroke volume are reflected by variations in pulse pressure with inspiration and expiration, which are referred to as pulse pressure variation.

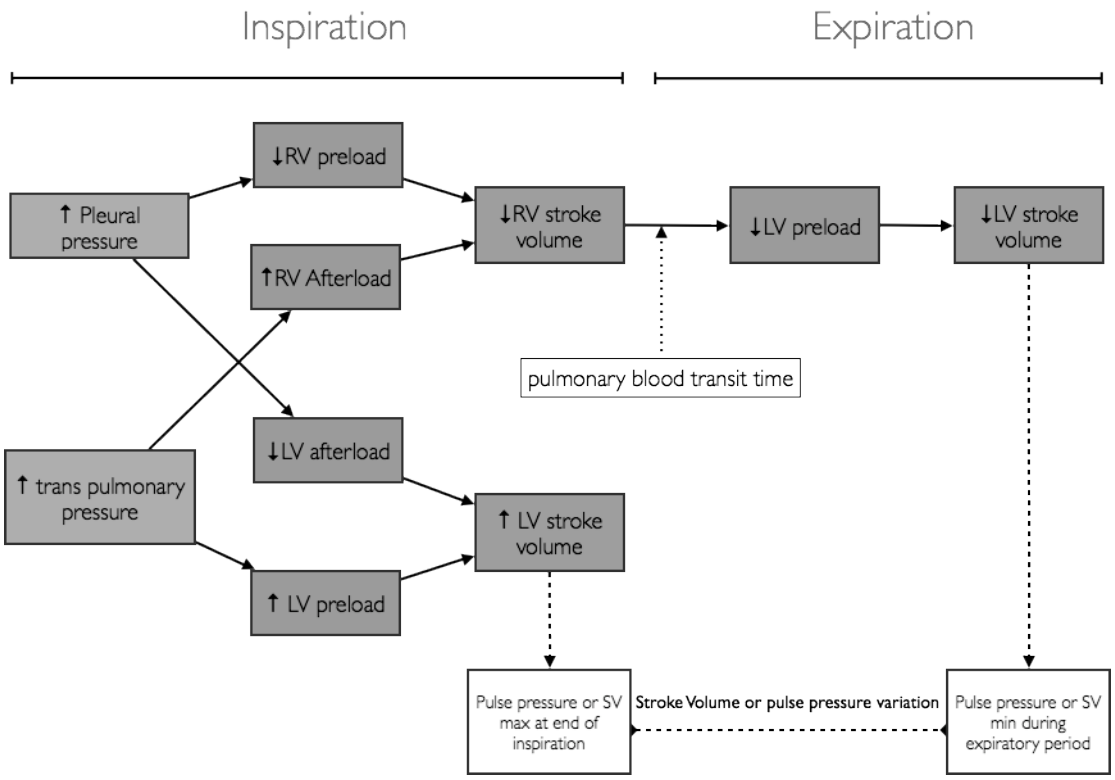

Figure 3 Haemodynamic variation with positive pressure ventilation leading to cyclical changes in stroke volume

Pulse pressure variation (133)and stroke volume variation (134), have been shown to be predictive of fluid responsiveness in patients undergoing major surgery. In a study by Kramer and colleagues (133) of patients receiving a 500ml fluid bolus CVP and PAOP were not predictive of fluid responsiveness, whereas responders, who increased their cardiac output by ≥12%, had a significantly higher PPV and systolic

pressure variation. A PPV of ≥ 11% was found to predict those individuals who were responders with a sensitivity if 100% and a specificity of 93%.

In a study of 25 patients undergoing coronary artery bypass grafting comparison of readings of PPV (calculated manually) and Stroke Volume Variation (SVV) as measured by the Flotrac/Vigileo (version 1.10) Both PPV and SVV were higher in patients who responded, with an increase in cardiac index ≥ 15%, to volume expansion (15 v 6%, 15 v 7%, $p<0.01$). ROC curve analysis showed that PPV and SVV were better at predicting fluid responsiveness than CVP, pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) (Table 20) ($p<0.05$), there was no significant difference between the predictive ability of SVV and PPV ($p=0.78$).

Measurement	**AUC**
PPV	0.85
SVV	0.53
CVP	0.38
PCWP	0.30
CI	0.12

Table 20 Comparison of predictive ability of measurements for fluid responsiveness adapted from Cannesson and colleagues (134)

Hofer and colleagues (135) used a fluid shift manoeuvre (angling the operating table between 30 degrees head up and down) in 40 cardiac surgery patients identified

optimal SVV thresholds were identified ass 9.6% for FloTrac and 12.1% for PiCCO in order to predict a change in SVV post-manoeuvre.

However, there appears to be a range of values where PPV and SVV may be inconclusive as a predictor for fluid responsiveness, termed the 'gray zone' Cannesson and colleagues (136) identified a PPV range of 9-13% to be inconclusive in predicting a change in cardiac output with an equal proportion of patients responding or not responding to a fluid challenge.

Comparison of the ability of LIDCO rapid and Flotrac/Vigileo with Oesophageal Doppler to predict fluid responsiveness in patients undergoing major vascular, urological and bariatric surgery by Davies *and colleagues*(137) indicates mixed results. Stroke volume variation as calculated by the LIDCO rapid had a weak predictive ability (ROC AUC 0.64, 95% CI 0.52-0.78) for predicting a rise in 10% rise in stroke volume as measured by oesophageal Doppler in response to a fluid bolus. SVV as detected by Flotrac/Vigileo was not predictive of fluid responsiveness with ROC AUC 0.57 (0.43-0.72). There was correlation between SVV as measured by LIDCO rapid and Flotrac/Vigileo with 88% concordance. However, concordance with oesophageal Doppler was poor (LIDCO rapid 57% and Flotrac/Vigileo 45%). Whilst poor concordance with oesophageal Doppler measurements may be due to poor specificity of Oesophageal Doppler, a high percentage error between LIDCO rapid and Flotrac/Vigileo indicates that more work is needed to determine the accuracy of these methods as other studies have shown lack of concordance in stroke volume estimation between these methods (138) Oesophageal Doppler is often used as a

comparator as it has a largest body of evidence in improving outcomes in patient groups undergoing elective surgery. Later versions of the Flo-trac/Vigileo algorithm have shown improvement in accuracy of stroke volume estimation, with a recent systematic review (139) showing an improved percentage error rate (<30%) in hypo or normo-dynamic states when using the a third generation version (3.02) compared to other available dynamic indices including thermodilution.

Cardiac output and fluid responsiveness derived from arterial waveform analysis is being used to deliver goal directed therapy, and a there is a reasonable body of evidence that the use of this technology in a protocolised fashion improves perioperative outcomes. A meta-analysis by Benes and colleagues (140) has shown goal directed fluid therapy based on protocols using PPV and SVV have improved post-operative outcomes, with a statistically significant reduction in post-operative morbidity (OR 0.51, 95% CI 0.34-0.75) and length of stay in intensive care units (mean difference -0.75 days 95% CI -1.37 to -0.12 days). However there was no significant difference in hospital length of stay (mean difference -1.33 days 95% CI – 2.90 to 0.23 days).

The recent large multi-centre OPTIMISE trial (91) of 734 patients undergoing major gastrointestinal surgery failed to show a significant difference in post-operative outcome amongst high risk patients who were fluid optimised using arterial pulse contour analysis using LiDCO rapid. Whilst post-operative complication rate (36.6 v 43.4%) and 30-day mortality (4.9 v 6.5%) were lower in the intervention group, these reductions in risk failed to reach statistical significance. However, this may reflect an

under-powering of the study, with a lower than expected event rate in the control group alongside a cross-over use of cardiac output monitoring within 'usual care' for the controls. Interestingly though if the first 10 patients were removed from analysis as is presented in the supplementary data there was a significant difference in morbidity and mortality (OR 0.59, 95% CI 0.41-0.84) suggesting that there is a learning effect, with improved outcomes in the hands of those experienced at using the protocol, meaning that the lack of a significant difference in outcome may have been due to how the protocol was applied rather than the technology itself.

A single study has focused on the value of post-operative haemodynamic optimisation in major non-cardiac surgery. A protocol used by Pearse and colleagues (141) optimised delivery in patients after in the first eight hours following major general surgery to greater than 600ml/min/m2 using goal directed therapy using calibrated pulse power analysis (LiDCO plus) targeting stroke volume and dopexamine infusion. A significantly smaller number of patients developed complications in the intervention group (44% v 68% p=0.003) and this was associated with a reduction in median post-operative hospital length of stay (11 v 14 days p=0.001). This study suggests that post-operative protocols may improve outcomes, however, it would require a critical care admission to provide this protocol.

Limitation exists in using respiratory variation in stroke volume, pulse pressure and plethysmographic waveform for predicting fluid responsiveness in that, patients are required to be mechanically ventilated with positive pressure. Heenen *and*

colleagues(142)in a study of 22 spontaneously breathing patients showed that PPV did not reliably predict fluid responsiveness. This may be because variation in intrathoracic volume is not regular during spontaneous ventilation(143).

Secondarily SVV, PPV and ΔPOP may become inaccurate if low tidal volumes are used meaning that the change in intrapleural pressure is not enough to induce a change in pulmonary venous flow and impact on ventricular stroke volume. A 2005 study by DeBacker and colleagues (144) looked at mechanically ventilated patients receiving tidal volumes of less than 8ml/kg requiring volume expansion. In patients with lower tidal volumes (i.e. <8ml/kg) a threshold PPV of 12% had a lower sensitivity (39% v 88%) and specificity (65% v 89%) for fluid responsiveness compared to those who had tidal volumes greater than 8ml/kg.

Whilst the benefit of using pulse contour and pulse power analysis has been shown in a small number of trials in high risk patients, there remains questions regarding uncalibrated systems. Whilst later versions of Flotrac/Vigileo show improved performance, validation studies for LIDCO rapid remain lacking.

Complications following arterial cannulation include permanent ischaemic damage, sepsis, local infection, pseudo-aneurysm, haematoma and bleeding (145). Use of the oesophageal Doppler probes is not without risk either, with case reports existing of tearing of the oesophageal mucosa and subsequent haematoma formation(146). Therefore the use of non-invasive monitoring is desirable as it reduces exposure of patients to these risks, and reduces the need for unnecessary procedures yet

provides information on fluid responsiveness allowing patients to benefit from an individualised approach to fluid management.

In low risk patients who do not require arterial catheter placement for blood pressure monitoring or arterial blood sampling, the development of the use of the plethysmograph variability index as a target for fluid therapy offers a non-invasive alternative that avoids risks of invasive monitoring and reduces the expense of consumables for arterial monitoring, whilst allowing patients to benefit from goal directed fluid therapy.

1.3.4 Non-invasive monitoring

Plethysmograph Variability Index

Pulse oximetry is routinely used to monitor oxygen saturation of haemoglobin., and is traditionally measured using a probe placed at a peripheral site. Two light emitting diodes within the probe emit a high intensity monochromatic signal which is detected on the other side of the tissue by a photodetector. The absorption of light as it travels through the digit is described by the Beer-Lambert law and varies depending on the arterial pulsation. There is a difference in the absorption spectra of oxyhaemoglobin with de-oxyhaemoglobin which is utilised by the pulse-oximter to calculate the relative proportions of oxyhaemoglobin and de-oxyhaemoglobin. An electronic processor analyses pulsatile changes resulting from changes in arterial blood flow to produce a pulsatile waveform.

The variation in the amplitude of the plethysmographic waveform (**Δ**POP) has been shown to predict fluid responsiveness in mechanically ventilated patients. In a study of 22 mechanically ventilated ICU patients that mean baseline **Δ**POP was significantly higher in patients who responded to a fluid bolus of 500mls by increasing their cardiac index when measured by thermodilution using a PAC (21v12% P=0.034)(147).

The Pleth Variability Index (PVI) is an algorithm that allows the continuous calculation of **Δ**POP providing a numerical value. PVI measures the percentage changes in perfusion index (PI) over time, and is described by the equation

PVI= [(PImax-PImin)]/PImax] x 100% (148)

The PI is the percentage of light absorbed during an arterial pulsation relative to the total amount of light absorbed and is described by the equation PI = (AC/DC) x 100% (148).

Cannesson and colleagues (149) in a study of 25 patients undergoing coronary artery bypass grafting showed a good correlation between **Δ**POP and PVI prior to, and following volume expansion ($r=0.97$ $p<0.01$). Both **Δ**POP and PVI were shown to be higher in patients who responded to a fluid bolus with an increase in cardiac index >15% (responders) when compared to non-responders (19 v 9% and 18 v 8%, $P<0.01$). Baseline **Δ**POP and PVI were shown to be related to the percentage change in cardiac index following volume expansion ($r=0.69$ and $r=0.67$, $p<0.01$). Using ROC

curve analysis a PVI >14% differentiated between responders and non-responders with a 81% sensitivity and a 100% specificity.

PVI has been shown to predict fluid responsiveness in low risk patients undergoing colorectal surgery in an observational trial of 25 patients (148). In this study an initial 500ml bolus was given prior to commencement of surgery followed by 250 ml colloid boluses if there was a 10% decrease in stroke volume as measured by the oesophageal Doppler. Mean PVI was noted to be significantly higher in patients who responded to fluid boluses with a 10% increase in stroke volume as detected by oesophageal Doppler compared to those who failed to increase their stroke volume (Table 21). In this cohort of patients ROC curve analysis showed that a PVI cut-off of 10% for predicting intraoperative fluid responsiveness, with an AUC of 0.71 (95%CI 0.57 – 0.85), with a specificity of 67% and sensitivity of 65%. This was not as good as its predictive ability for fluid responsiveness to an initial bolus at the beginning of surgery where AUC was 0.96 (0.88-1.00) with 86% sensitivity and 100% specificity. This may reflect changes in vascular tone during the intraoperative period due to the onset of sympathetic blockade with the establishment of epidural analgesia or the use of vasopressor therapy.

	>10% rise in SV Mean PVI (%)	**<10% rise in SV Mean PVI (%)**	**P-value**
Initial 500 ml bolus colloid	15	7	0.012
Intraoperative 250ml boluses colloid	13	9	0.006

Table 21 Mean PVI and stroke volue changes in patients receivbing fluid boluses undergoing colorectal surgery. Adapted from Hood (148)

PVI guided goal directed therapy may improve post-operative outcome compared to standard care as suggested by results from a randomised control trial by Forget and colleagues *(150)*, where 82 patients of mixed risk levels were randomised to either PVI targeted goal directed fluid therapy or standard care. Patients in the both groups received an initial 500ml bolus of crystalloid, following which patients in the intervention group received a 2ml/kg/hour infusion of crystalloid with boluses of colloid if the PVI rose to greater than 13%. Patients in the control group received 4-8 ml/kg/hour with colloid boluses if there was acute blood loss, a decreased MAP or CVP. Patients in the intervention group received a significantly greater volume of fluid overall intra-operatively (2394 v 2918 mls p=0.049), and there was a significant reduction in mean intra-operative and post-operative serum lactate (intra-operative 1.2 v 1.6 mmol/l p=0.04, 24 hours 1.4 v 1.8 mmol/l p=0.02, 48 hours 1.2 v 1.4 mmol/l p=0.03) suggesting a possible reduction in the peri-operative inflammatory process, and improved tissue perfusion. Despite these lower lactate levels, there was no significant decrease in length of stay (15.1 v 16.0 days p=0.78) or in the incidence of complications. But it is to be noted that the patients underwent a variety of different upper and lower gastrointestinal operations including oesophagectomies and pancreatectomies, patients undergoing these higher risk procedures may benefit from more invasive monitoring to improve their post-operative outcomes, in contrast to patients undergoing less high-risk procedures.

As with SVV and PPV, ΔPOP and PVI are limited by the need for the patient to be mechanically ventilated with an adequate tidal volume. As it is based on the same

principles of variation in venous return to the heart with inspiration and expiration, the technology relies on a consistent depth of ventilation at a volume adequate to impact on venous return to the heart from the pulmonary circulation. Further as PVI is reliant on adequacy of peripheral perfusion, its use is limited in the shocked, peripherally shut down patient.

Other technologies are being developed to deliver non-invasive monitoring for cardiac output. These include ClearSight (Edwards Lifesciences, Irvine, CA, USA) which uses an algorithm based on analysis of the finger arterial pressure waveform, and the non-invasive CO monitor (NICOM) (Cheetah Medical, Vancouver, WA, USA). NICOM is a bioreactance monitor that can be used to estimate stroke volume and stroke volume variation. A recently published study (151) showed that goal directed fluid therapy as targeted by NICOM had similar post-operative outcomes in ASA I-III patients undergoing elective colorectal surgery to stroke volume maximisation using Oesophageal Doppler. More trial fluid was given to patients in the NICOM group (1370 v 1076 mls $p<0.05$) compared to the oesophageal Doppler groups. However, it is noted that there was no blinding for outcome measurement in this trial as it was carried out in two phases with the first 50 patients recruited being in the OD group and subsequent patients in the NICOM group.

Currently there are no published outcome studies looking at PVI. Further investigations are required in order to evaluate if goal-directed therapy targeted using variations in the plethysmograph index or other non-invasive technologies can

provide a clinically significant benefit to patients and whether in low risk patients it offers an equivalent non-invasive alternative method to more invasive technologies.

Whilst goal directed therapy has been shown to benefit patients by its use through out the peri-operative period, pre-operative and post-operative protocols are less desirable than intra-operative protocols for low-risk patients as they require elective critical care admissions, which would not otherwise be necessary in this patient population. Therefore in the current climate with limited access to critical care beds these protocols may prove less cost-effective than an intra-operative protocol which would allow patients to be discharged to ward level care. Development of less invasive technologies has allowed the use of goal directed therapy without the need for highly invasive procedures. The development of PVI allows the use of a completely non-invasive technology in low risk patients, avoiding the need for insertion of invasive probes or catheters. Controversies exist in the use of goal directed therapy in these patients with Challand and colleagues (127) suggesting that oesophageal Doppler targeted stroke volume maximisation could cause harm in low risk patients. Further as suggested by the OPTIMISE (91) trial the effect of the protocol and operator may need to be separated from the benefits conferred by the use of technology. Therefore further investigations are required to determine the optimal technology to be used in low risk patients and how the information gained from these technologies should be applied.

1.4 Post-operative outcome measures

In order to evaluate the clinical significance of different interventions during the intra-operative period it is necessary to analyse post-operative outcome. Whilst mortality is commonly focused upon, its low event rate in elective surgery, especially amongst low risk patients, means that its usefulness is limited as an outcome measure. Presence of post-operative complications leading to morbidity is clinically important due to its association with long-term mortality(10). Finally hospital length of stay is relevant both as a reflection on the presence of morbidity and also for economic reasons, with increased bed-occupancy being detrimental for patient throughput and cost-effectiveness in a system of socialised healthcare.

1.4.1 Mortality

As an outcome mortality data is simple to obtain, it is a binary value with no inter-operator variability. In elective surgery however, its event rate is low and hence it has limited applicability except in large cohorts, and requires a large treatment effect to show differences in treatment interventions. Data from the National Bowel Cancer Audit 2013 showed an overall mortality rate of 2.9% at 30 days and 4.5 % at 90 days following surgery for colorectal cancer. In low risk patients the mortality rate is even lower, data from Wilson and colleagues (51) showed a 0.5% mortality at 90 days in 388 patients undergoing major colorectal or urological surgery.

Further to this discrepancies can arise depending on the length of follow up. Visser and colleagues (3) showed extending follow up of elective and emergency colectomies from 30 to 90 days increased mortality rates from 4.3% to 9.1% showing the temporal effect of follow up duration on outcomes, and the potential under-estimate of outcomes measurements.

1.4.2 Morbidity

The occurrence of complications following surgery is an important outcome measure both due to the long-term impact of developing a complication in terms of reduced quality and quantity of life, and also due the cost implications of treatment and increased length of stay to the healthcare system. In terms of an outcome measure following an intervention, due to their far higher incidence following major surgery then a smaller treatment effect can be more easily detected.

Complications can be divided by when they occur in relation to the timing of surgery (early or late), where they occur in the body (system specific), and by their severity (minor or major). Comparing outcomes from different studies is often complex due to the different methods of classifying and reporting complications. A simple and quick to use tool for identifying morbidity significant enough to delay discharge from hospital is the post-operative morbidity survey (POMS). Developed by Bennett-Guerrero *and colleagues*(152), the POMS uses 18 items across nine domains (Table 22), and data is collected from a combination of patient notes, blood test results and

through the direct observation and questioning of patients. The presence or absence of morbidity is recorded in a binary fashion for each domain.

Morbidity Type	Criteria
Pulmonary	New requirement for oxygen or respiratory support (including mechanical ventilation or CPAP)
Infection	Antibiotic therapy or temperature >38^{o}C in previous 24 hours
Renal	Oliguria (urine output <500ml/24 hours), increased serum creatinine (>30% from preoperative level), urinary catheter in situ for non-surgical reason
Gastrointestinal	Inability to tolerate an enteral diet for any reason (including nausea, vomiting or abdominal distension)
Cardiovascular	Diagnostic tests or therapy over previous 24 hours for any of: new myocardial infarction or ischaemia, hypotension (requiring pharmacological therapy or fluid therapy >200ml/hour) atrial or ventricular arrhythmias or cardiogenic pulmonary oedema
Neurological	New focal deficit, coma, confusion or delirium
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound
Haematological	Requirement over previous 24 hours for any of : packed red cells, platelets, fresh frozen plasma or cryoprecipitate
Pain	Post-operative pain significant enough to require parenteral opiods or regional analgesia

Table 22 The Postoperative Morbidity Survey adapted from Bennett-Guerrero and colleagues (152)

Originally derived from a cohort of 438 patients (152) undergoing elective orthopaedic, general, urological, vascular and gynaecological surgery, the POMS

identified 98% (CI 96-100%) of patients who required prolonged hospitalisation of greater than 7 days.

A validation study (153) from the United Kingdom assessed 439 patients undergoing major orthopaedic, general and urological surgery. In 34 patients inter-rater reliability was analysed using the kappa co-efficient of agreement between two raters, agreement for 11 out of 18 items was perfect (kappa = 1.0), and good for six items 0.94. Agreement was lowest in assessment of gastrointestinal complications where kappa was 0.71, suggesting that this domain needs further modification. Morbidity as defined by POMS was present in 98.0% of general surgical patients remaining in hospital at postoperative day 3, 78.2% at day 5, 49.5% at day 8 and 33.7% at day 15.. Analysis of the patients remaining in hospital without a POMS defined morbidity showed that no patient had morbidity related reason to remain in hospital. Analysis of internal consistency using the Kunder-Richardson formula revealed that internal consistency between the domains was below the accepted minimum standard of 0.70 on days 3 (0.60), 5 (0.57), 8 (0.51) and 15 (0.54), therefore although the POMS can be used to show the presence or absence of morbidity, it can not be used to measure its severity.

A further weakness of POMS is that routine interventions can be recorded as morbidity. Presence of an epidural catheter, intravenous opiod or an urinary catheter are routine interventions which are frequently present at day 1 and 3, leading to a falsely high POMS score early in the post-operative period. Therefore

careful thought needs to be paid as to when in the post-operative period the POMS is to be used.

More complex measures of post-operative morbidity include the Clavien-Dindo system that classifies surgical complications. Modified in 2004 (154) this classifies complications according to degree of deviation from an expected standard post-operative course (Table 23). It was validated in a cohort of 6336 patients where the classification correlated with length of hospital stay ($p<0.0001$) and complexity of surgery ($p<0.0001$). A survey of 144 surgeons from 6 countries to assess reproducibility showed 90% of answers to be correctly classified, with no significant difference between countries of origin or level of training.

Grade	**Definition**
I	Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic and radiological interventions. Simple pharmacological therapies – including anti-emetics, antipyretics, diuretics, electrolytes and physiotherapy are allowed
II	Requiring pharmacological treatment beyond what is allowed in grade I, blood transfusions, total parenteral nutrition
III **IIIa** **IIIb**	Requiring surgical, endoscopic or radiological intervention Not under general anaesthesia Under general anaesthesia
IV **IVa** **IVb**	Life threatening complication requiring Intermediate or Intensive Care Management Single organ dysfunction Multi-organ dysfunction
V	Death

Table 23 Clavien-Dindo classification of post-operative complications adapted from Dindo and colleagues(154)

The Clavien-Dindo classification is less prescriptive than POMS, with less evidence available regarding its reproducibility. Therefore for prospective evaluation of development of complications by a team of researchers there is a greater degree of evidence regarding the consistency of POMS.

1.4.3 Hospital Length of Stay

The optimal hospital length of stay is the minimum required stay prior to a safe discharge home, and as such it acts as a surrogate for the speed of patient recovery. Data from the hospital episodes statistics (HES) database on patients undergoing major colorectal resections in the UK between 1996 and 2006 (155) showed a median length of stay of 11 days (± 6) in colonic surgery, and 13 (± 8) in rectal surgery. Hospital length of stay reflects the speed of patient recovery, and development of complications will delay discharge and hence is reflected as a longer length of stay. With the average cost of an excess bed day being £273, the national cost of excess bed days has been calculated to be over 150 million pounds(156). Therefore in addition to the impact on the patient there is a cost implication that in a socialised health care such as the national health system has repercussions on the population as a whole.

Hospital length of stay as an outcome measure is confounded by the fact that non-medical reasons can contribute to delays in discharge. It has been shown that unmarried patients have a longer length of stay than married patients (adjusted OR length of stay >24 days 1.20 (1.00-1.43) (157) reflecting the impact of social support on discharge planning. Further it assumes that patients are discharged from different units in the same physical condition. Each individual unit will have its own discharge criteria which may mean that comparison of length of stay is unreliable as a measure of outcome.

2. AIMS

To compare goal directed fluid therapy targeted by the plethysmographic variability index with the established technology of oesophageal Doppler in low risk patients undergoing major colorectal surgery.

2.1. Primary

To investigate whether fluid volumes administered were equivalent using both technologies.

2.2. Secondary

To investigate whether there is a difference in:

24 hour fluid balance.

Serum levels of biochemical markers of tissue perfusion (lactate and base excess)

Morbidity at post-operative days 1,3,5 and 7 as defined by Postoperative Morbidity Survey (POMS).

Length of stay in hospital after surgery

Incidence of major and minor complications during hospital admission.

Use of post-operative inotropic or vasopressor support.

3. METHODOLOGY

The trial protocol was approved by the NRES Committee Yorkshire and The Humber – Leeds West (reference 12/YH/0406) and by the York Teaching Hospital NHS Foundation Trust Research and Development Unit (reference YOR-A02089). The trial was registered on clinicaltrials.gov (US National Library of Medicine reference NCT02142816).

3.1 Recruitment of Patients

All patients undergoing major elective colorectal surgery were screened by a member of the research team prior to attending pre-assessment clinic. Patients considered eligible for the study received a patient information sheet regarding the study via post, and a member of the research team was available at the pre-assessment clinic to offer an explanation of the study and to answer any questions from the patients prior to obtaining informed consent.

3.1.1 Inclusion criteria

Low risk patients undergoing major elective laparoscopic or open colorectal surgery (excision or reanastomosis procedures of colon and rectum) were recruited for participation in the study. Patients were considered low risk if at CPET their anaerobic threshold was ≥ 11 ml/kg/min and $VE/VCO_2 \leq 34$ at AT. If patients did not undergo CPET per local guidelines (Appendix 1), then a Consultant Anaesthetist determined their risk status.

3.1.2 Exclusion Criteria

Patients were excluded if they were less than 18 years of age, if they refused or were unable to give informed consent, or had less than 24 hours to consider the patient information sheet. Patients undergoing emergency procedures were excluded, as were those with ASA Grade 5, those weighing greater than 100kg (unsuitable for Doppler algorithm) or if they had a previously diagnosed dysrhythmia (unsuitable for PVI algorithm). Patients with renal failure with oliguria or anuria (unrelated to hypovolaemia) or undergoing dialysis were also ineligible (unable to receive starches). Finally patients were also excluded if there was a contraindication to the insertion of an oesophageal Doppler probe or if they had a known hypersensitivity to starch and gelatin based infusion solutions.

3.2. Trial Protocol

3.2.1 Pre-operative

All patients were admitted on the day of surgery. They were encouraged to drink clear fluids until 2 hours before attending the operating theatre suite. Oral carbohydrate drinks were prescribed to be taken on the evening before and the morning of surgery. Bowel preparation was avoided when possible but used at the discretion of the consultant surgeon if needed. Written informed consent was obtained from the patient prior to arriving in the theatre suite.

3.2.2. Intra-operative

On arrival in the anaesthetic room routine monitoring (ECG, NIBP, Pulse-oximetry) was attached and vascular access was secured using a large bore peripheral cannula. At the discretion of the consultant anaesthetist an epidural catheter was sited prior to induction of anaesthesia with a test dose of 0.5% bupivacaine administered.

Anaesthesia was induced with propofol (1-2mg/kg) and fentanyl (1-2mcg/kg), with muscle relaxation to facilitate tracheal intubation achieved using atracurium (0.5mg/kg) or rocuronium (0.6mg/kg). Anaesthesia was maintained using isoflurane or desflurane in oxygen enriched air. Patients were mechanically ventilated with a tidal volume of 8mls/kg and a PEEP of 5cm H_20

Following induction all patients had an oesophageal Doppler probe (Deltex Medical, Chichester, UK) placed into the oesophagus and its position was adjusted to obtain an optimal signal, with the highest obtainable peak velocity and the sharpest audible pitch as recommended by the manufacturer(158). A pulse oximeter was placed onto the index finger and connected to Rainbow Set monitoring platform (Massimo Corporation, Irvine, CA, USA) to measure Pleth Variability Index (PVI) and Perfusion Index (PI). Once monitoring via the Doppler and PVI probes were established a period of two minutes was permitted for signal acquisition by the Rainbow Set monitoring platform. Baseline measurements of stroke volume from the ODM, and PVI and perfusion index (PI) were recorded, and venous lactate and base excess

were measured using an point of care testing device (i-STAT system, CG4+ cartridges, Abbott Laboratories, Maidenhead, UK)

Subjects were then randomised to receive fluid management guided by the oesophageal Doppler (Group D) or PVI (Group P). Boluses were delivered as indicated by the study protocol, no background infusion was administered. Intraoperative fluid therapy was administered using 6% hydroxyethyl starch 130/0.4 (Volulyte™ Fresenius Kabi Ltd, Runcorn), however patients recruited after 27th June 2013 received Geloplasma™ (Fresenius Kabi Ltd, Runcorn) due to withdrawal of the product licence for Volulyte™ along with all other Hydroxyethyl Starch products by the Medicines and Healthcare products Regulatory Agency (MHRA) (159). All fluid boluses administered as a part of the trial protocol were delivered as a rapid intravenous bolus using a 50 ml syringe via a fluid warmer over a 2 minute period.

Patients allocated to Oesphageal Doppler (Group D)

Patients allocated to group D (ODM) received a 250ml bolus of the trial infusion solution at the end of the stabilisation period. The SV was recorded before and after the bolus. If the stroke volume increased by greater than 10% a further 250ml bolus was given until the increase in stroke volume was less than 10%. If during the procedure the stroke volume fell by greater than 10% a further fluid challenge was administered (Figure 4).

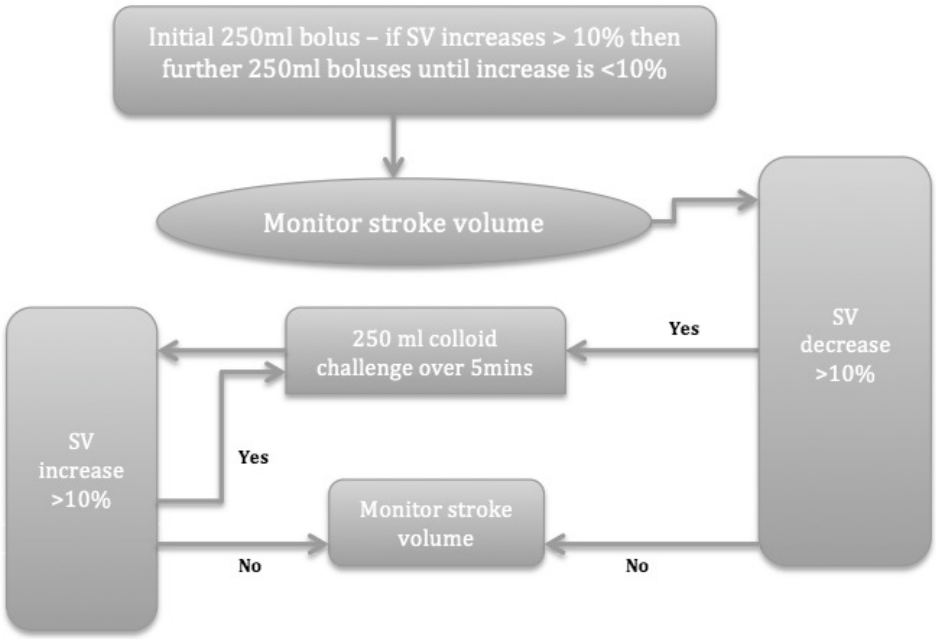

Figure 4 Protocol for intraoperative fluid therapy for group D using goals derived from oesophageal Doppler monitoring

Patients allocated to PVI (group P)

The PVI was monitored after the end of the stabilisation period and subjects received a bolus of the trial infusion solution if the PVI was greater than or equal to 14%. Following completion of the bolus the patient was re-assessed after 5 minutes and if the PVI remained greater than or equal to 14% a further bolus was delivered as illustrated in figure 5.

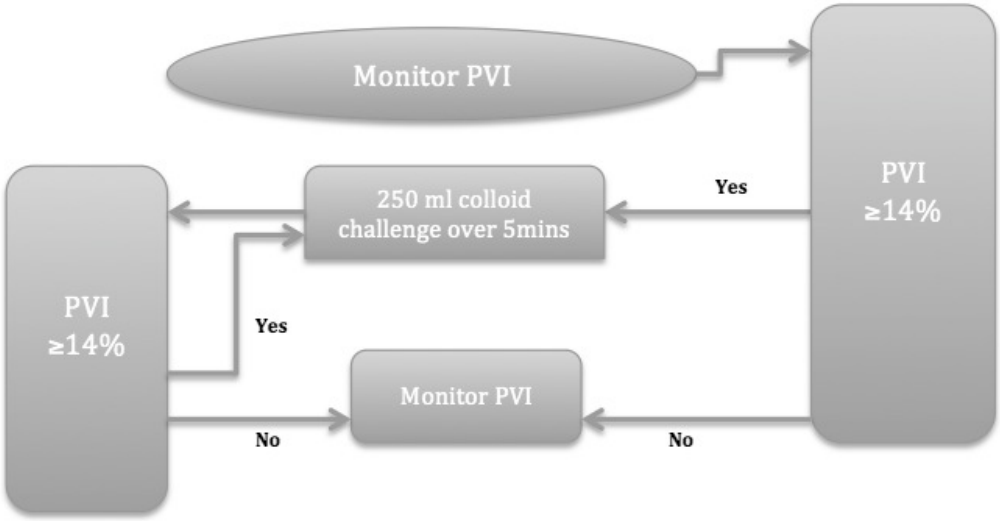

Figure 5 Protocol for intraoperative fluid therapy for group P with goals derived form a PVI probe (Massimo Corp).

Both groups

Intraoperative and post operative analgesia was maintained using either an epidural infusion or intravenous opiate therapy (remifentanil infusion or morphine boluses). Muscle relaxation was maintained with atracurium or rocuronium, and vasopressors (ephedrine, metaraminol or phenylephrine) were administered at the anaesthetist's discretion. The anaesthetist retained the ability to overrule the researcher at any point during the case if needed to maintain patient safety. Any interventions by the anaesthetist were recorded on the case record file and data was analysed on an intention to treat basis.

Venous lactate and base excess were measured hourly during surgery and on arrival into the post-anaesthetic care unit. The pre-operative creatinine was recorded as the measured value from the patient's routine pre-operative blood tests.

3.2.3. Post-operative

Post-operative follow-up was carried out by blinded members of the research team, who were not involved in intra-operative care, and were unaware of the patient's group allocation.

Patients were visited on post-operative days 1, 3, 5 and 7 by a member of the research team who performed a Post-Operative Morbidity Survey (POMS) (Table 22) (152). On post operative day 1 venous lactate and base excess were measured. Post-operative creatinine was documented as the value measured on the first routine post-operative test. The presence of any predefined major or minor complications (see appendix 2) was documented.

At discharge medical notes were examined to determine length of stay and the presence or absence of predefined major and minor complications (appendix 2) between day 7 and discharge.

3.3 Statistics

3.3.1. Sample Size

A total sample size of 34 patients was derived from previous work performed in this institution and by other researchers (148), (127), (14) in order to give the study a power of 90% at the 5% significance level in order to detect a 500ml difference in the volume of fluid administered regardless of operation type. The sample size was calculated using the equation:

$$n=f(\alpha,\beta) \times 2 \times \sigma^2/d^2$$

Where d is the equivalence limit, σ is the standard deviation and $f(\alpha,\beta)=[\Phi^{-1}(\alpha)+ \Phi^{-1}(\beta/2)]^2$. The equivalence limit (d) was set at a difference of 500mls and a standard deviation (σ) of 400mls with $f(\alpha,\beta)=[\Phi^{-1}(\alpha)+ \Phi^{-1}(\beta/2)]^2$ where α is the probability of rejecting the null hypothesis when it is true, β is the probability of failing to reject the null hypothesis when it is false and Φ is the cumulative distribution function of a standardised normal deviate. 40 patients were recruited in order to allow for drop out.

3.3.2 Randomisation and blinding

Patients were randomised using block randomisation in blocks of 4 in order to ensure an equal spread between the two groups and to keep the size of the groups similar. Group allocation was documented in sealed, opaque envelopes created by the Research and Development unit prior to the recruitment of the first patient. These sequentially numbered envelopes were held in a locked filing cabinet and the

envelope with the lowest available number was taken into theatre when the patient arrived for their operation. The envelope was not opened until the patient was anaesthetised. Randomisation codes were held securely until the last patient was discharged from hospital and all trial related activity was complete.

The researcher administering the intra-operative trial protocol was aware of which group the patient was in. The anaesthetist and surgeon were blinded to the patient's group as were the investigators gathering post-operative data.

3.3.3 Analysis of Data

Data was entered into separate intra-operative and post-operative databases using Microsoft Access version (Microsoft Corp, USA) by two separate members of the research team. Data was held securely and separately until locked at which point post-operative data was unblinded.

Statistical analysis was carried out using IBM SPSS Statistics Version 20 (IBM Corp, USA). Normality of data was checked using a Kolmogorov-Smirnov Test. Continuous data was analysed using an independent samples T-test, Mann-Whitney U-test or one-way analysis of variance. Categorical Data was analysed using Fisher's Exact test or a Chi-squared test. Length of stay data was analysed using Kaplan-Meier graphs. A p-value of less than 0.05 was considered significant.

4. RESULTS

One hundred and sixty six patients were screened for the study between January 2013 and February 2014. From this total group forty patients were recruited to the study. Patients not recruited following screening are summarised in Table 24. Two patients were excluded from the study due to protocol violations see figure 6. Demographics of the remaining 38 patients are presented in Table 25. There were no significant differences in demographic data between the groups.

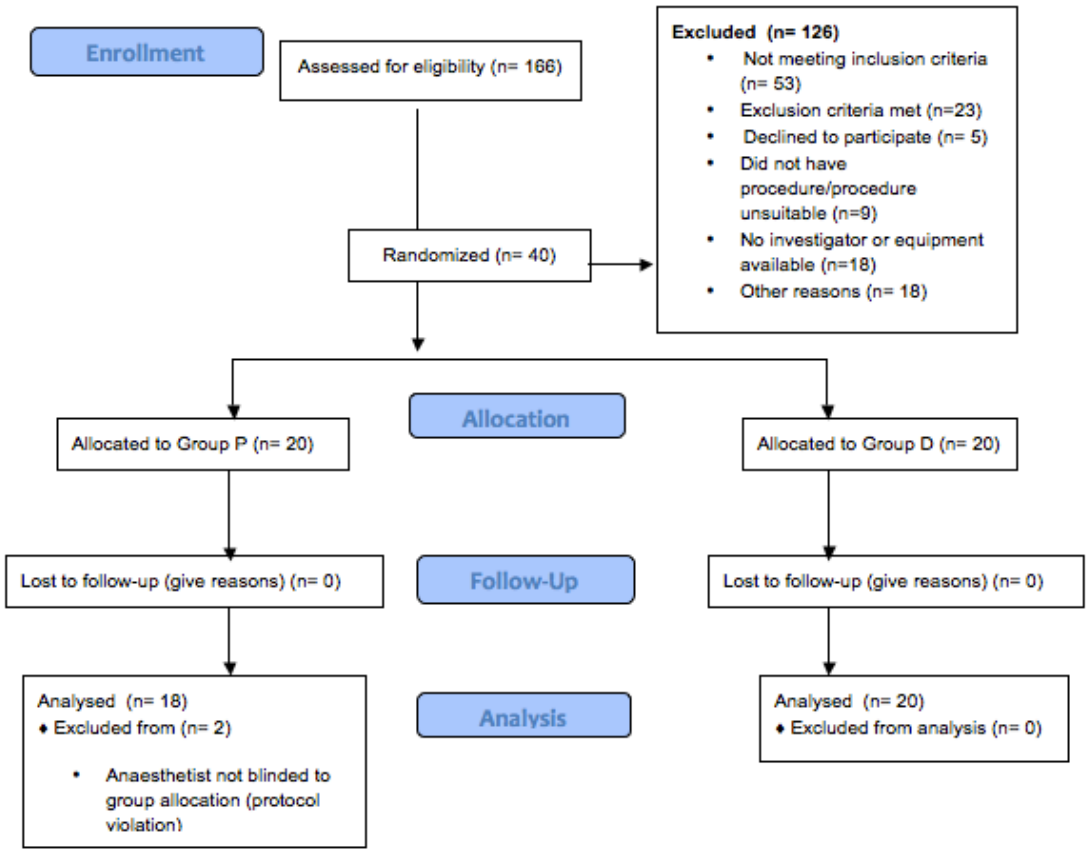

Figure 6 Trial flow diagram summarising patient progression through trial

Reason for Exclusion	
Declined to take part	5
No investigator or equipment available	18
Did not meet inclusion criteria (CPET)	53
Exclusion criteria met	23
Did not have surgery/Procedure did not meet inclusion criteria	9
Did not receive information in time	7
Reason unclear/date of surgery missed	11

Table 24 Summary of patients excluded following screening

	Overall (n=38)	**Group P (n=18)**	**Group D (n=20)**	**P-value**
Mean age (yrs) (SD)	62.6 (12.5)	59.8 (13.5)	65.1 (11.4)	0.205
Mean weight (kg) (SD)	73 (12.2)	73.8 (12.7)	72.3 (12.0)	0.695
Mean height (cm) (SD)	167.8 (8.5)	168.6 (7.0)	167.0 (9.8)	0.579
Female (%)	17 (44.7)	7 (38.9)	10 (50.0)	0.532
Male (%)	21 (55.3)	11 (61.1)	10 (50.0)	0.532

Table 25 Summary of patient demographics

30 patients were recruited following cardiopulmonary exercise testing. CPET variables are presented in Table 26. 8 further patients did not undergo CPET as they were considered low risk by consultant anaesthetists, therefore not eligible for routine pre-operative CPET according to local guidelines. There was no significant difference in CPET variables between the two groups. Pre-operative haemoglobin was significantly higher in the PVI group (p=0.036).

	Overall	Group P	Group D	P-value
Number CPET tested	30	12	18	0.117
Mean AT (SD)	13.9 (2.6)	13.4 (1.7)	14.1 (3.1)	0.709
Mean VE/VCO_2 (SD)	30.5 (2.6)	30.1 (2.7)	30.7 (2.4)	0.603
Mean Hb (SD)	135.2 (17.3)	141.2 (12.2)	129.8 (19.5)	0.036
Mean Creatinine (SD)	71.8 (16.2)	71.1 (19.1)	72.4 (13.5)	0.849

Table 26 Variables measured at pre-assessment

Co-morbidities and medications present are shown in Table 27.1 and 27.2.

	Overall (n=38)	Group P (n=18)	Group D (n=20)
Hypertension (%)	6 (15.8)	3 (16.7)	3 (15.0)
Ischaemic Heart Disease (%)	1 (2.6)	1 (5.6)	0 (0)
Asthma (%)	4 (10.5)	3 (16.7)	1 (5.0)
COPD (%)	1 (2.6)	0 (0)	1 (5.0)
Inflammatory Bowel Disease (%)	6 (15.8)	3 (16.7)	3 (15.0)
Previous VTE (%)	2 (5.3)	1 (5.6)	1 (5.0)
Previous CVA (%)	1 (2.6)	1 (5.6)	0 (0)
Diabetes Mellitus (%)	3 (7.9)	2 (11.1)	1 (5.0)
Anaemia(%)	3 (7.9)	0 (0)	3 (15.0)

Table 27.1 Co-morbidities present in trial patients

	Overall (n=38)	Group P (n=18)	Group D (n=20)
ACE-i/ARB (%)	4 (10.5)	1 (5.6)	3 (15.0)
Diuretic (%)	3 (7.9)	1 (5.6)	2 (10.0)
Calcium Channel Blocker (%)	3 (7.9)	2 (11.1)	1 (5.0)
Aspirin (%)	4 (10.5)	3 (16.7)	1 (5.0)
Statin (%)	9 (23.7)	5 (27.8)	4 (20.0)
Oral Steroid (%)	4 (10.5)	2 (11.1)	2 (10.0)
Insulin (%)	0 (0)	0 (0)	0 (0)
Oral Hypoglycaemic (%)	1 (2.6)	1 (5.6)	0 (0)

Table 27.2 Medications taken by trial patients

Operative details are presented in Table 28 and Table 29

	Overall (n=38)	PVI (n=18)	Doppler (n=20)	P-value
Mean Duration of Surgery (mins) (SD)	178.3 (59.2)	194.1 (66.2)	164.3 (49.5)	0.123
Laparoscopic (%)	9 (23.7)	7 (38.9)	2 (10.0)	0.074
Open (%)	26 (68.4)	10 (55.6)	16 (80.0)	0.087
Laparoscopic to Open (%)	3 (7.9)	1 (5.6)	2 (10.0)	1.000
Intra-op Epidural (%)	26 (68.4)	12 (66.7)	14 (70.0)	1.000
Intra-op Spinal (%)	1 (2.6)	0 (0)	1 (5.0)	1.000

Table 28 Operative and Anaesthetic Parameters

	Overall (n=38)	PVI (n=18)	Doppler (n=20)
Anterior Resection (%)	14 (36.8)	8 (44.4)	6 (30.0)
Completion Proctectomy (%)	1 (2.6)	0 (0)	1 (5.0)
Exploratory laparoscopy (%)	1 (2.6)	1 (5.6)	0 (0)
Hartman's Procedure (%)	2 (5.3)	0 (0)	2 (10.0)
Ileocolic anastomosis (%)	1 (2.6)	1 (5.6)	0 (0)
Left hemicolectomy with anterior resection (%)	1 (2.6)	0 (0)	1 (5.0)
Left hemicolectomy (%)	2 (5.3)	1 (5.6)	1 (5.0)
Removal of pouch (%)	1 (2.6)	0	1 (5.0)
Reversal of Hartman's (%)	3 (7.9)	2 (11.1)	1 (5.0)
Right Hemicolectomy (%)	7 (18.4)	4 (22.2)	3 (15.0)
Sigmoid Colectomy (%)	1 (2.6)	0 (0)	1(5.0)
Subtotal Colectomy (%)	3 (7.9)	1 (5.6)	2 (10.0)
Total Colectomy (%)	1 (2.6)	0 (0)	1 (5.0)
Summary procedure			
Colon	20 (52.6)	9 (50.0)	11 (55.0)
Rectum	17 (44.7)	8 (44.4)	9 (45.5)
Other	1 (2.6)	1 (5.6)	0 (0)

Table 29 Summary of surgical procedures

Initial baseline data did not significantly vary between groups (see Table 30)

	Overall (n=38)	PVI (n=18)	Doppler (n=20)	P-value
Mean SV (SD)	67.4 (18.7)	62.7 (16.7)	71.8(19.8)	0.135
Mean PVI (SD)	17.6 (10.2)	14.7 (7.0)	20.2 (12.2)	0.101

Table 30 Baseline stroke volume and pleth variability index values

4.1. Intraoperative fluid balance

There was no significant difference in volume of fluid administered nor intraoperative fluid balance using either PVI or Doppler to target fluid administration (see Table 31). IV fluid administered per kilogram weight per minute was significantly higher in the PVI group.

	Overall (n=38)	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Mean Volume of Fluid Administered (SD)				
IV Colloid (ml)	1322.4 (569.2)	1180.6 (652.0)	1450.0 (463.1)	0.148
Total IV Fluid (Crystalloid* and Colloid) (ml)	1409.2 (668.7)	1286.1 (798.9)	1520.0 (522.0)	0.300
IV Fluid/kg/min (Crystalloid and Colloid) (ml/kg/min)	0.120 (0.064)	0.098 (0.064)	0.139 (0.059)	0.028
* Crystalloid given at anaesthetist's requestf				
Mean Intraoperative Fluid Balance (SD)				
Intraoperative Balance (ml)	999.7 (650.9)	838.6 (713.3)	1144.8 (568.5)	0.150
Mean Intraoperative Output (SD)				
Estimated Blood Loss (ml)	267.2 (236.0)	307.8 (315.5)	230.8 (128.1)	0.344
Urine Output (ml)	142.5 (145.3)	140.3 (116.4)	144.5 (170.2)	0.930

Table 31 Volumes of fluid administered and fluid balance

Table 32 and figure 7 illustrates the cumulative volume of fluid administered over the duration of the procedure. The volume of IV fluid administered in the first 30 minutes, 1 hour and 2 hours was significantly greater in the Doppler group. Beyond 2 hours there was no significant difference in the volume administered.

Mean Cumulative IV fluid administered (ml) at time period (SD)	**Overall (n=38)**	**PVI (n=18)**	**Doppler (n=20)**	**P-Value**
30 mins	499.5 (198.2)	398.1 (186.4)	590.8 (163.9)	**0.002**
1 hour	683.1 (353.6)	498.5 (296.1)	849.2 (322.0)	**0.001**
2 hours	1067.9 (460.9)	875.9 (432.9)	1240.8 (423.9)	**0.013**
3 hours	1311.8 (582.8)	1122.2 (628.8)	1482.5 (492.9)	0.060
4 hours	1360.5 (605.4)	1197.2 (676.4)	1507.5 (506.3)	0.123
5 hours	1389.5 (630.4)	1244.4 (719.8)	1520.0 (522.0)	0.191
6 hours	1409.2 (668.7)	1286.1 (798.9)	1520.0 (522.0)	0.300

Table 32 Cumulative Volume of Fluid Administered

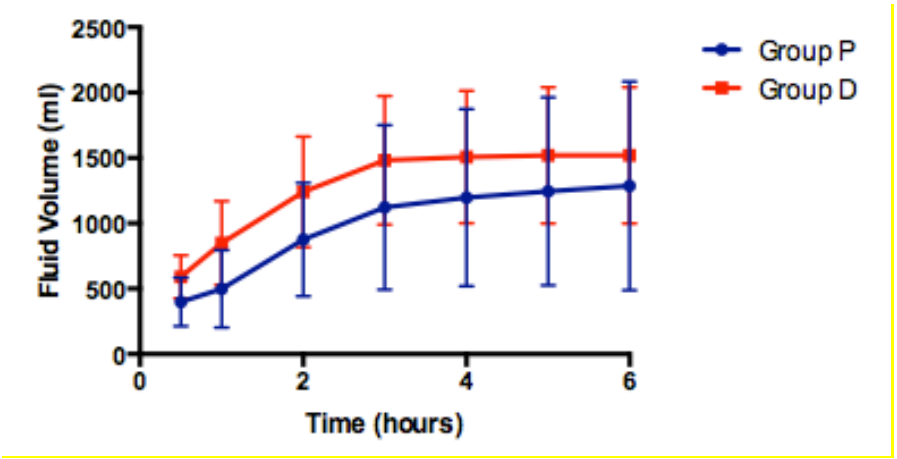

Figure 7 Cumulative volume of fluid administered over time

4.2. Lactate and Base Excess measurements

As shown in Tables 33 and 34 and figures 8 and 9 there was no significant difference in initial lactate and base excess between the two groups. Intraoperative lactate and base excess measured at hourly intervals did not differ significantly between groups. Lactate measured at recovery was significantly higher in the PVI group compared to the Doppler group (p=0.007). Lactate and base excess did not vary significantly between groups at day 1.

Mean Lactate at time period (mmol/l)	**Overall (n=38)**	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Initial (SD)	1.06 (0.52)	1.17 (0.60)	0.95 (0.43)	0.210
1 hour (SD)	1.02 (0.49)	1.19 (0.57)	0.87 (0.35)	0.057
2 hours (SD)	1.21 (0.71)	1.41 (0.79)	0.97 (0.54)	0.094
3 hours (SD)	1.76 (1.04)	1.97 (1.19)	1.49 (0.84)	0.420
4 hours (SD)	3.36 (0.86)	3.63 (1.03)	2.83 (0)	0.637
5 hours (SD)	4.50 (1.41)	4.50 (1.41)	n/a	n/a
Recovery (SD)	1.57 (0.84)	1.98 (0.95)	1.21 (0.53)	**0.007**
Day 1 (SD)	1.42 (0.73)	1.40 (0.63)	1.44 (0.84)	0.876

Table 33 Serum Lactate Measurements in the peri-operative period

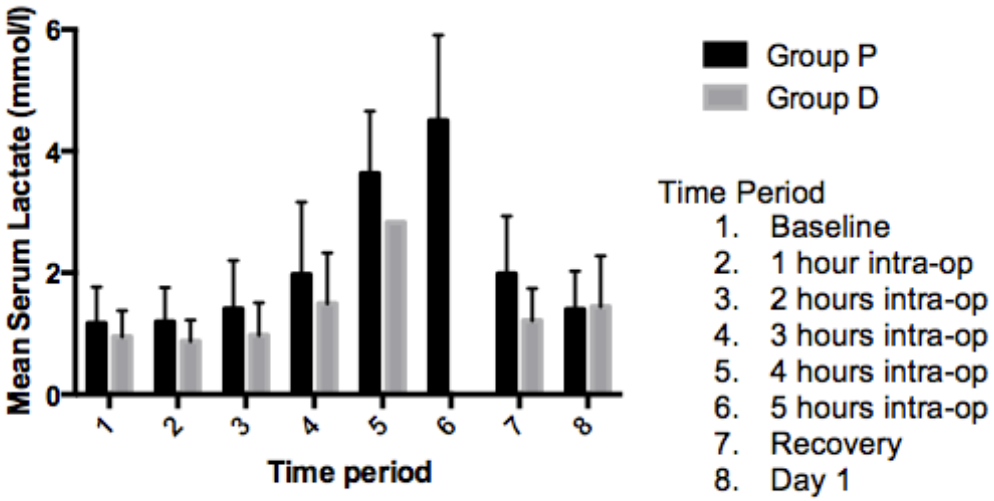

Figure 8 Mean serum lactate (mmol/l) during the perioperative period

Mean Base Excess at time period (mmol/l)	**Overall (n=38)**	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Initial (SD)	0.8(4.5)	1.4 (5.5)	0.2 (3.3)	0.451
1 hour (SD)	-0.4 (3.2)	-0.5 (3.8)	-0.3 (2.4)	0.827
2 hours (SD)	-0.0 (3.0)	0.1 (3.2)	-0.2 (2.9)	0.844
3 hours (SD)	-0.6 (4.5)	-0.3 (4.9)	-1.2 (4.3)	0.721
4 hours (SD)	-1.0 (3.2)	-1.5 (5.0)	-0.5 (2.1)	0.817
5 hours (SD)	0.0 (0)	0.0 (0)	n/a	n/a
Recovery (SD)	-0. (3.0)	-0.7 (3.9)	0.4 (1.9)	0.279
Day 1 (SD)	3.4 (6.9)	3.4 (6.9)	3.1 (3.0)	0.850

Table 34 Base Excess Measurements in the peri-operative period

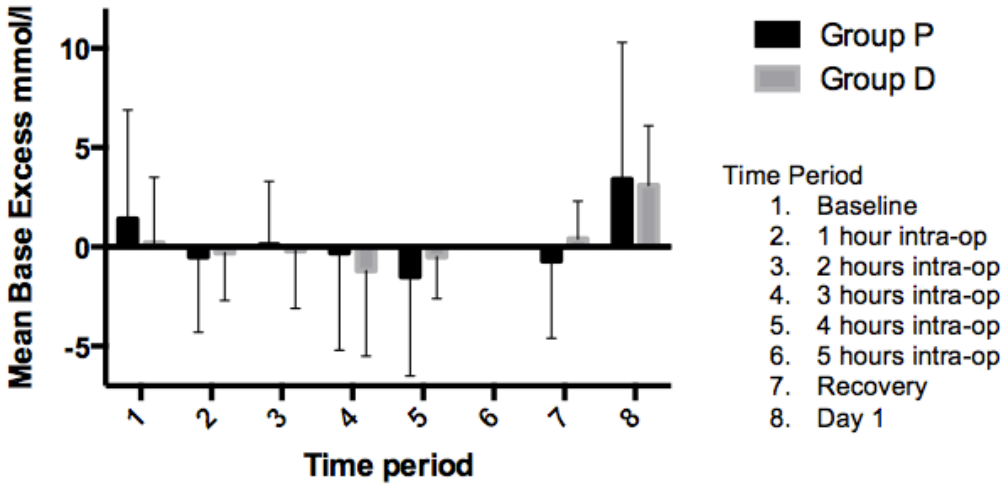

Figure 9 Mean Base Excess (mmol/l) during the perioperative period

4.3. 24-hour fluid balance

It was possible to calculate a 24-hour fluid balance in 22 of the patients. Amongst these patients (10 PVI and 12 Doppler) mean 24-hour balance was +2501ml (SD 1348). There was no significant difference in 24-hour fluid balance (mean volume +2252 v +2708 ml p=0.442) between the two groups. Unfortunately as data for this secondary outcome was collected retrospectively from ward fluid balance charts there was considerable variation in quality of data. It was only possible to obtain a full fluid balance in 22 patients where an accurate input – output chart had been kept including oral intake. Patients where only output or only intravenous input had been recorded were excluded from this section of data analysis.

4.4 Post-operative Creatinine

Mean postoperative creatinine was 81 (SD 22.3). Mean creatinine change was calculated as the percentage change in creatinine between the pre-operative measurement and the first post-operative measurement. There was an overall mean rise in creatinine rise of 13.0% (95% CI 3.6 to 24.9). Whilst the percentage rise

in creatinine was higher in the PVI group, this was not significantly different to the Doppler group (19.1 (95% CI -1.85 to 40.0) v 7.5% (95% CI -2.7 to 17.7), p=0.280).

4.5 Post-operative Morbidity Survey (POMS)

The percentage of patients with morbidity defined by POMS on days 1, 3, 5 and 7 were not significantly different between the PVI and Doppler groups (Table 35). There was no significant difference between POMS scores on any days in the pulmonary, cardiovascular, renal or GI morbidity domains (Tables 36-39).

Proportion of patients with Positive POMS Scores (%)	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Day 1	94.4	100.0	0.285
Day 3	72.2	85.0	0.256
Day 5	44.4	55.0	0.450
Day 7	27.8	40.0	0.428

Table 35 Patients experiencing morbidity according to POMS

Proportion of patients with cardiovascular morbidity on POMS (%)	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Day 1	22.2	35.0	0.386
Day 3	5.6	0	0.386
Day 5	5.6	0	0.184
Day 7	5.6	0	0.310

Table 36 Patients experiencing cardiovascular morbidity according to POMS

Proportion of patients with pulmonary morbidity on POMS (%)	PVI (n=18)	Doppler (n=20)	P-value
Day 1	55.6	55.0	0.973
Day 3	26.4	20.0	0.504
Day 5	0.0	5.0	0.256
Day 7	5.5	10.0	0.621

Table 37 Patients experiencing pulmonary morbidity according to POMS

Proportion of patients with renal morbidity on POMS (%)	PVI (n=18)	Doppler (n=20)	P-value
Day 1	88.9	95.0	0.595
Day 3	55.6	80.0	0.180
Day 5	27.8	45.0	0.303
Day 7	22.2	25.0	0.622

Table 38 Patients experiencing renal morbidity according to POMS

Proportion of patients with GI morbidity on POMS	PVI (n=18)	Doppler (n=20)	P-value
Day 1	66.7	70.0	1.0
Day 3	38.9	35.0	0.555
Day 5	33.3	20.0	0.141
Day 7	16.7	10.0	0.402

Table 39 Patients experiencing GI morbidity according to POMS

4.6. Complications

Fourteen patients developed a post-operative complication, (4 PVI, 10 Doppler). The presence of complications did not vary between the two groups (p=0.101). When complications were divided into minor and major (see Table 40) there was a significantly greater number of minor complications in the Doppler group compared to the PVI group (p=0.033). Complications are summarised in Table 41. All patients survived until discharge.

Proportion of patients experiencing complications	**Overall (n=38)**	**PVI (n=18)**	**Doppler (n=20)**	**P-value**
Minor (%)	28.9	5.0	45.0	0.033
Major (%)	7.9	11.1	11.1	0.595

Table 40 Patients Experiencing Complications

Number of patients experiencing specific complications	**Overall**	**PVI**	**Doppler**
Anastomotic Leakage	1	1	0
Sepsis	2	0	2
Bleeding requiring transfusion or procedure	2	2	0
ACS	1	1	0
Superficial Wound Infection	4	0	4
Ileus >7 days	3	1	2

Ileus requiring TPN	3	1	2
Pneumonia	1	1	0
Arrythmia	1	1	0
Cystitis	2	0	2
New Confusional State	1	1	0

Table 41 Summary of Complications that occurred

4.7. Length of Stay

Median hospital length of stay was 7 days (IQR 4). This did not vary between PVI and Doppler groups (median 7 (IQR 5) v 7 days (IQR 3), p=0. 735). Kaplan Meier analysis of time to discharge from hospital is illustrated in figure 10, a log rank test showed no significant difference between the two groups with regard to time to discharge from hospital.

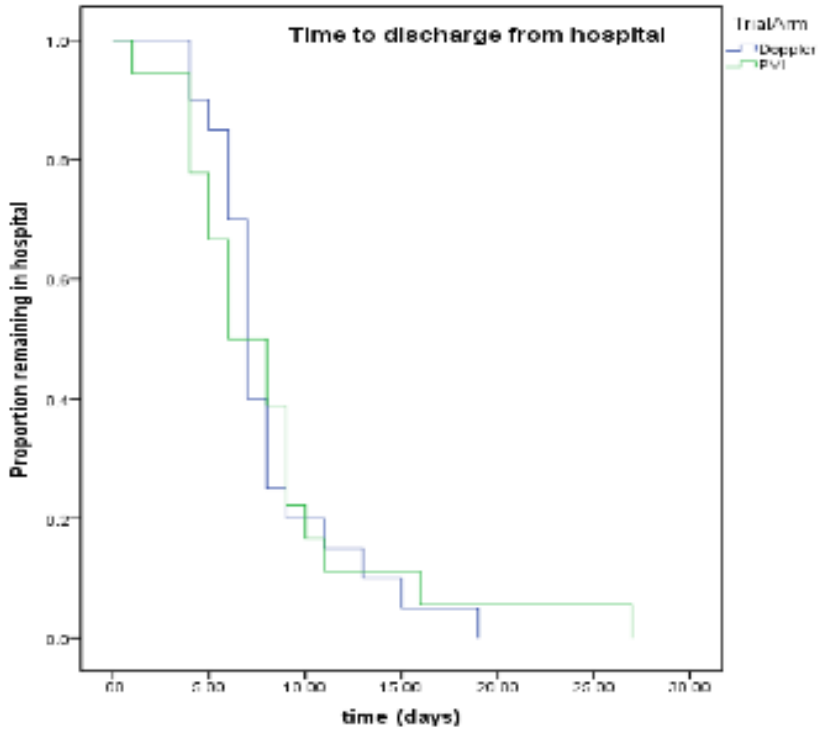

Figure 10 Kaplan Meier curve illustrating time to discharge from hospital

4.8. Type of Fluid Used

There were no significant differences in intraoperative fluid administration, post-operative morbidity or hospital length of stay between patients who received either Volulyte™ or Geloplasma™ (Table 42).

	Volulyte	Geloplasma	P-value
No. of patients	18	20	
No. of patients Group D	8	10	
No. of patients Group P	10	10	
Mean total IV fluid (ml)(SD)	1328	1483	0.484
Mean total colloid (ml) (SD)	1167	1462	0.111
Mean intraoperative balance (ml) (SD)	989	1009	0.926
No of complications	5	9	0.224
Proportion of patients POMS positive day 1 (%)	94.4	100.0	0.474
Proportion of patients POMS positive day 3 (%)	72.2	85.0	0.455
Proportion of patients POMS positive day 5 (%)	44.4	55.0	0.504
Proportion of patients POMS positive day 7 (%)	33.3	35.0	1.00
Median Hospital length of stay (days) (IQR)	7.00 (4)	7.50 (4)	0.385

Table 42 Comparison of patient fluid balance and outcome with regard to fluid type

5. DISCUSSION

This randomised controlled study of low risk patients undergoing major colorectal surgery has shown there is no significant difference in the volume of intraoperative fluid administered when PVI is used to target fluid therapy compared to the oesophageal Doppler. There is also no significant difference in post-operative morbidity or hospital length of stay between the two groups.

There are various technologies available for directing intra-operative fluid management, many of which require invasive procedures such as arterial cannulation. The low risk surgical population do not require arterial cannula placement for continuous blood pressure monitoring or repeated blood sampling in the peri-operative period, as there is no benefit conferred in this group beyond information that may be gained on fluid status. In this group a truly non-invasive method of quantifying the need, or at least ability to respond to a fluid challenge would provide valuable information to the anaesthetist and allow goal directed fluid therapy to be performed avoiding potentially harmful invasive interventions. As goal directed fluid therapy has been shown to improve post-operative outcomes, the PVI is ideally placed to be used in the low risk population in order to achieve this.

Low risk patients were identified either by cardiopulmonary exercise testing (CPET) or by an experienced clinician. CPET can be used to identify patients at high risk of post-operative morbidity and mortality, and conversely can therefore also be used to identify the patient at a lower risk of complications (51, 84). Anaerobic threshold (AT) and VE/VCO_2 can be used to risk stratify patients as those with an AT <11 ml/kg/min or VE/VCO_2 >34 have been shown to have an increased relative risk of mortality (51). However, whilst studies are in agreement that a decreasing AT and increasing VE/VCO_2 increases risk, there have been different values suggested as an optimal cut-offs with some evidence for a lower value of 10.1 ml/kg/min as a predictive value for risk stratifying patients using AT(84, 85). The cut off of an AT > 11 in this study whilst possibly excluding some low risk patients, ensured that high risk patients were not inadvertently recruited. Not all patients had fitness assessed by

CPET, as departmental policy is only test patients over the age of 55 unless they have multiple co-morbidities. Therefore in order to include patients less than 55 in the study, these patients were screened by experienced consultant anaesthetists to stratify their risk according to co-morbidity and self reported exercise tolerance and were considered low-risk in the absence of co-morbidity and reduced exercise tolerance.

There is a paucity of published studies examining goal directed therapy in low risk patients with the only comparable cohort seen in the study by Challand and colleagues (127) in which patients underwent stroke volume maximisation using the oesophageal Doppler. Similar to this study, patients were considered aerobically fit if the AT was greater than 11 ml/kg/min.

In comparison to Challand and colleagues(127) who suggested that goal directed fluid therapy targeted by oesophageal Doppler could be deleterious to fit patients, there was a large difference in overall fluid administered compared to this study (Table 43), despite a similar Doppler algorithm for stroke volume maximisation being used. This larger volume of fluid delivered in the work by Challand may account for the increased hospital length of stay (median 8.8 v 6 days) and complication rates (68 v 50%) that were seen. Therefore it may be that the possible deleterious effect of using oesophageal Doppler in fit patients suggested by Challand is not related to the use of goal directed fluid therapy in these patients, but rather the specific algorithm used when goal directed therapy was used in conjunction with a background untargeted fluid infusion.

Mean volume administered (ml) via GDFT	Challand and colleagues 'aerobically' fit patients	Doppler Group in this study
Total Crystalloid and Colloid	5242	1520
Total Colloid	1753	1450
Red cells	97	0

Table 43 Comparison of volumes of administered fluid targeted by oesophageal Doppler through stroke volume maximisation in our study compared to fit patients receiving GDFT within Challand and colleagues (127).

Significantly more fluid was administered in the Doppler group at 30 minutes, one hour and two hours, suggesting that fluid administration was front-loaded in the Doppler group. This is likely to be due to the technique of stroke volume maximisation, where SV has to be challenged to see a negative response before fluid administration ceases, compared to PVI, a measure of the likelihood of fluid responsiveness, which indicates when fluid administration is unlikely to be of benefit. In a larger group of patients with more variance in operative duration, patients with short procedures where fluid was targeted using stroke volume maximisation may receive increased intraoperative fluid. However, these procedures would have to be less than 120 minutes in length as there was no significant difference after 2 hours of operative time. These results are supported by the findings of Noblett and colleagues (14) who found that when using the oesophageal Doppler to target fluid in patients undergoing colorectal resections approximately 50% of the trial fluid boluses was administered in the first quarter of the operative period. Once again this may reflect the nature of the oesophageal Doppler where the first bolus has to be administered in order to determine if the patient is fluid deplete, in contrast PVI offers a static target which indicates whether the patient is likely to be fluid responsive. This also offers an intrinsic stop signal to halt further administration of fluid once the patient is adequately filled, whereas when using the Doppler it is only apparent after the target is achieved that no further stroke volume maximisation is achievable through fluid administration, necessitating an additional fluid challenge, beyond what is required.

Over the past decade there has been much debate over the optimal strategy for management of patients undergoing major abdominal surgery, with debate regarding 'liberal' and 'restrictive' regimes, and the benefits of goal-directed fluid optimisation. Restrictive regimes which aim for a 'zero-balance' between input and surgical losses have been shown to improve post-operative outcomes when compared to more liberal regimes which aimed to replace third-space losses (88). However, achieving a 'zero-balance' requires not only the meticulous calculation and replacement of intra-operative blood losses, but also accurate calculation of post-operative input, output and body weights with a requirement of pharmacological diuresis with furosemide to maintain pre-operative weight. Comparison of a 'zero-balance' strategy with intra-operative stroke volume maximisation using the oesophageal Doppler has shown no difference in post-operative morbidity or mortality (160). In practice introducing a protocol based on intra-operative goal-directed therapy is a more achievable and pragmatic target compared to a zero balance regime. In addition the results of the 'liberal' and 'restrictive' fluid trials are inconsistent in terms of outcome, which may be for various reasons including variations in both the type, volume and duration of fluid therapy. The inherent weakness of these strategies is that it is assumed that all patients within a cohort will be fluid optimised at a preset volume of fluid, which is inconsistent with variations in fasting status, intraoperative blood loss, fluid shifts, and individual patient cardiac function amongst others

In this study less fluid was administered to patients in either group than in the intervention groups of other studies of intra-operative goal directed fluid therapy (14, 124, 125, 127) as this is one of very few studies where all intraoperative fluid was targeted without a background infusion. Mean volume of fluid administered was similar to Davies and colleagues (161) where, similar to our study (Table 44), all fluid administered was directed by cardiac output monitoring (colloid targeted to stroke volume variation as determined by the Flotrac/Vigileo system, and similar to the intraoperative fluid administered in the stroke volume maximisation group studied by Brandstrup and colleagues(160) (Table 44) where patients received fluid

to target stroke volume as determined by oesophageal Doppler on top of an infusion intended to maintain a zero balance. Volume of fluid administered was also less than in a study by Forget and colleagues (150) who targeted fluid according to PVI, however, in this study patients also received a background infusion of 2ml/kg/hour and were drawn from a mixed risk population undergoing, upper or lower GI procedures with a mean operative duration of 295 minutes. This questions the need for background infusion that seem to lead to increased fluid loading in the intraoperative period, as target fluid replacement based on fluid responsiveness and cardiac output measurement alone should theoretically be adequate for patients, and minimises the unnecessary administration of fluid and the possible detrimental effects .

Mean volume administered (ml) via GDFT	Doppler Group in this study	Davies and Colleagues	Brandstrup and Colleagues
Total Crystalloid and Colloid	1520	1250	1798
Total Colloid	1450	1250	810
Red cells	0	261	78

Table 44 Comparison of volumes of administered fluid targeted by oesophageal Doppler through stroke volume maximisation in our study compared Davies and Colleagues (161) and Brandstrup and Colleagues (160).

Mean serum lactate was higher when measured in the recovery room in the PVI group, which could reflect the trend to the lower amount of fluid administered. However, this was not raised to a clinically significant level. Further this difference was not sustained at day one post-operatively, suggesting that this fit group of patients are better able to cope with a restricted level of fluid administration than with more liberal regimes where additional fluid may be detrimental as shown in previous studies (88). It should also be considered whether this is a type I error in light of no significant differences in lactate intraoperatively or at day 1 post-

operatively, especially in the light of previous work by Forget and colleagues who showed that using PVI, there was no significant difference in intraoperative lactate when compared to a standard care group, along with significantly lower lactate levels at 24 and 48 hours. However, there were no results for lactate in the immediate post-operative period in this study, and the lactate levels measured in the recovery period may correspond to the peak levels of inflammation as suggested by peaking of interleukin – 6 at six hours post-operatively in the cohort studied by Noblett and Colleagues(14) an effect which reduces at 24 and 48 hours post-operatively. An alternative interpretation could reflect that the Doppler group received more significantly more fluid per kg per minute of operative time, this could have resulted in a haemodilution effect reflected in a lower serum lactate in the immediate post-operative period.

There was no significant difference between the two groups in morbidity as defined by post-operative morbidity score on any post operative day. Use of the POMS allows an objective, prospective measure of morbidity. However whilst the individual nine domains are analysed, the lack of internal consistency between domains (153) means that a linear measure of morbidity can not be calculated, but rather it has to be used as a binary score indicating the presence or absence of any morbidity. A further weakness of POMS is that the presence of a routine therapeutic intervention such as an epidural or urinary catheter is considered as a morbidity, which could lead to misleading positive scores particularly early in the course of recovery, however by day 3 onwards this should be less of an issue as these routine therapies are withdrawn. In order to account for this weakness we also collected data on absolute incidence of more specific and defined complications.

A predefined list of complications was used to record the development of major or minor complications. Whilst it should be noted that the study was not powered to detect complications and the absolute number of complications was small, there was a significantly higher number of minor complications in the Doppler group (45 v 5% p=0.033). The low event rate of major complications amongst low risk patients would require a very large sample in order to detect any significant difference. The

increase in the proportion of subjects with minor complications is consistent with the evidence that the technique of stroke volume maximisation is deleterious to fit patients (127). This marked increase in minor complications was mainly in the rate of post-operative ileus and the development of superficial wound infections in the Doppler group, both of these complications have been associated with excess fluid administration. Whilst there was no significant difference in total volume of fluid administered, there was a trend to a higher volume of fluid administered in the Doppler group and a significantly higher volume per kilogram weight per minute time. A difference of 500ml of administered fluid was considered to be a significant when the study was powered, however, it may be that a lower volume can cause a significant clinical difference, and that this is reflected in the higher rate of minor complications in the Doppler group.

Recovery of gut function is an important consideration in patients undergoing colorectal surgery and increased rates of post-operative ileus would indicate that this may be delayed in low risk patients receiving oesophageal Doppler guided fluid therapy. Mythen (162) showed maximising stroke volume as measured by the oesophageal Doppler reduced the incidence of gut hypoperfusion, as determined by measuring intramucosal gastric pH (pHi) using a gastric tonometer and it is thought that improved recovery of gut function shown in previous studies (126) could be due improved intra-operative gut perfusion in patients who were fluid optimised using the oesophageal Doppler. However, the requirement for gut perfusion in low risk patients may be lower and therefore stroke volume maximisation may lead to gut oedema and increased risk of ileus.

Hospital length of stay in this study (median 7 days) was less than that of the aerobically fit patients receiving goal directed fluid therapy in work by Challand and colleagues (127) (median 8.8 days), and the 10 day median length of stay of patients who received goal directed therapy targeted by a combination of SV and CVP in Wakeling and colleagues(125). Our data is similar to nationwide data from the National Bowel Cancer Audit Project which shows a median hospital length of stay of 7 days for patients undergoing colonic resection, and 8 days for subjects having

rectal resections (11). This length of stay is also consistent with patients receiving goal directed therapy as targeted by FTc as reported by Noblett and colleagues (14) where median length of stay was 7 days. However, it is to be noted that the proportion of colonic resections was higher in our study that could also account for the reduced length of hospital stay. In addition caution is needed when comparing hospital length of stay data as local policies may vary regarding when a patient is considered ready for discharge and it is likely also to be affected by social factors (157).

5.1. Strengths of the study

This is the first randomised control trial to compare volumes of fluid administered when goal directed therapy is targeted by PVI with an established monitoring technology. Whilst Forget and colleagues (150) have shown an outcome benefit of using PVI in a randomised control trial, their control group targets were blood loss, arterial blood pressure and central venous pressure, which have been shown to be poor predictors of fluid responsiveness and post-operative outcome, and hence they may have been inadequately resuscitated (93) (92). Randomised control trials are considered to be the most rigorous test of a relationship between an intervention and outcome (163) as patients in both groups are treated identically except for the intervention under examination with random allocation into groups reducing the risk of a systematic bias. A prospective study with blinded follow-up, data was collected contemporaneously, further eliminating sources of bias. Whilst it was not possible to blind the intra-operative researcher due to the nature of the study, all post-operative follow up was carried out by a blinded member of the research team and data was kept separately until all data was collected and data entry was locked.

The two groups were well matched with similar demographics, operative and anaesthetic parameters were also similar. Only pre-operative haemoglobin was significantly different between the groups. The homogeneity of the patient groups with regard to age and co-morbidity may reflect that only patients who were considered ‘low-risk’ were eligible for recruitment.

All intraoperative fluid was administered by a medically qualified researcher. All analysed cases were conducted by the same researcher. This researcher was independent of the anaesthetic, surgical and follow-up teams. Two patients where blinding of the anaesthetist was not carried out were excluded from the study. All patients received the intended therapy and only 4 patients (10.5%) received additional crystalloid at the direction of the anaesthetist. The study was designed so that all fluid administered was directed using targets from the trial protocol, with no additional untargeted background infusions delivered.

5.2. Weaknesses of the study

Due to local policies CPET variables were not available for all patients, therefore some patients were stratified as low risk based on subjective assessment of risk based on co-morbidity and functional ability by a consultant anaesthetist. Ideally we would have objectively risk stratified all patients using CPET as co-morbidity and functional ability may not identify all low-risk patients (73).

The study was only powered to detect a difference in intra-operative fluid administration. Secondary outcomes showed no significant difference, except for a trend towards increased minor complications in the Doppler group. There may be an overall increase in complications if a larger population was studied, which would support the findings that delivering goal directed fluid therapy using the an algorithm for stroke volume maximisation using oesophageal Doppler may be harmful in fit patients as evidenced by Challand and colleagues (127).

In contrast to earlier studies (14) (124) (126) which included FTC values in the algorithm, this study alongside more recent studies by Challand and Sennagore did not include FTC values but rather used stroke volume as a sole indicator in line with the manufacturer's current recommended algorithm. The use of stroke volume as the sole parameter is challenged by by results from a study by Hood and

colleagues(148) where it was noted that where a 10% decrease in stroke volume as measured by oesophageal Doppler had only a sensitivity of 37% in predicting fluid responsiveness. This is supported by Davies and colleagues (137) where on ROC curve analysis a 10% decrease in stroke volume as measured by the oesophageal Doppler did not predict fluid responsiveness (AUC, 95% CI 0.32-0.81). Therefore using stroke volume as a sole parameter for filling in the Doppler arm could be considered a weakness of the study. A high FTC is an indication of a well-filled patient and including this in the algorithm would create a stop signal, preventing stroke volume maximisation from reaching a point where it becomes detrimental.

Data collected on the secondary outcome of 24-hour fluid balance relied on documentation of fluid balance by the ward nursing staff on standard hospital fluid balance charts, in some cases it was difficult to discern if oral fluid intake had been accurately documented.

Finally our study had a mixture of laparascopic and open procedures reflecting the increasing popularity of the laparoscopic approach in patients undergoing colorectal surgery. Both abdominal insufflation and the steep Trendelenberg position adopted in laparoscopic surgery can lead to fluid shifts affecting PVI as shown in a study of fluid responsiveness by Hoiseth and colleagues (164) where there was a 2.6% change in PVI on establishment of a pneumoperitoneum ($p=0.025$). The numbers involved in this study make it difficult to assess the impact of laparoscopy on PVI directed fluid therapy, the larger number of laparoscopic cases in the PVI group may be a confounding factor. A larger population would be able to investigate if administered fluid volumes using goal directed fluid therapy varied in this particular group.

5.3 Further Work

An appropriately powered study with a primary outcome of incidence of complications is necessary to determine if stroke volume maximisation is related to an increase in post-operative complications when compared to PVI as seen in this study. As discussed previously, it may be that a smaller difference in the volume of

fluid administered intra-operatively can result in clinically significant effect of tissue oedema leading to an increase in development of ileus and wound infections. Further to this work should enquire into what fluid responsiveness in the low risk patient indicates. These patients may be more able to increase oxygen delivery to the tissues without an increase in pre-load than those with less ability to increase myocardial contractility. Thereby risks of tissue oedema associated with increasing pre-load outweigh the benefits of increased oxygenation.

As shown in this study there is a marked difference in total volume of intra-operative fluid administered when no-background infusion is used. Therefore further thought should be paid to the protocol for fluid administration, as this is also a factor influencing outcome, not just the technology used, a factor previously shown by the OPTIMISE trial (91) where sub-group analysis showed that experience with using protocol improved outcomes.

A larger sample size may also allow to control for the length of procedure and to determine if the front-loading of fluid when therapy is directed by oesophageal Doppler results in a significant difference for patients who have shorter procedures, and whether in these cases PVI would provide a more restrictive regime and an outcome benefit or to see if front-loading has any beneficial effects such as on reduced inflammatory markers as noted by Noblett (14).

Patients with arrhythmias were excluded from this study. However, following CPET testing it may be found that these patients are stratified as low risk. There is limited evidence of how PVI would perform in this patient group, therefore it would be interesting to evaluate its performance in this group.

Finally, further work is also necessary to investigate the effect of positioning and pneumoperitoneum on PVI guided fluid therapy. Increasingly colorectal surgery is being carried out laparascopically and the fluid shifts associated with abdominal insufflation or positioning manoeuvres have been shown to have effect on stroke

volume as measured by oesophageal Doppler and on PVI (164), however, evidence is limited on outcomes following goal directed therapy in this specific population.

5.4 Conclusion

Due to recent government directives intra-operative fluid management is now a standard of care during major colorectal surgery for all patients. In the low risk group it is important that iatrogenic harm is not caused by over treatment, and hence choice needs to be made towards balancing invasiveness of monitoring technology and the information derived. In addition thought needs to be given to the particular protocol to be used. In this study, using stroke volume maximisation, considerably less fluid was delivered compared to other published studies targeting haemodynamic variables derived from oesophageal Doppler, because no background infusion was used. Similar volumes were delivered when fluid therapy was directed by PVI compared to Doppler. Morbidity and length of stay compared favourably to studies of similar patient groups. Liberal regimes have been shown to be harmful in patients undergoing colorectal surgery (89), our study has shown that using a protocol targeting PVI delivers similar volumes to zero-balance regimes (160). PVI is unlikely to be clinically utilised outside the low risk group as in higher risk patients the need for intra-arterial blood pressure monitoring and sampling will favour the use of techniques utilising arterial cannulation. Further work is required regarding the role of goal directed fluid therapy in low risk patients, due to the uncertainty raised regarding the effects of stroke volume maximisation in this patient group, but this study reveals PVI as a option suitable for use in low-risk patients.

In conclusion, amongst fit patients undergoing major colorectal surgery there was no significant difference in volume of fluid administered when targeted by non-invasive PVI technology compared to stroke volume maximisation technique using oesophageal Doppler. There was no significant difference in post-operative outcomes between the groups. Therefore PVI offers a non-invasive, consumable free alternative for intra-operative fluid optimisation in fit patients undergoing major colorectal surgery, where intra-operative goal-directed therapy is a standard of care

but there is no requirement for arterial cannulation or to introduce an oesophageal Doppler probe.

Appendix 1

Local CPET Guidelines (York Hospital)

Patients with meeting the following criteria should undergo cardiopulmonary exercise testing at the pre-operative assessment clinic if undergoing:

- Major upper GI, colorectal, urological or vascular surgery

AND

- And are aged greater than 55 years of age

OR

- With major cardio-respiratory co-morbidities

Appendix 2 - Pre-defined Complications

Pre-defined minor/major complications

MAJOR

Anastomotic leakage
- Requiring operation
- Percutaneous drainage
- Antibiotic treatment

Leakage of rectum
- Drainage of deep abscess

Peritonitis without leakage
- Requiring operation

Sepsis
- HR >90
- RR >20
- PaCO2 <4.3 KPa
- Core temp <36oC Core temp >38oC
- WCC <4000 cells/mm3 > 12000 cells/mm3 +>10% immature neutrophils
- Infection suspected/proven by culture/stain/PCR
- Evidence of a perforated viscus
- Abnormal CXR consistent with pneumonia

Necrosis of stoma
- Requiring operation

Wound dehiscence
- requiring suturing of fascia

Bleeding
- Requiring transfusion
- Requiring operation

Stroke

Pulmonary Emboli (on CTPA)

Pulmonary Oedema
- Requring FiO2 >0.6 CPAP/BiPAP Medical Treatment

Acute Coronary Syndrome
- ECG changes
- Troponin rise

Ventricular Arrhythmias
- ECG changes Requiring Medical treatment or Cardioversion

Bradycardia
- Requiring Medical Treatment or Pacing

Renal Failure
- Requiring CVVHF or Dialysis

Urinary extravasation
- requiring operation

MINOR

Superficial Wound infection, Haematoma or Dehiscence
- Requiring secondary suture

Prolonged nursing care

Paralytic Ileus

>7 days without flatus needing TPN

Pneumonia

Elevated temperature

Radiological changes

Pleural Effusion requiring drainage

Minor cardiac arrhythmias

ECG changes Requiring medical treatment or Cardioversion

Cystitis

Elevated Temperature

Dysuria

Positive culture

New confusional state

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GLOSSARY

ABBREVIATIONS

ASA	American Society of Anaesthesiologists
AT	Anaerobic Threshold
AUC	Area under curve
BNP	Brain natriuretic peptide
BUN	Blood urea number
CI	Cardiac Index
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise testing
CR POSSUM	Colorectal Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
CRP	C-reactive protein
CVC	Central venous catheter
CVP	Central Venous Pressure
DASI	Duke Activity Status Index
DO_2	Oxygen delivery
DO_2I	Oxygen delivery index
DSE	Dobutamine stress echocardiograph
ECG	Electrocardiography
FTc	Corrected flow time
GDFT	Goal directed fluid therapy
Hb	Haemoglobin
HDU	High Dependency Unit
HR	Heart rate
ICU	Intensive Care Unit
IHD	Ischaemic heart disease
IL	Interleukin

IQR	Interquartile Range
ISWT	Incremental Shuttle Walk Test
LiDCO	Lithium Dilution Cardiac Output
LOS	Length of stay
MACE	Major adverse cardiac event
MAP	Mean arterial pressure
METS	Metabolic equivalents
MI	Myocardial infarction
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NIBP	Non-invasive blood pressure
NSQIP	National Surgical Quality Improvement Program
NT-proBNP	N-terminal pro brain natriuretic peptide
ODM	Oesophageal Doppler Monitoring
OR	Odds ratio
P-POSSUM	Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PCO_2	Partial pressure of carbon dioxide
PCWP	Pulmonary capillary wedge pressure
pHi	Gastric intramucosal pH
PI	Perfusion Index
PO_2	Partial pressure of oxygen
POMS	Post-operative Morbidity Survey
POSSUM	Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
PPV	Pulse pressure variation
PVI	Plethysmograph Variability Index
ROC	Receiver operating characteristic

RR	Relative risk
SD	Standard deviation
SV	Stroke volume
SVI	Stroke volume index
SVV	Stroke volume variation
UK	United Kingdom
UO	Urine output
USA	United States of America
VE/VCO_2	Ventilatory equivalents for carbon dioxide
VE/VO_2	Ventilatory equivalents for oxygen
VO_2	Oxygen consumption
VO_2 max	Maximal oxygen uptake achieved
ΔPOP	Variation in the amplitude of the plethysmographic waveform
95% CI	95% confidence interval