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"Well, here's another nice mess you've gotten me into!"

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ABSTRACT

Studies in the early 2000s suggested that the introduction of flow or cardiac output monitoring could improve outcome in major surgery, especially in high-risk patients. This led the National Institute of Health and Care Excellence (NICE) in the UK to issue guidance in 2011 recommending the use of the Deltex Cardio Q Doppler flow monitor in these patients both to improve outcome and also reduce costs. This advice was subsequently extended to include all "flow monitors" in 2012. However, recent systematic reviews and major randomized controlled trials have failed to confirm the benefits of adding "flow" to conventional monitoring in the perioperative period. This paper examines physiological and methodological reasons behind this failure and introduces an alternative management strategy in high risk patients which incorporates cardiac output monitoring alongside the additional monitoring of cortical suppression and cerebral and tissue oxygenation.

Key words: multi-modal monitoring, cardiac output monitoring, depth of anaesthesia monitoring, cerebral oxygenation,venodilation

INTRODUCTION

The title of this article is taken from a very famous and oft quoted saying of the Anglo-American movie comedy duo, Laurel and Hardy. "NICE" is the abbreviation for the UK based National Institute for Health and Care Excellence which is an organisation targeted with the responsibility of improving outcomes for people using the NHS and other public health and social care services, in part by producing evidence-based guidance and advice for health, public health and social care practitioners (www.nice.org.uk). In 2011 NICE produced guidelines suggesting that the adoption of the Deltex CardioQ intra-operative flow (cardiac output, CO) monitor is:

"supported by the evidence that in high risk surgery there is a reduction in post-operative complications, use of central venous catheters and in-hospital stay (with no increase in the rate of re-admission or repeat surgery) compared with conventional clinical assessment with or without invasive cardiovascular monitoring. The cost saving per patient, when the CardioQ-ODM is used instead of a central venous catheter in the peri-operative period, is about £1100 based on a 7.5-day hospital stay". (1)

The advice was later extended to include all "flow monitors".

This article will review the evidence behind this statement in 2017 and suggest that much more still needs to be done beyond the simple addition of flow or CO measurement to conventional anaesthesia monitoring to improve outcome of high risk surgical patients. Indeed, as we shall see, due to a lack of demonstrable benefit in recent trials, many opinion leaders are now suggesting abandonment of this new technology and consider it irrelevant. A NICE mess we have gotten into!

THE INCREASINGLY HIGH-RISK SURGICAL POPULATION

It was estimated that 1 million of the estimated 3 million operations carried out in the UK NHS in 2013 as part of the National Audit Project 5 (NAP5) survey on accidental awareness under general anaesthesia were on patients aged over 65. (2) In a recent Australian and New Zealand study, 5% of patients over 70 died within 30 days of surgery. (3) The "Reason" study investigators commented that "strategies are needed to reduce complications and mortality in older surgical patients". Strategies and protocols need to be guided by monitors not "recipe books" and we need to individualise patient care. (4) Anaesthetists must also recognise that deficiencies in intraoperative management may not produce immediate mortality but may set in motion pathological changes which are deleterious for long-term patient outcome. Multimodal monitoring (MMM) using CO but in combination with depth of anaesthesia and tissue oximetry as described in the article is an attempt to reduce those complications and overall mortality after high risk surgery, especially in the elderly.

Two questions arise from these statistics:

1. What could account for such a high mortality after major surgery in the high risk, elderly patient?
2. Can we intervene to reduce the risk of mortality?

NEW MONITORING TECHNOLOGY AND ITS USE IN THE OPERATING ROOM

There have been very few advances in routine intraoperative monitoring in anaesthesia in the last 30 years since the clinical introduction of the pulse oximeter in 1984. The addition of flow monitoring to routine monitoring in the latest trials does not appear to have had much benefit in reducing mortality or complications (5, 6) with 30 day mortality still around 5% in the elderly surgical population. (3) Although there is now evidence to suggest that the use of in-

dividual new monitors (such as CO, depth of anaesthesia and tissue oximetry) can improve outcome, it will probably only be their combination that will radically improve the perioperative management and outcome of high-risk surgical patients. (7 – 9)

BLOOD PRESSURE AND CO MONITORING AS PART OF A MULTIMODAL MONITORING STRATEGY

Most anaesthetists try to maintain mean arterial pressure (MAP) during surgery within about 20% of the pre-induction value. What is the evidence that low MAP is harmful? A recent retrospective study from the Veterans Administration (VA) system in the USA showed that a systolic, mean or diastolic pressure less than 70, 50 or 30 mmHg respectively for more than just 5 minutes was associated with a roughly 3 fold increase in 30 day mortality. (10)

USING FLUIDS TO MAINTAIN MAP

Intraoperative fluid management is still influenced by the then ground breaking paper from Shires et al from Dallas published in 1961 in the Annals of Surgery. (11) The investigators used a triple indicator dilution technique which suggested that there was a profound loss of functional extracellular fluid during major surgery, later nicknamed "third space", which could amount to up to 15ml.kg-1 body weight hr-1 during major surgery and needed to be replaced by a balanced salt solution (e.g. Lactated Ringer's or Hartmann's) to maintain circulating volume and MAP. The volume required (up to 15ml.kg-1 hr-1) is equivalent to 24 hours water and 6 days Na+ requirement in a 3 hour procedure! The technique that Shires et al used to calculate this "third space loss" was flawed and recent evidence confirms that "there is no convincing evidence supporting the existence of the non-anatomical third space loss neither in haemorrhagic shock nor in surgery of any kind". (12 – 15) This highlights another problem. Third space loss does exist in conditions such as septic shock, anaphylaxis and burn injury and it is important to distinguish fluid and flow requirements in elective surgery in contradistinction to haemodynamic changes in the intensive care unit where sepsis may well be a serious problem. Reviews of fluid management often mix up these two completely different scenarios and thus cause unnecessary confusion! The dangers of excessive fluids and volume overload have recently been re-iterated by Marik. e.g. pulmonary oedema and increased extravascular lung water, impaired oxygenation, altered pulmonary and chest wall mechanics, increased work of breathing, myocardial oedema etc. The list is long. (16)

USING VASOACTIVE AGENTS TO MAINTAIN MAP

It is very easy to restore MAP to "normal" using vasoactive agents such as metaraminol, phenylephrine or noradrenaline. (17) However, MAP may then be maintained by increasing systemic vascular resistance (SVR) rather than CO and oxygen delivery (DO2). The detrimental effects of the increase in SVR and reduction on CO due to vasoactive agents are clearly shown in Figure 1. which may also adversely affect cerebral oxygenation. (18)

CARDIAC OUTPUT CHANGES FOLLOWING INDUCTION AND MAINTENANCE OF ANAESTHESIA: IMPORTANT CONCEPTS OF THE PHYSIOLOGY OF ANAESTHESIA

The effect of venodilation as opposed to vasodilation

MAP fall following induction of anaesthesia is often ascribed to a fall in SVR due to peripheral vasodilation. Kamenik and Petrun, using the LiDCO rapid (LiDCO, UK), were able to demonstrate that the fall in MAP following BIS (Medtronic, USA) targeted induction using either propofol or

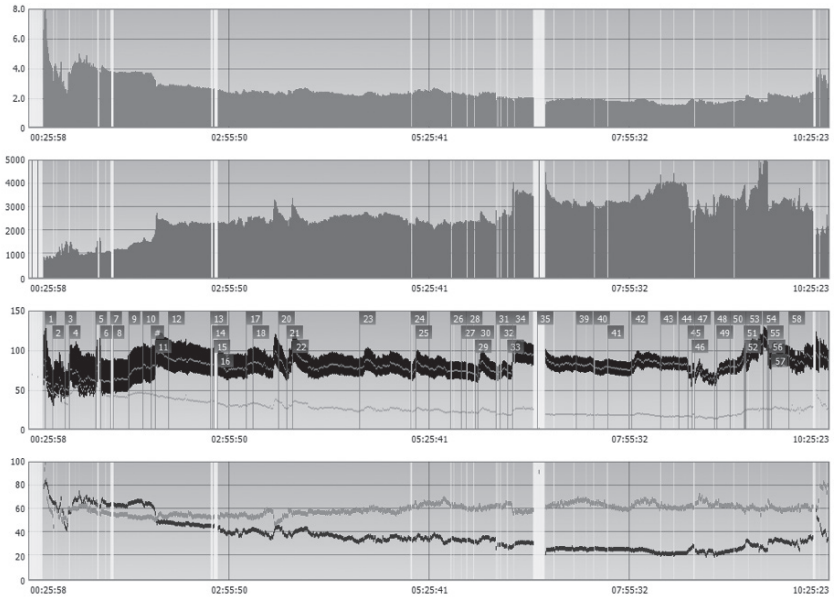

Figure 1. Haemodynamic changes during major surgery showing the deleterious effects of vasoconstrictors on cardiac output.

The traces are taken from a LiDCOrapid monitor. This was employed at the same time as another flow monitor which was used to manage the case. The operation duration is over 10 hours (x axis on all 4 traces).
The top red trace is nominal cardiac output (nCO) with a starting value of approximately 7 lpm prior to induction indicated by the horizontal red line. As can be seen, during the majority of the procedure the nCO fell to around 3 lpm a <>60% drop.
The next green trace is systemic vascular resistance (SVR) which shows a considerable increase throughout the procedure from baseline shown by the horizontal black line.
The next trace is blood pressure with systolic and diastolic indicated by the width of the trace and the mean arterial pressure in red. An horizontal yellow line has been drawn from the pre-induction value throughout the whole 10 hour procedue and shows that this value has been maintained at around 75mm Hg.
The bottom trace shows the starting nominal stroke volume (nSV) in dark blue with a horizontal blue line drawn from the starting value of around 80 mls with the blue arrow showing that for the majority of the procedure the value is around 20 to 30 ml., again an <> 60 ml drop. The purple trace and horizontal line shows that heart rate (HR) is maintained throughout at around 60 bpm.

etomidate was mainly due to a fall in CO and not due to a fall in SVR. (19)
Why do MAP and CO fall during anaesthesia? In studies of the causes of hypotension with ganglion blocking drugs it was found that it was mainly due to venodilation not a change in SVR. (20) Subjects with the greatest underlying venous tone were the elderly and anaemic and thus would suffer the greatest effects from venodilation on SV, CO and MAP. Does this apply to anaesthesia? Experiments in dogs showed that propofol produced an increase in venous capacitance due to venodilation (not peripheral arteriolar vasodilation). (21) Following venodilation the fall in MAP is due not only to falling preload, SV and CO with a consequent reduction in DO2 but also due to a shift of volume out of the arterial tree into the dilated venous compartment. (22) This mimics the effects of hypovolaemia. I believe venodilation is a key feature of anaesthesia that has been very little recognised. (22)

The question is whether we should try to maintain MAP by restoring effective venous capacitance with liberal fluids or by administration of a venoconstrictor? Phenylephrine, in low dose infusion (0.25-0.5 µg.kg-1.min-1), commenced pre-induction, with the effect monitored by the LiDCOrapid (see later), can maintain venous tone (without increasing SVR), venous capacitance, SV, CO and MAP obviating the need for liberal fluid administration. (23) It seems that liberal fluid replacement in surgery (see above) was simply given historically to overcome the effects of increase in venous capacitance and reduced venous return rather than a true loss of functional extracellular fluid. This excess fluid can lead to complications in the later postoperative period. (16)

Factors regulating cardiac output

Following the work of Guyton in the 50s, Wolff enumerated the factors controlling CO, DO2 and oxygen extraction. He pointed out that tissues (except skin and kidney) regulate (pull) their own flow and DO2 according to their metabolic demands and the heart responds to this oxygen demand by increasing output. (24) Post induction measurement of CO greatly underestimates the true resting CO/DO2 and therefore any intervention which is supposedly designed to "optimise stroke volume" (whatever that means) rather than maintain pre-induction CO/DO2 will be flawed and may result, as above, in unnecessary excess fluid and Na+ administration without improving outcome in high-risk patients. (6, 16, 25) Increasing CO artificially with fluids by a SV maximisation strategy to try and push supply oxygen to the tissues is looking at the problem the wrong way round. (24) This inevitably leads to excessive fluid administration and thence poor outcome. (16)

Recommendation by NICE to add flow (CO) monitoring

As mentioned in the introduction, in 2011 NICE in the UK recommended the addition of flow monitoring using Doppler (Oesophageal Doppler, Deltex UK) technology for a distinct group of high-risk surgical patients undergoing particular surgical operations. (1) Even then, the guidance was questioned and argued over in editorials. (26, 27)

Circulatory physiology during anaesthesia and the implications for adding CO monitoring

Before expecting the addition of a CO monitor to improve outcome it is important to be clear about the physiological effects of anaesthesia as mentioned above. This not only includes distinguishing between venodilation and vasodilation but also the role of the intact endothelial glycocalyx layer (EGL) in controlling fluid exchange in the tissues. (28) This has important implications for surgical fluid management. (22) Excess fluids and Na+ to replace non-existent "third space loss" are not only unnecessary (15) but may actually damage the EGL directly by compression and distortion and also lead to an increase in atrial natriuretic peptide (ANP) which itself damages the layer. The implication is that "third space loss" may actually be precipitated by excess fluids!

Does the use of flow monitoring and goal directed fluid therapy (GDFT) on its own when added to conventional monitoring improve outcome and reduce mortality?
In a recent Cochrane collaboration review entitled "Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery", the investigators noted that using this strategy did not decrease mortality. Length of stay was decreased on average by only one day. (29) There were reductions in complications which accounted for the reduction in length of stay. However, the investigators concluded "the balance of current evidence does not support widespread implementation of this approach to reduce mortality but does suggest complications and duration of hospital stay are reduced". The Optimise trial, did not show reduction in a composite outcome of complications or 30 day mortality. (5) A recent editorial concluded that SV optimisation/maximisation provides "no marginal benefit in aerobically fit patients having elective surgery within a contemporary enhanced recovery pathway". (30) The reasons for this lack of benefit in a recent trial (6) have been suggested. (25) It is also to be noted that an analysis of a subset of patients from the Optimise trial showed a high proportion of patients (40%) in both the control and intervention groups with significantly raised troponin levels at 1 and 3 days postoperatively. (31) This increase in troponin has also been found to occur in 8% of all risk patients aged over 45 in the recent prospective Vision trial. (32) Sub clinical myocardial damage, possibly as a result of hypotension, which may lead to mortality is occurring in a high percentage of surgical patients.

Conclusion

Sadly, there has not been as much benefit as expected following the introduction of GDFT. This has been highlighted by a Pro Con editorial in 2016 where leading advocates of Pro (33) versus Con (34) GDFT put forward their rationale for and against this management strategy in the context of improved surgical management. There is even a call for a return to "usual perioperative care" and to abandon this new technology. (35) What is the way forward?

THE ROLE OF INDIVIDUALISED HAEMODYNAMIC THERAPY

In a review of perioperative haemodynamic therapy the authors stated that "once an individualised approach will be identified, the terms of liberal, restrictive and supra-normal values could eventually be replaced by adequate haemodynamic support that fits every patient's own needs". (4) The question is, can we identify a better individualised approach to further improve outcomes and in particular reduce mortality in this high-risk patient group?
I believe that the goal should be directed towards avoiding the build-up of oxygen debt as this has been shown by Shoemaker et al to contribute to poor outcome. (36) MMM can be used to assess and maintain DO2 as close to the pre-induction level as possible during surgery and into the

immediate postoperative period, thereby avoiding the build-up of oxygen debt. Lack of oxygen debt at the end of the procedure means that goal directed therapies intended to increase DO2 by fluids and inotropes in HDU/ICU and thus repay debt (5) or bring DO2 values up to pre-induction levels are no longer necessary and indeed may not benefit the patient anyway. (37)
This is in contradistinction to current strategies of trying to "optimise" or maximise SV and CO to nominal, population based values such as 2.5.min-1.m2 BSA values by injudicious use of fluids. (9) It should be remembered that CO is determined by the metabolic needs of the tissues and not the other way round. (24)

CEREBRAL AND TISSUE OXYGEN MONITORING AS PART OF THE MMM STRATEGY

"The proper management of brain oxygenation should be one of the principal endpoints of all anaesthesia procedures yet the brain remains one of the least monitored organs during clinical anaesthesiology". (38) Near infrared technology (NIRS) using a reflectance technique can be used to measure cerebral tissue oxygenation to a depth of about 2.5 cm below the measuring electrodes which are usually placed on the forehead. Regional brain oxygen saturation (rSO2 or ScO2) reflects overall tissue rather than arterial oxygen saturation or Sp02 as is the case with a pulse oximeter. (39) Cerebral rSO2 is venous weighted with a characteristic value in healthy patients of around about 70%, a similar value to jugular venous oxygen saturation. However, values as low as 40% or as high as 80% may be found in normal healthy patients. A detailed consideration of this technology is outside the scope of this article so the reader is referred to to the following reviews. (38, 40, 41) These monitors work best as trend monitors rather than absolute monitors (38) emphasising the importance of getting a pre-induction value in elective patients.
Apart from those neurological conditions where brain oxygenation is obviously suspect, for example carotid endarterectomy (42), many operations on the elderly may lead to reductions in rSO2 (43) and poor outcome. (44) The problem is to define suitable interventions if rSO2 diminishes by more than about 10% from starting value. (8) A MMM strategy which maintains flow and DO2 almost always insures that rSO2 will remain at or above the pre-induction level. (45)
Consideration of the role of cerebral oximetry in cardiac surgery where its clinical applicability is greatest is outside the scope of this article. However, the jury is out on it's true role (46) but several studies have indicated possible benefits. (47, 48)

My own experience with this monitoring technology amounts to nearly 1000 cases. These mainly include high-risk cases with an average ASA class of 3 or above, long duration where the build-up of oxygen debt will potentially be a problem and in the elderly population (average age 68) where oxygen debt is likely to cause most problems. Maintaining tissue oxygenation as assessed by the cerebral oximeter should lead to a reduction of oxygen debt and complications. (40) A recent review even suggests that cerebral and tissue oximetry should become the standard monitor of the future. (49) Reasons why this has not happened despite the technology being available for nearly 20 years and now 4 commercially available cerebral oximeters were suggested in a recent review. (41)

Conclusion

Although there is not overwhelming evidence to mandate the use of cerebral oxygen monitoring in major surgery I believe it is useful in carotid endarterectomy, shoulder surgery in the beach chair position, major thoracic and cardiac surgery and major abdominal and orthopaedic surgery in high risk patients.

DEPTH OF ANAESTHESIA MONITORING AS PART OF THE MMM STRATEGY

Figure 2 indicates why monitoring the effect of the anaesthetic on cortical suppression is important for high-risk patients yet may not be as important for fit and healthy patients. Looking along the x-axis from left to right, increasing anaesthetic concentration will inevitably lead to increasing cardiovascular depression and decreased DO2. This obviously has implications for build- up of oxygen debt, complications in the post-operative period and poor outcome. It also is likely to produce neuronal toxicity as the concentration of anaesthetic increases. (50) On the other hand, moving from right to left along the x-axis, too little anaesthetic obviously gives one a risk of patient explicit recall and also we may lose the benefits of anaesthetic neuronal protection. So, there is a balance to be struck.

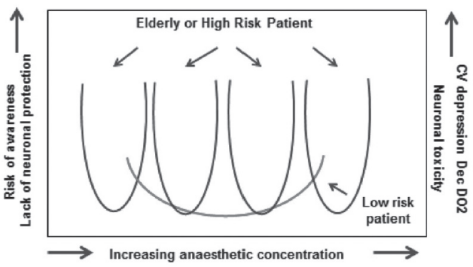

Figure 2. The potential effects of changes in depth of anaesthesia (cortical suppression) on cardiovascular and neuronal function in high versus low risk patients

Key: the x axis indicates that increasing anaesthetic concentration from low to high has an effect on the risk of awareness and lack of neuronal protection if the concentration is too low (left y axis) or on the other hand excessive cardiovascular depression and risk of neuronal toxicity in the concentration is too high (right y axis).
The low-risk patient is indicated by the red line which suggests that there is a wide margin of safety when choosing a suitable anaesthetic concentration and the risk of harm is minimal. This is indicated by the shallowness of the curve. On the other hand, with an elderly or high-risk patient, the implications for getting it wrong as indicated by the blue curves are much greater (steeper curves) and there is a much narrower margin of safety. Conventional wisdom suggests that most elderly or high-risk patients need very little anaesthesia as indicated by the left-hand blue curve. However, there is a wide spectrum of anaesthesia requirements in the elderly or high-risk patient which means that they may require even more anaesthetic than the low-risk patient. Use of a cortical suppression monitor allows us to adjust for these differences and administer the correct amount of anaesthesia for the individual high risk patient.
Reproduced with permission from Perioperative Medicine (ref 8)

The red curve indicates a low risk patient where the target anaesthetic concentration is rather broad and the implications of a small clinical misjudgement of the depth of anaesthesia (as indicated by the shallowness of the curve) means that not too much harm will likely come to the patient.

This is not the same situation in the elderly or high-risk patient in whom it is usually assumed that the amount of anaesthetic required is less and too light anaesthesia will lead to the patient waking up and moving around whereas a slight increase to deepen the anaesthetic may result in profound cardiovascular depression. All anaesthetists have observed this in their practice! However, 10 years' experience with the BIS monitor in high-risk patients, especially the elderly, have shown that some older patients require much more anaesthetic than others and indeed there is up to a fourfold variation in propofol anaesthesia requirement. (45) This variation cannot be predicted by clinical signs alone.

EXCESSIVE DEPTH OF ANAESTHESIA IS HARMFUL

This technology is now recommended by NICE in the UK for high-risk patients and the latest Recommendations for Standards of Monitoring during Anaesthesia and Recovery 2015 from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) include depth of anaesthesia monitoring during total intravenous anaesthesia when neuromuscular blockers are used. (51) Evidence shows that BIS guided anaesthesia decreases post-operative delirium (52) and cognitive decline (POCD) (53) and in the USA it is now recommended to reduce the incidence of delirium in older patients. (54) In addition, the latest "Triple Low" study has now confirmed that the combination of hypotension (MAP < 75mmHg) together with a low BIS (<45) and low anaesthesia requirement (MAC < 0.8) is associated with an increase in 30 and 90-day mortality by approximately 10% for every 15 cumulative minutes of triple low states. This was after controlling for known confounders for perioperative death which confirms that a low BIS number is not an epiphenomenon (i.e. as a result of the patient being sick and thus high risk) but is due to excess anaesthetic dose. (55) Depth of anaesthesia monitoring is an essential component of MMM!

USE OF COMBINED BIS AND CEREBRAL OXIMETRY TO REDUCE THE INCIDENCE OF POCD

In a cohort study and nested randomised controlled trial of high risk elderly patients undergoing major abdominal and orthopaedic surgery, using combined technology of BIS and cerebral oximetry as interventions, investigators were able to show a profound reduction in the intervention group in POCD. (56) Of interest was the fact that maintaining the BIS in the "normal" range 40-60 i.e. not too deep and not too light led to significantly lower levels of S100 B, an indicator of neuronal damage, in the intervention group.

SHOULD WE USE A MMM STRATEGY IN HIGH-RISK PATIENTS?

One of the highest risk patient categories that are dealt with on a routine basis are those elderly patients who suffer a proximal femoral fracture. Recent guidelines suggest that monitoring of CO, depth of anaesthesia and rSO2 should be considered alongside a basic monitoring setup in this high-risk group. (58)

HOW DO WE DO IT?

An in-depth discussion of using MMM is outside the scope of this article. However, the basic strategy and rationale of MMM in reducing oxygen debt is outlined in Figure 3.

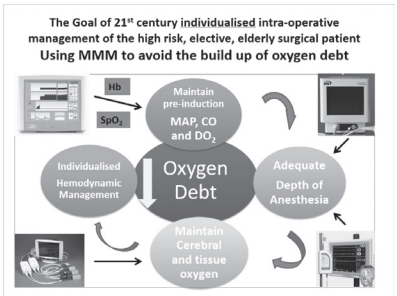

Figure 3. The basic strategy and rationale of multi-modal monitoring. Avoiding the build up of oxygen debt. For explanation see text.

- LiDCOrapid monitoring is established and this can use either the radial artery invasive or non-invasive arterial BP waveform (CNAP, CN systems, Graz, Austria)
- Record the baseline values for MAP, nCO and nDO2
- Attach BIS monitor to obtain a baseline and commence monitoring
- Attach cerebral oximeter electrode(s) and obtain a baseline rSO2 prior to pre-oxygenation
- Begin a low dose phenylephrine or noradrenaline infusion to maintain venous tone
- Induce and maintain anaesthesia (BIS 40 – 55) using ideally a total intravenous technique using remifentanil and propofol
- Maintain rSO2 by ensuring an adequate Hb concentration and nDO2 is at least 85% or greater than baseline. NB in the elderly, hypocapnia is one of the commonest reasons for an unexpected decline in rSO2

DOES THE MMM STRATEGY MAKE A DIFFERENCE TO OUTCOME IN HIGH-RISK SURGERY

An observational case series in 120 very high-risk patients undergoing major peripheral vascular surgery suggests that a mean nCO and rSO2 can be maintained at 87% or above of pre-induction value with a mean BIS of 45. The fluid requirement was only 5ml.kg-1.hr-1
30 day mortality was 0.8% (predicted 9%) and major amputation rate was 2% at 1 year. Only 8% of patients required postoperative HDU/ICU. (45) This compares very favourably with the outcome of recent randomised controlled trials using GDFT and SVO as seen in the Table 1.
It is crucial that future randomised controlled trials using flow monitoring should use the MMM approach mentioned above with efforts made to have appropriate levels of cortical suppression and maintain pre-induction values of CO and DO2 to within 10 to 15% of baseline. The technique of SV maximisation and GDT to a population-based target of 600 ml.m-2 BSA should be abandoned. (9) In addition, future trials should recognise that third space loss does not occur in elective major surgery and thus patients should only receive minimal maintenance fluid in addition to replacement of obvious volume losses, a point recognised in the Optimise trial (5) protocol but not in other recent trials. (6, 58)

THE FUTURE

It should become routine practice to use a MMM strategy to try to maintain perioperative DO2 to minimise build-up of oxygen debt as a key for successful outcomes in high-risk surgical patients. This is achievable now with the monitoring tech-

Table 1. Results of mortality outcome for recent randomized controlled trials of goal directed fluid therapy compared with outcome for Multi-Modal Monitoring

Trial	Intervention	Date	RCT?	Nos	Surgical group	Technology	ASA status % ASA II or <	Mortality % Intervention	Mortality % Control
POEMAS, Spain1	GDFT, SVO/M	2014	Yes	142	Colorectal gastrectomy	NICOM	50%	4.2	5.7
Optimise (UK)2	GDFT, SVO plus dopexamine	2014	Yes	734	GI tract Upper/lower	LiDCO intraop	60%	4.9	6.5
GDT post op in HDU (UK)3	GDFT to preop CI in HDU/ICU	2015	Yes	187	GI tract Upper/lower	LiDCO pre and postop	?	5	5
SV optimisation in major surgery4	SVO/M with fluids colloid (Gel)	2015	Yes	204	GI tract Upper/lower	LiDCO intraop	80%	2.3	2.3
SV optimisation in major surgery5	SVO/M with fluids colloid (starch)	2011	Yes	172	GI tract Upper/lower	Doppler (DCQ) intraop	63%	2.2	2.2
MMM in major vascular surgery6	Maintain status quo	2014	No	120	Major vascular surgery	LiDCO, BIS Invos (MMM)	1%	0.8	9

CI, cardiac index
GDFT, goal directed fluid therapy
SVO/M, stroke volume optimization/maximization.
RCT, randomized controlled trial.

Key: As can be seen many of the patients (50 to 80%) were ASA II or less and thus not strictly high risk. Nevertheless, the mortality ranges between 2.2 and 4.9% in the intervention groups. The MMM in vascular surgery trial was not a RCT and the expected mortality was based on V Possum scores. (see reference). Only 1 patient was ASA II the remainder were ASA III or IV.

References to Table:

1. Pestana D, Espinosa E, Eden A, Najera D, Collar L, Aldecoa C, Higuera E, Escribano S, Bystritski D, Pascual J, Fernandez-Garijo P, de Prada B, Muriel A, Pizov R: Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). Anesth Analg 2014; 119: 579-87
2. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA : the journal of the American Medical Association 2014; 311: 2181-90
3. Ackland GL, Iqbal S, Paredes LG, Toner A, Lyness C, Jenkins N, Bodger P, Karmali S, Whittle J, Reyes A, Singer M, Hamilton M, Cecconi M, Pearse RM, Mallett SV, Omar RZ, group P-Os: Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. Lancet Respir Med 2015; 3: 33-41
4. Lai CW, Starkie T, Creanor S, Struthers RA, Portch D, Erasmus PD, Mellor N, Hosie KB, Sneyd JR, Minto G: Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness. Br J Anaesth 2015; 115: 578-89
5. Challand C, Struthers R, Sneyd JR, Erasmus PD, Mellor N, Hosie KB, Minto G: Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. Br J Anaesth 2012; 108: 53-62
6. Green D, Bidd H, Rashid H: Multimodal intraoperative monitoring: An observational case series in high risk patients undergoing major peripheral vascular surgery. International Journal of Surgery 2014; 12: 231-236

nology available. (25) The recent arrival of finger-based non-invasive and continuous blood pressure monitoring with provision for converting the waveform into flow means that in the future all high risk patients could benefit from this strategy. (59)

CONCLUSION

MMM has advantages for the anaesthetist, the patient and the healthcare system. It pinpoints very clearly the physiological changes associated with anaesthesia and surgery from pre-induction to post anaesthesia care unit. It allows intervention strategies to be more focused and physiologically appropriate and allows a more rational approach to intraoperative haemodynamic management. As we get greater insight into intraoperative physiological change in our patients we can individualise management using strategies designed and centred on minimising the build-up of oxygen debt and thus this should improve outcome. The burgeoning of the elderly high-risk patient population mandates a new perioperative anaesthetic management strategy alongside ERAS. It would appear that MMM reduces the requirement for expensive HDU and ICU facilities and may decrease hospital length of stay and therefore reduce the cost of perioperative care by reducing patient morbidity and mortality.

REFERENCES

1. National Institute for Health and Clinical Excellence. Medical technologies guidance MTG3: CardioQODM oesophageal doppler monitor., http://www.nice.org.uk/MTG3, 2011
2. Sury MR, Palmer JH, Cook TM, Pandit JJ: The state of UK anaesthesia: a survey of National Health Service activity in 2013. British Journal of Anaesthesia 2014; 113: 575-84
3. Story DA, Leslie K, Myles PS, Fink M, Poustie SJ, Forbes A, Yap S, Beavis V, Kerridge R: Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study*. Anaesthesia 2010; 65: 1022-1030
4. Kirov MY, Kuzkov VV, Molnar Z: Perioperative haemodynamic therapy. Curr Opin Crit Care 2010; 16: 384-92
5. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA : the journal of the American Medical Association 2014; 311: 2181-90
6. Lai CW, Starkie T, Creanor S, Struthers RA, Portch D, Erasmus PD, Mellor N, Hosie KB, Sneyd JR, Minto G: Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness. Br J Anaesth 2015; 115: 578-89
7. Green D, Paklet L: Latest developments in peri-operative monitoring of the high-risk major surgery patient. Int J Surg 2010; 8: 90-99
8. Bidd H, Tann A, Green DW: Using bispectral index and cerebral oximetry to guide hemodynamic therapy in high-risk surgical patients. Perioperative Medicine 2013; 2: 1-9
9. Vincent JL, Rhodes A, Perel A, Martin GS, Della Rocca G, Vallet B, Pinsky MR, Hofer CK, Teboul JL, de Boode WP, Scolletta S, Vieillard-Baron A, De Backer D, Walley KR, Maggiorini M, Singer M: Clinical review: Update on hemodynamic monitoring--a consensus of 16. Crit Care 2011; 15: 229
10. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE: Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology 2015; 123: 307-19
11. Shires T, Williams J, Brown F: Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961; 154: 803-10
12. Brandstrup B, Svensen C, Engquist A: Hemorrhage and operation cause a contraction of the extracellular space needing replacement--evidence and implications? A systematic review. Surgery 2006; 139: 419-32
13. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. Anesthesiology 2008; 109: 723-40
14. Jacob M, Chappell D, Rehm M: The 'third space'--fact or fiction? Best practice & research. Clinical anaesthesiology 2009; 23: 145-57
15. Minto G, Mythen MG: Perioperative fluid management: science, art or random chaos? British Journal of Anaesthesia 2015; 114: 717-721
16. Marik PE: Iatrogenic salt water drowning and the hazards of a high central venous pressure. Annals of intensive care 2014; 4: 21
17. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE: Restrictive Deferred Hydration Combined with Preemptive Norepinephrine Infusion during Radical Cystectomy Reduces Postoperative Complications and Hospitalization Time: A Randomized Clinical Trial. Anesthesiology 2013
18. Meng L, Cannesson M, Alexander BS, Yu Z, Kain ZN, Cerussi AE, Tromberg BJ, Mantulin WW: Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth 2011; 107: 209-17
19. Moller Petrun A, Kamenik M: Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. Br J Anaesth 2013; 110: 388-96
20. Sharpey-Schafer EP: Venous tone. British Medical Journal 1961; 2: 1589-95
21. Goodchild CS, Serrao JM: Cardiovascular effects of propofol in the anaesthetized dog. Br J Anaesth 1989; 63: 87-92
22. Wolff CB, Green DW: Clarification of the circulatory patho-physiology of anaesthesia - Implications for high-risk surgical patients. International journal of surgery 2014; 12: 1348-1356
23. Green DW: Cardiac output decrease and propofol: what is the mechanism? Br J Anaesth 2015; 114: 163-4
24. Wolff CB: Normal cardiac output, oxygen delivery and oxygen extraction. Adv Exp Med Biol 2007; 599: 169-82
25. Green D, O'Brien T: Restoration to normal physiology without the use of excessive fluids. British Journal of Anaesthesia 2016; 117: 264-266
26. Ghosh S, Arthur B, Klein AA: NICE guidance on CardioQ(TM) oesophageal Doppler monitoring. Anaesthesia 2011; 66: 1081-3
27. Singer M: Oesophageal Doppler monitoring: a not-so-NICE editorial. Anaesthesia 2012; 67: 428-30; author reply 431-2
28. Alphonsus CS, Rodseth RN: The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia 2014; 69: 777-84
29. Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K: Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review. Br J Anaesth 2013; 111: 535-48
30. Minto G, Struthers R: Stroke volume optimisation: is the fairy tale over? Anaesthesia 2014; 69: 291-296
31. Gillies MA, Shah AS, Mullenheim J, Tricklebank S, Owen T, Antonelli J, Strachan F, Mills NL, Pearse RM: Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. Br J Anaesth 2015; 115: 227-33
32. Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, Guyatt G, Cruz P, Graham M, Wang CY, Berwanger O, Pearse RM, Biccard BM, Abraham V, Malaga G, Hillis GS, Rodseth RN, Cook D, Polanczyk CA, Szczeklik W, Sessler DI, Sheth T, Ackland GL, Leuwer M, Garg AX, Lemanach Y, Pettit S, Heels-Ansdell D, Luratibuse G, Walsh M, Sapsford R, Schunemann HJ, Kurz A,

Thomas S, Mrkobrada M, Thabane L, Gerstein H, Paniagua P, Nagele P, Raina P, Yusuf S, Devereaux PJ, Devereaux PJ, Sessler DI, Walsh M, Guyatt G, McQueen MJ, Bhandari M, Cook D, Bosch J, Buckley N, Yusuf S, Chow CK, Hillis GS, Halliwell R, Li S, Lee VW, Mooney J, Polanczyk CA, Furtado MV, Berwanger O, Suzumura E, Santucci E, Leite K, Santo JA, Jardim CA, Cavalcanti AB, Guimaraes HP, Jacka MJ, Graham M, McAlister F, McMurtry S, Townsend D, Pannu N, Bagshaw S, Bessissow A, Bhandari M, Duceppe E, Eikelboom J, Ganame J, Hankinson J, Hill S, Jolly S, Lamy A, Ling E, Magloire P, Pare G, Reddy D, Szalay D, Tittley J, Weitz J, Whitlock R, Darvish-Kazim S, Debeer J, Kavsak P, Kearon C, Mizera R, O'Donnell M, McQueen M, Pinthus J, et al.: Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology 2014; 120: 564-78

33. Cannesson M, Gan TJ: PRO: Perioperative Goal-Directed Fluid Therapy Is an Essential Element of an Enhanced Recovery Protocol. Anesth Analg 2016; 122: 1258-60

34. Joshi GP, Kehlet H: CON: Perioperative Goal-Directed Fluid Therapy Is an Essential Element of an Enhanced Recovery Protocol? Anesth Analg 2016; 122: 1261-3

35. Raghunathan K, Wang XS: In support of 'usual' perioperative care. British Journal of Anaesthesia 2016; 117: 7-12

36. Shoemaker WC, Appel PL, Kram HB: Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. Chest 1992; 102: 208-15

37. Ackland GL, Iqbal S, Paredes LG, Toner A, Lyness C, Jenkins N, Bodger P, Karmali S, Whittle J, Reyes A, Singer M, Hamilton M, Cecconi M, Pearse RM, Mallett SV, Omar RZ, group P-Os: Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. Lancet Respir Med 2015; 3: 33-41

38. Murkin JM, Arango M: Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth 2009; 103 Suppl 1: i3-13

39. Murkin JM: Cerebral oximetry: monitoring the brain as the index organ. Anesthesiology 2011; 114: 12-3

40. Scheeren TW, Schober P, Schwarte LA: Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. J Clin Monit Comput 2012; 26: 279-87

41. Green DW, Kunst G: Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia 2017; 72 Suppl 1: 48-57

42. Ritter JC, Green D, Slim H, Tiwari A, Brown J, Rashid H: The Role of Cerebral Oximetry in Combination with Awake Testing in Patients Undergoing Carotid Endarterectomy under Local Anaesthesia. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2011; 41: 599-605

43. Green DW: A retrospective study of changes in cerebral oxygenation using a cerebral oximeter in older patients undergoing prolonged major abdominal surgery. Eur J Anaesthesiol 2007; 24: 230-4

44. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, Fierro G, De Cosmo G, Servillo G: Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg 2005; 101: 740-747

45. Green D, Bidd H, Rashid H: Multimodal intraoperative monitoring: An observational case series in high risk patients undergoing major peripheral vascular surgery. International Journal of Surgery 2014; 12: 231-236

46. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW: Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesth Analg 2013; 116: 663-76

47. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S: Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8

48. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM, 3rd, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV: Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009; 87: 36-44; discussion 44-5

49. Moerman A, De Hert S: Cerebral oximetry: the standard monitor of the future? Current Opinion in Anesthesiology 2015; 28: 703-9

50. Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ, Fiskum G, Giffard RG, Herold KF, Loepke AW, Ma D, Orser BA, Planel E, Slikker W, Jr., Soriano SG, Stratmann G, Vutskits L, Xie Z, Hemmings HC, Jr.: Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. Br J Anaesth 2013; 111: 143-51

51. Checketts MR, Alladi R, Ferguson K, Gemmell L, Handy JM, Klein AA, Love NJ, Misra U, Morris C, Nathanson MH, Rodney GE, Verma R, Pandit JJ: Recommendations for standards of monitoring during anaesthesia and recovery 2015 : Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 2016; 71: 85-93

52. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD: Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. British Journal of Anaesthesia 2013; 110 Suppl 1: i98-105

53. Chan MT, Cheng BC, Lee TM, Gin T: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25: 33-42

54. American Geriatrics Society Expert Panel on Postoperative Delirium in Older A: Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. J Am Coll Surg 2015; 220: 136-48 e1

55. Willingham MD, Karren E, Shanks AM, O'Connor MF, Jacobsohn E, Kheterpal S, Avidan MS: Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death. Anesthesiology 2015; 123: 775-85

56. Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, Lowery D, Corbett A, Wesnes K, Katsaiti E, Arden J, Amaoko D, Prophet N, Purushothaman B, Green D: Optimised Anaesthesia to Reduce Post Operative Cognitive Decline (POCD) in Older Patients Undergoing Elective Surgery, a Randomised Controlled Trial. PLoS One 2012; 7: e37410

57. Griffiths R, Alper J, Beckingsale A, Goldhill D, Heyburn G, Holloway J, Leaper E, Parker M, Ridgway S, White S, Wiese M, Wilson I: Management of proximal femoral fractures 2011: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia 2012; 67:

85-98
58. Challand C, Struthers R, Sneyd JR, Erasmus PD, Mellor N, Hosie KB, Minto G: Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. Br J Anaesth 2012; 108: 53-62
59. Saugel B, Reuter DA: III. Are we ready for the age of non-invasive haemodynamic monitoring? British Journal of Anaesthesia 2014; 113: 340-3