Lifting the lid on perioperative goal-directed therapy

Martin, Daniel S.

Published in:
British Journal of Anaesthesia

DOI:
10.1016/j.bja.2021.07.009

Publication date:
2021

Title: Lifting the lid on perioperative goal-directed therapy

Daniel S Martin OBE

Professor of Perioperative and Intensive Care Medicine

Peninsula Medical School, University of Plymouth, John Bull Building, Plymouth Science Park, 16 Research Way, Plymouth, Devon, PL6 8BU, United Kingdom

daniel.martin@plymouth.ac.uk

Word count: 1595

Recently, extraordinary advances have been made in the understanding and treatment of a number of diseases, through the advancement of basic science, and translational and stratified medicine.[1–3] However, the treatment of less precisely defined conditions and syndromes such as the generalised deterioration and multiple organ failure that can occur after major surgery is potentially a far more complex puzzle to solve. Perioperative morbidity is unlikely to be the result of a single gene defect that can be repaired with a sophisticated molecular tool or a distinct biological pathway amenable to pharmacological manipulation. Whilst we are awash with perioperative risk stratification tools[4] we lack molecular approaches to predicting outcomes for patients undergoing major surgery. The latter would require us to have a comprehensive understanding of the pathophysiology of postoperative morbidity. Yet we find ourselves is in the somewhat back-to-front situation of testing therapies for a disease we do not understand. For example, ongoing studies continue to evaluate the efficacy of goal-directed therapy (GDT) in the hope that it will reduce postoperative morbidity and mortality despite the absence of a clear molecular roadmap.[5, 6] Countless studies have investigated the value of GDT as a perioperative intervention but their findings have been inconsistent.[7–9] It is currently uncertain whether or not we should be

using GDT as part of our routine care to reduce perioperative harm and the results of these further trials are awaited.

Heywood et al. have provided another piece to the puzzle by exploring patterns of protein expression in skin biopsies taken from patients before and two days after major surgery.[10] The purpose of their study was to explore biological pathways linked to inflammation in this easily accessible but often forgotten organ system in order to seek mechanistic support for a GDT intervention. The skin samples were taken from participants enrolled into a randomised controlled trial (RCT) designed to assess the efficacy of protocolised GDT (intravenous fluids with or without a continuous infusion of dobutamine) delivered for six hours after surgery.[11] For participants in the GDT group, the aim was to maintain an individual's postoperative systemic oxygen delivery (DO_2) at its preoperative value. The outcome of the trial was noteworthy because although there was no difference in morbidity between the GDT and control groups, when patients in whom preoperative DO_2 was maintained (regardless of trial group allocation) were compared to those in whom it had not been maintained, a reduction in postoperative morbidity was noted.[11] These results suggest that maintenance of an individual's resting DO_2 early in the postoperative recovery phase (regardless of how this arises) is clinically beneficial. The question is why?

As obligate aerobic organisms we require a continuous supply of oxygen to the inner mitochondrial membrane, where it acts as the final key to unlock ATP from the substrates we consume. Our circulatory system has evolved such that there is usually an abundance of oxygen in circulation, acting as a buffer for when demand increases or supply declines. What we need to remember about this arrangement is that it is demand driven, although it can be supply limited. The rapid increase in oxygen demand triggered by exercise is an excellent example of this system in action.[12] In its simplest terms, effective oxygen delivery is comprised of oxygenated arterial blood, sufficient haemoglobin to carry the oxygen and a

well-functioning cardiovascular system to provide an appropriate cardiac output. Most GDT algorithms therefore aim to protect arterial oxygenation, avoid significant anaemia and maintain a normal or supranormal cardiac output. The concept of preventing a perioperative 'oxygen debt' was popularised by William Shoemaker in the latter part of the last century.[13] Whilst the data speaks for itself, from a physiological perspective it is hard to understand how relatively small reductions in DO_2 led to such devastating postoperative outcomes given the remarkable ability of most organs have to increase oxygen extraction in times of trouble. Another issue with GDT is that we cannot guarantee what is dispatched from the left ventricle is delivered intact to every organ in the body. [14] The concept is agnostic to disruptions in microcirculatory blood flow[15] and tissue metabolism.[16]

If a reduction of DO_2 is really to blame for the majority of postoperative morbidity that we encounter, surely the findings of RCTs evaluating GDT would be more consistent. One key barrier to progression in this field is our inability to detect subtle warning signs from organs that they are in trouble. Reliable clinical markers of cellular bioenergetic failure are virtually non-existent. The wide-spread use of lactate as a measure of perfusion has undoubtedly saved the lives of countless patients, yet it is blunt tool that lacks specificity and only has the potential to alert us when the horse has already bolted. Were oxygen supply truly the culprit here, one would expect lactate values to differ between those receiving and not receiving GDT, or between those achieving and not achieving their preoperative oxygen delivery following surgery, but this was not the case in Ackland et al.'s RCT or the current sub-study.[10, 11]

The proteomic findings in Heywood et al.'s study provide clues to the mechanisms underlying perioperative morbidity and how these relate to GDT. Failure to maintain preoperative DO_2 was associated with an upregulation of intracellular proteins involved in counteracting oxidative stress (mitochondrial heat shock protein, deglycase and the

mitochondrial antioxidant manganese superoxide dismutase). Integral to the ability of cells to function, is their ability to regulate reduction-oxidation (redox) homeostasis. Numerous noxious stimuli result in increased oxidative stress, including surgery.[17] Disruption to redox homeostasis through excessive release of reactive oxygen species modifies the activity and/or structure of vital functional molecules, such as enzymes, lipid membranes and DNA, with consequent impairment of cell and overall organ function. The effect of oxidative stress on mitochondria has been proposed as the underlying mechanism for aging, degeneration and ultimately death[18], and is thought to be closely interlinked with inflammation and ischaemia-reperfusion injury. Innate protection from these indiscriminate effects of oxidative stress exists within cells, in the form of a complex array of antioxidants (such as the mitochondrial antioxidant manganese superoxide dismutase, measured in Heywood et al.'s study), which are upregulated in response to increasing cellular oxidants. For example, non-survivors of critical illness have been shown to have markedly higher levels of both measures of lipid peroxidation and total antioxidant capacity.[19]

Heywood et al.'s findings suggest that failure to maintain adequate DO_2 after surgery leads to a burst of oxidative stress, triggering the activation of innate cellular protective systems, such as heat shock protein, and upregulation of antioxidants, and that this response is greater in magnitude to that seen when DO_2 is maintained. However, it was not the intervention that resulted in either clinical and biological differences but rather the maintenance of a 'normal' DO_2, which may have been either innate or augmented. One explanation for their findings may be that those patients with more severe preoperative cardiovascular comorbidity, in whom cardiac output decreases as a result of surgery and is not restored by a GDT intervention there is a greater degree of oxidative damage. Alternatively, it may be that more robust cellular antioxidant responses exist in patients less able to maintain their DO_2 in response to stress. In other words, this may not be a simple tale of tissue hypoxia, but a more intricate story of redox imbalance. Thus, many questions

remain about the potential relationship between maintenance of DO_2 and the cellular regulation of redox homeostasis. Other pathways of importance detected by Heywood et al.'s experiments included those related to leukocyte activation and wound healing. All of these findings make sense when thinking through the mechanisms required to mount an effective response to surgery.

What, though, are the relevance of findings from skin biopsies? No single sampling method is perfect for the overall question being posed here. When seeking the answer to why pathology occurs in multiple organs distant to a surgical site, which organs should we biopsy? Blood samples can provide a summation of the entire system but cannot give us organ-specific insights into intracellular function and structural alterations. Muscle biopsies are a more traditional tissue source for proteomic analysis but perhaps using skin may offer easier and more relevant results. Skin is an incredibly complex organ with important immunological and endocrine functions.[20, 21] It is our first line of defence to the outside world and must be breached to allow surgery to proceed. Alterations in its function may act as an early warning system that other organs may be under threat and yield answers that blood is unable to provide. It would have been interesting if transcutaneous oxygen tension were to have been measured during Heywood et al's study, as it is known to be a reasonable marker of low cardiac output.[22, 23] Relating these measurements to their findings may have bridged the gap in our understanding of the response of skin to reduced DO_2 following surgery.

In summary, Heywood et al. have sought to use the framework of an RCT to explore the complex cellular interactions that may underlie the development of pathologies related to reduced DO_2 following surgery. Seeking molecular answers to clinical problems is a vital but often thankless pursuit in a world dominated by confidence intervals and p values. Attempting to fix a broken car, by trial and error, without first knowing what is wrong with the engine is both time- and resource-consuming, and rarely successful. Similarly, our lack of

understanding of the cellular physiology that underlies perioperative morbidity will continue to hamper our attempts to improve clinical outcomes for patients, so deserves greater attention than it sometimes enjoys.

References

1. Ribeil JA, Hacein-Bey-Abina S, Payen E et al. Gene Therapy in a Patient with Sickle Cell Disease. *N Engl J Med* 2017; 376:848-855.
2. Thompson AA, Walters MC, Kwiatkowski J et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. *N Engl J Med* 2018; 378:1479-1493.
3. Trusheim MR, Burgess B, Hu SX et al. Quantifying factors for the success of stratified medicine. *Nat Rev Drug Discov* 2011; 10:817-833.
4. Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MP. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. *Anesthesiology* 2013; 119:959-981.
5. Edwards MR, Forbes G, MacDonald N et al. Optimisation of Perioperative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) trial: study protocol for a multicentre international trial of cardiac output-guided fluid therapy with low-dose inotrope infusion compared with usual care in patients undergoing major elective gastrointestinal surgery. *BMJ open* 2019; 9:e023455.
6. FLuid Optimisation in Emergency LAparotomy (FLO-ELA) Trial. https://www.floela.org.
7. Grocott MP, Dushianthan A, Hamilton MA et al. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review. *Br J Anaesth* 2013; 111:535-548.
8. Kaufmann T, Clement RP, Scheeren TWL, Saugel B, Keus F, van der Horst ICC. Perioperative goal-directed therapy: A systematic review without meta-analysis. *Acta Anaesthesiol Scand* 2018; 62:1340-1355.

9. Pearse RM, Harrison DA, MacDonald N et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014; 311:2181-2190.
10. Heywood W. Proteomic signatures of perioperative oxygen delivery in skin after major elective surgery: mechanistic sub-study of a randomised controlled trial. *Br J Anaesth* 2021;
11. Ackland GL, Iqbal S, Paredes LG et al. 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.
12. Richardson RS, Harms CA, Grassi B, Hepple RT. Skeletal muscle: master or slave of the cardiovascular system? *Med Sci Sports Exerc* 2000; 32:89-93.
13. 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; 102:208-215.
14. Mythen M, Clutton-Brock T. The oxygen trail: measurement. *Br Med Bull* 1999; 55:109-124.
15. Jhanji S, Lee C, Watson D, Hinds C, Pearse RM. Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications. *Intensive Care Med* 2009; 35:671-677.
16. Jeganathan J, Saraf R, Mahmood F et al. Mitochondrial Dysfunction in Atrial Tissue of Patients Developing Postoperative Atrial Fibrillation. *Ann Thorac Surg* 2017; 104:1547-1555.
17. Stevens JL, Feelisch M, Martin DS. Perioperative Oxidative Stress: The Unseen Enemy. *Anesth Analg* 2019;
18. Cui H, Kong Y, Zhang H. Oxidative stress, mitochondrial dysfunction, and aging. *J Signal Transduct* 2012; 2012:646354.
19. McKenna HT, O'Brien KA, Fernandez BO et al. Divergent trajectories of cellular bioenergetics, intermediary metabolism and systemic redox status in survivors and non-survivors of critical illness. *Redox Biol* 2021; 41:101907.

20. Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. *Immunity* 2011; 35:857-869.
21. Zouboulis CC. The skin as an endocrine organ. *Dermatoendocrinol* 2009; 1:250-252.
22. Rowe MI, Weinberg G. Transcutaneous oxygen monitoring in shock and resuscitation. *J Pediatr Surg* 1979; 14:773-778.
23. Yu M, Morita SY, Daniel SR, Chapital A, Waxman K, Severino R. Transcutaneous pressure of oxygen: a noninvasive and early detector of peripheral shock and outcome. *Shock* 2006; 26:450-456.