Prehabilitation: Expanding the Role of Perioperative Medicine

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Introduction

Technical advances in the fields of anaesthesia and surgery in combination with our aging population has led to an expanding volume of complex surgery being performed on older patients. Patients often present for surgery with reduced functional capacity mediated by the biological effect of their surgical disease e.g. cancer, the associated therapies e.g. neoadjuvant chemoradiation therapy, their underlying comorbid disease and/or through their lifestyle choices e.g. inactivity. These factors combine to accelerate a 'deconditioning storm' with reduced functional capacity, with reduced ability of the body to deliver and/or utilize oxygen (O_2) leading to reduced exercise capacity, impaired health related quality of life, and reduced ability to withstand major stressors such as complex surgery. As such, decreased functional capacity associates with an increased incidence of post-operative morbidity and mortality, length of hospital stay, healthcare expenditure, reduced quality of life, and reduced longevity. This provides the impetus for prehabilitation—the optimisation of functional capacity following diagnosis and prior to elective major surgery.

Risk Stratification

Perioperative morbidity represents a major public health challenge. It is estimated that 12.3% of surgeries are performed on high-risk patients (expected mortality >5%), with an estimated risk of postoperative morbidity between 7%-50% and accounting for 80% of all deaths following surgery. The presence of a single post-operative complication increases the risk of mortality for up to 8 years after surgery, independent of baseline comorbidities.

Patient-centred risk assessment and cardiopulmonary exercise testing (CPET or CPX), using gas exchange-derived variables such as oxygen consumption at Anaerobic Threshold (AT) and oxygen consumption at peak exercise (pVO2), allows for objective measurement of functional capacity and is used to guide surgical risk assessment and perioperative strategies for patient optimisation to reduce postoperative morbidity and mortality. These gas exchange derived variables reflect the integrative capacity of components in the O_2 cascade. Lack of sufficient tissue O_2 supply reduces exercise capacity and physical function, leading to impairments in abilities to participate in activities of daily living and increased risk of postoperative complications. Other benefits of improved functional capacity may be mediated through improved anti-inflammatory and microcirculatory function mediated by signaling via the endothelial-nitric oxide pathways during exercise.

Impaired functional status of surgical patients has been consistently shown to predict adverse postoperative outcomes and mortality (Figure 1) and increasing levels of evidence suggest that CPET is a suitable and effective method for objective quantifying of surgical risk. For rectal surgery West et al estimated that AT and pVO_2 gave an area under the ROC curve of 0·87 (95 per cent confidence interval 0·78 to 0·95; $P < 0{\cdot}001$) and 0·85 (0·77 to 0·93; $P < 0{\cdot}001$) respectively, indicating that they can help discriminate patients at risk of postoperative morbidity. The optimal cut-off points identified were 10·6 and 18·6 ml/kg/min for VO_2 at AT and at peak, respectively.

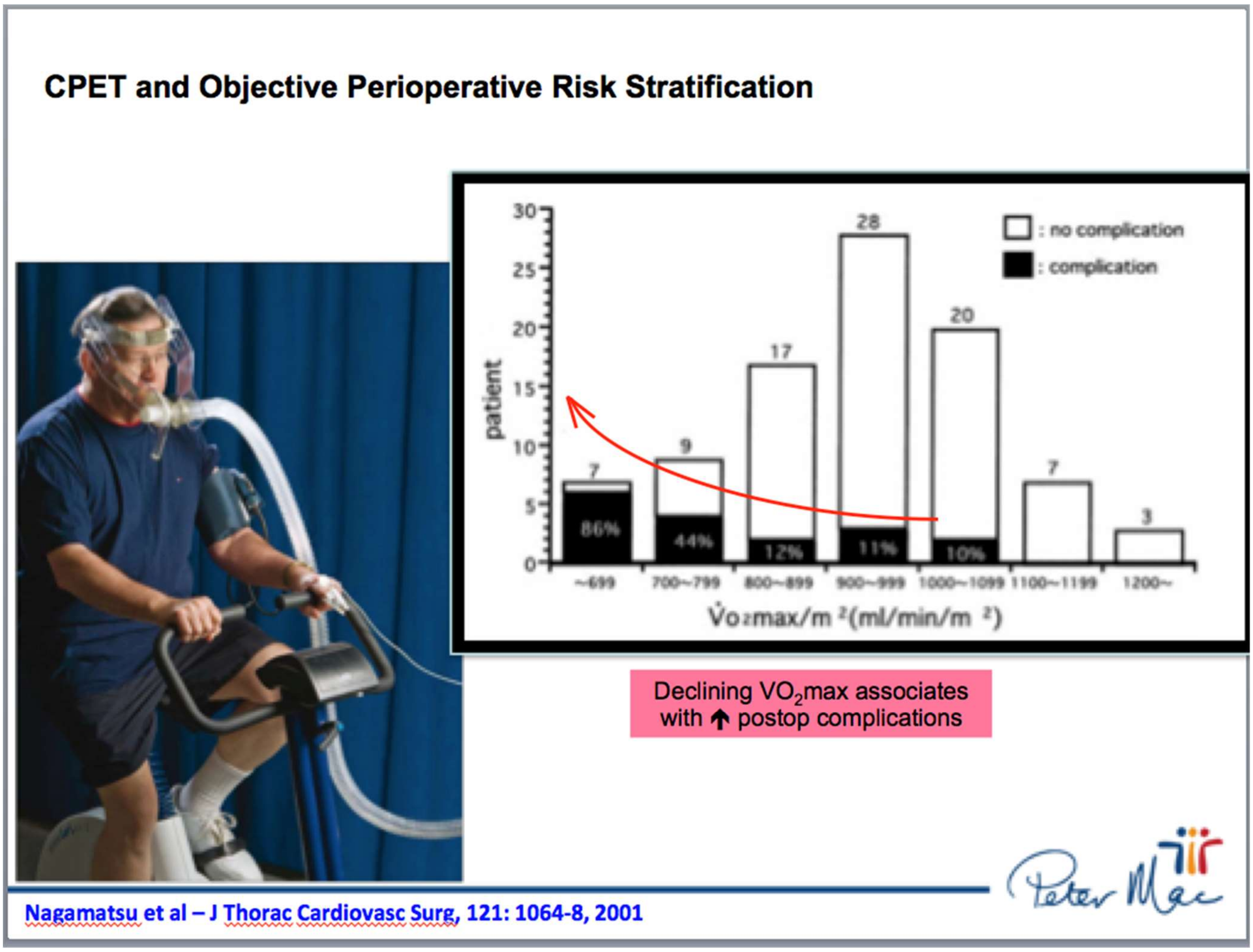

Figure 1. Objective risk stratification with cardiopulmonary exercise testing (CPET). *A decline in functional capacity, as measured by VO2 max, shows an increase in postoperative complications (black shaded columns).*

In a more recent study and specific to colorectal surgery, West et al., exploring the relationship between CPET-derived parameters and in-hospital morbidity, showed that using multivariable logistic regression selected CPET variables associated significantly with increased odds of in-hospital morbidity (AT <11·1 ml/kg/min; OR = 7·56 [95 %CI 4·44 to 12·86]; P <0.001) and pVO2 <18·2 ml/kg/min; OR 2·15 [95%CI 1·01 to 4·57]; P = 0·047).

In a recent systematic review Moran et al. (2016) confirmed the utility of CPET as a preoperative risk-stratification tool with ability to predict postoperative outcome following major intra-abdominal surgery. Cardiopulmonary exercise testing-derived cut-points for AT and pVO2 predicted: intensive care unit admission (AT <9.9-11 ml/kg/min) and 90 day - 3 year survival (AT 9-11 ml/kg/min) after hepatic resection and transplant, morbidity and length of stay after pancreatic surgery (AT <10-10.1 ml/kg/min), and mortality and morbidity after intra-abdominal surgery (AT 10.9 and <10.1 ml/kg/min, respectively).

Declining Physiologic Capacity after Preoperative n-CRT

While less invasive and arguably less accurate means of assessing functional status include the Eastern Cooperative Oncology Group (ECOG) performance status, incremental shuttle walk test and six minute walk test, there is an extensive body of evidence that supports the use of CPET for risk stratification of cancer patients. CPET is the logical choice of assessment in patients with cancer because of the effects of disease, loco-regional and systemic treatments on multiple stages of the O_2 cascade (cardiovascular system, respiratory system, anaemia, autonomic dysfunction and skeletal myopathy).

Neoadjuvant chemoradiation therapy (n-CRT) adversely affects functional capacity, with 10-15% decline in AT and pVO_2. As such, previously relatively 'fit' patients (AT >11 ml/kg/min) may now fall below this threshold (10-11 ml/kg/min) and are thus at increased risk for adverse postoperative outcomes. These reductions in turn are significant predictors of postoperative morbidity and one year mortality. To this end, CPET derived parameters can guide postponement of surgery until functional capacity has recovered or preferably guide the implementation of a prehabilitation exercise program to expedite recovery after n-CRT. West et al (2015) reported the feasibility of a 6-week structured responsive exercise-training program in rectal cancer patients receiving neoadjuvant therapy, with return to baseline exercise capacity in the treated group but not in the control group.

Adoption and Accreditation of CPET in Perioperative Medicine

Given that CPET is an integrated, dynamic test of the cardio-respiratory-metabolic systems and is considered the gold standard in assessing cardio-respiratory functional reserves it is increasingly adopted in the preoperative assessment of patients scheduled for major surgery. A survey conducted in 2011 by Huddart et al. (2013) reported that an estimated 32% of all adult anesthetic departments in England had access to preoperative CPET services. Five years on, it is expected that more than half of all hospitals in the UK will now have access to such services. Importantly, this survey highlighted that there was a lack of consistency in the way tests are reported and utilized. As the uptake of CPET services continue to expand, and as the evidence expands that prehabilitation programs (with exercise as a pivotal component) before and after surgery may improve fitness and thus reduce complications and death after surgery, it is essential that testing is of high quality and is reproducible if it is to benefit patient care. As a result, the Perioperative Exercise Testing and Training Society (POETTS), established in the UK in 2016, has set out to introduce guidelines for perioperative CPET, with standardized education and accreditation for practitioners. The society will also provide educational resources, an opportunity to identify local mentors for training, and facilitate collaborative research for CPET, including the establishment of a national CPET database, housed in the Health Services Research Centre (HSRC) at the Royal College of Anaesthetists, to establish valid risk thresholds and to identify the best variable or combination of variables to predict surgical outcome. POETTS will likely also expand to have an international role in CPET training, education and research.

The POETTS website (http://poetts.co.uk/home) provides a useful resource with links to current evidence (majority of published single centre cohorts, systematic reviews etc.), accreditation and mentoring pathways, and a link to recommended exercise training programs.

Prehabilitation

The evidence is now irrefutable that exercise has significant physiological and psychological benefits and a pivotal role in preventing many cancers within the general population. An increasing body of evidence supports the fundamental notion that **functional capacity is an attractive modifiable therapeutic target** and thus exercise forms a central component of emerging prehabilitation programs prior to major surgery. Exercise training especially interval training has a long-term anti-inflammatory response that may offset the systemic inflammatory response associated with major surgery. Thus exercise training prior to and following major surgery may modify the inflammatory response and may be of benefit. This supports what a lot of clinicians already believe; high-risk, deconditioned patients, when given the opportunity to improve their physical function and activity before and after treatment, through a structured multidisciplinary bundled program, that also includes haematinic optimisation, nutritional optimisation, pain management, pharmacist review, smoking and alcohol cessation programs to improve their functional state, will suffer fewer postoperative complications, leave hospital quicker after major surgery, and return to their baseline functional capacity earlier (or even better).

Prehabilitation is defined as the process of enhancing the functional capacity of the individual to enable him or her to withstand a stressful event and reduce complication risk (Figure 2). As such, one of the top 10 (from 92) most important research questions identified for perioperative medicine, in a survey conducted by Boney et al. (2015) for the Royal College of Anesthetists/James Lind Alliance in the UK, was *"How can preoperative exercise or fitness training, including physiotherapy, improve outcomes after surgery"*.

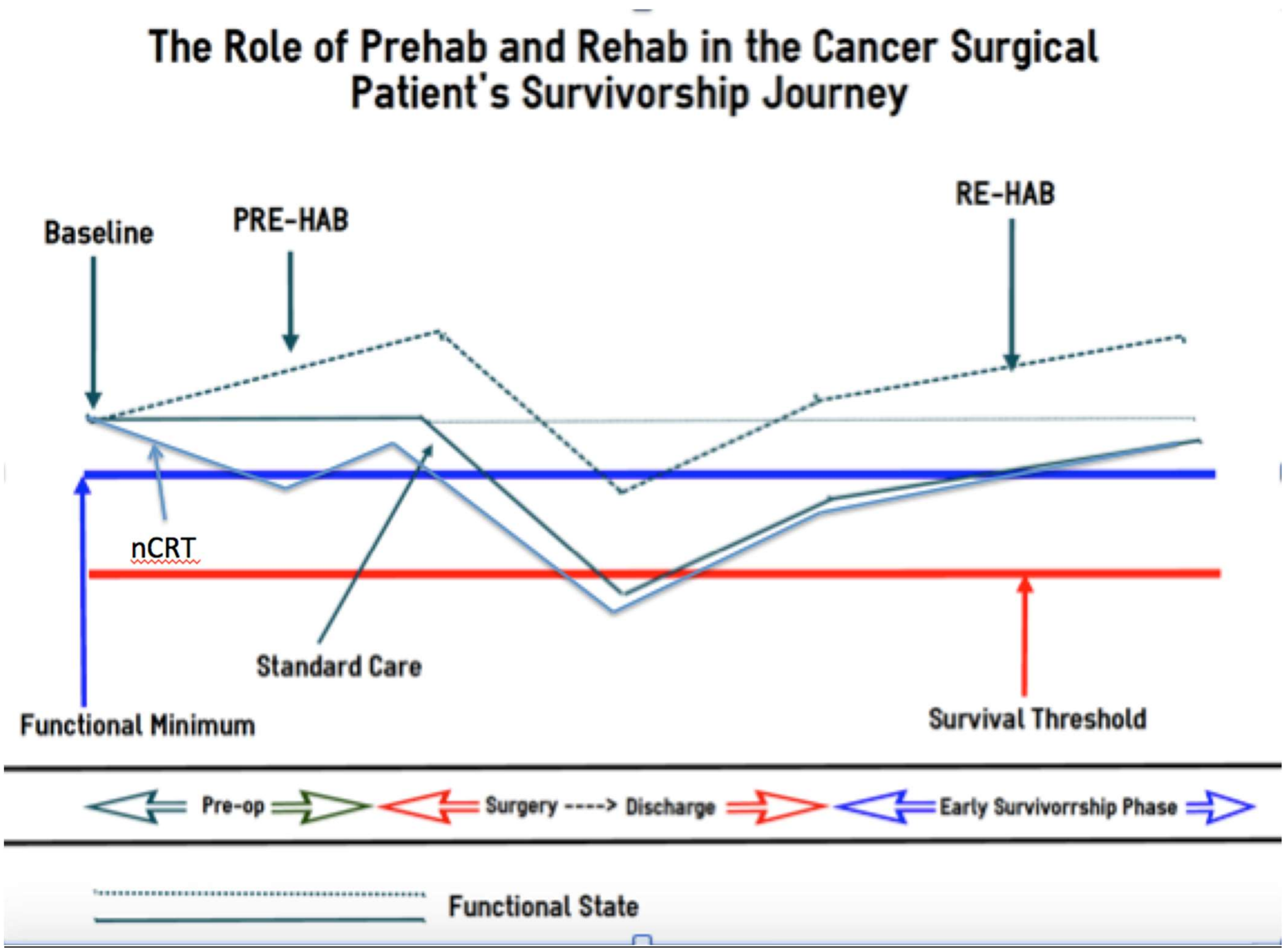

Figure 2. Schematic representing the role of prehabilitaion and rehabilitation in improving perioperative outcomes for major surgery. *Timely intervention with 'prehabilitation' (and rehabilitation) is aimed at ensuring patients do not descend below the theoretical physiological threshold to ensure an uncomplicated recovery (blue line).*

At Peter MacCallum Cancer Centre in Melbourne we have integrated CPET facilities into the preoperative workup of patients scheduled for major cancer surgery, with utility in identifying the high-risk surgical patient who would benefit from prehabilitation. Once risk stratified, high-risk patients scheduled for major surgery are optimised through multidisciplinary preoperative 'prehabilitation'. Their CPET derived data provides a validated guide to formulating patient specific exercise prescriptions. In addition to exercise therapy, prehabilitation is also tailored to include perioperative interventions such as haematinic optimisation, (immuno)nutritional optimisation, abstinence of smoking and alcohol, and psychological therapy to improve postoperative outcomes. Additionally, high risk patients may have their surgical procedures adjusted to reduce risk of surgical complications, and be stratified for postoperative care in high acuity areas (e.g. HDU / ICU) and if needed also scheduled for post-operative 'rehabilitation'.

Our 'prehabilitation' program has been able to train over 100 patients in the last 24 months prior to their major cancer surgery. In a retrospective cohort study (Huang et al; 2015) of prehabilitation in patients with cancer having major colorectal, oesophagogastrectomy, or lung resection surgery we reported a significant overall increase in pVO_2, with 'responders' to our prehabilitation program suffering fewer major postoperative complications. The optimal exercise-training program follows traditional guidelines consisting of either supervised and/or home-based endurance (aerobic) training combined with resistance training to induce skeletal muscle adaptation, prescribed at a moderate intensity (60–85% of a predetermined physiological parameter such as heart rate.
Prehabilitation is not a new concept; it is utilized successfully to improve patient outcomes in cardiac, colorectal and lung cancer surgery with positive outcomes achieved within short preoperative time frames. Prehabilitation has been shown to be feasible and safe, increasing the AT and pVO_2 within 4-6

weeks, as well as offering improvements in function and quality of life. Ongoing research will explore the role of high intensity training programs in achieving optimization in a shorter period prior to scheduled surgery. Li et al (2013) demonstrated that 81% (cf. 40% in the control group) returned to baseline functional capacity at 8 weeks after surgery. This has significant implications, with earlier return to baseline but also significant implications for the cancer patient who suffer less postoperative morbidity and who return to intended oncologic (adjuvant) therapy (RIOT – the cancer journey) in a timely manner. The introduction of neoadjuvant cancer treatment in the surgical pathway may provide a window of opportunity to intervene with exercise training before, during and after cancer treatments to ameliorate or reverse the harmful effects on physical fitness.

Prehabilitation leverages the 'teachable moment' of impending major surgery, with patients often more compliant due to being in better physical condition without acute post operative pain, and also ensures the advantageous use of surgery waiting time, especially when neoadjuvant therapies are needed or patients are on surgical waiting lists within the public healthcare systems. Large, prospective studies are required to evaluate the impact of these interventions, the optimal type of training program and the optimal timing through further research.
Useful information on current modalities of exercise programs can be found on the POETTS website: https://rayzume.com/POETTS/Interval-Exercise-Training-Programme.

Recommended Reading[1-22]

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