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Exercise: the new premed

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Life is movement
—Aristotle (Fourth century, BC)

Distance runner Steve Way captured the imagination recently with his inspirational story. At 33, he weighed 16 stone and smoked a pack of cigarettes a day. He took up jogging to get himself in shape, and 7 yr later has come 10th in the Commonwealth Games marathon, breaking the UK age group record for the distance.

In this issue of the BJA, West and colleagues2 report the effects of a preoperative exercise programme to restore patients’ functional capacity after neoadjuvant chemoradiotherapy before major rectal cancer surgery. They showed that 22 patients who followed a 6 week Structured Responsive Exercise Training Programme (SRETP) had an oxygen
consumption at anaerobic threshold 2.12 ml kg$^{-1}$ min$^{-1}$ higher than that of 17 contemporaneously recruited controls.

There is now strong evidence supporting the association between measured cardiorespiratory fitness (CRF) and postoperative outcomes in several settings. $^{2–4}$ It appears that on the whole, fitter people do better with major surgery and fitness bears more importance in this regard than chronologic age. $^{5}$ It follows that improvement of preoperative CRF through exercise training provides a plausible interventional strategy for improving surgical outcome. However, this has previously remained largely unproven within the short timeframes and heterogeneity of the surgical pathway, $^{6,7}$ thus the positive effect on fitness demonstrated by West and colleagues represents a significant advance.

However, as in the case of Steve Way, it is reasonable to ask whether these impressive results are applicable to ‘ordinary’ people. And in particular to elderly people, given that 35% of those having elective major bowel surgery in the UK are over the age of 75. $^{8}$

The ability of an individual to deal with insults created by life events appears to be fundamental in defining their longevity. This functional capacity is a major component in the constantly emerging concept of frailty. There are two main frailty theories: one postulates a clinical phenotype characterized by at least three of low physical activity, weakness, self-reported exhaustion, and unintentional weight loss; $^{9}$ the other characterizes frailty as an accumulation of multiple comorbidities over a lifetime. $^{10}$ Both have their supporters: what is clear is that CRF plays an important part in the process.

Reduced cardiorespiratory function is one of the leading problems facing the modern world and in terms of attributable mortality risk, leads obesity, hypertension, and diabetes. $^{11}$ Training improves CRF in health and disease and while the inexorable loss in fitness that occurs with advancing age from about 45 yr onwards is seemingly unpreventable, $^{12}$ the effects can be mitigated by regular exercise.

Aerobic fitness, as objectively characterized by cardio-pulmonary exercise testing (CPET), is strongly linked with long-term survival and slows the progression of many chronic disease states including heart failure, dementia, and stroke. $^{13,14}$ So when faced with the acute physiological stress that defines major surgery, an appropriate baseline level of CRF is undoubtedly important to individual response and recovery. This may especially be the case for oncological surgery, now dominated by the development of multimodal therapy, incorporating multiple hits on functional reserve, often in short succession.

Where ‘prehabilitation’ is the process of enhancing an individual’s functional capacity to enable them to withstand a forthcoming stressful event, what the current study in fact shows is something different. Importantly, the investigators are the first to objectively measure the adverse effect of a typical regimen of neoadjuvant chemoradiotherapy (NACRT) before surgery on CRF and to define a possible role for exercise therapy in counteracting this.

All patients included in the trial were treated with a standardized 5 week regimen of external beam radiation daily on weekdays along with twice weekly oral capecitabine. The overt adverse effects of such therapy are easily recognized, including muscle wasting, fatigue, and decreased appetite related to nausea. $^{15}$ Capecitabine is an oral pro-drug of 5-fluorouracil, a fluoropyrimidine whose therapeutic action depends on interference with tumour RNA expression. NACRT can affect physical activity, cardiorespiratory, microcirculatory, and mitochondrial function $^{16,17}$ in a covert manner which is accepted but previously unmeasured. Demonstration with CPET of a profound reduction in CRF removes the subjective nature of these observations and has important implications for future management. The finding that a post-intervention, structured exercise programme can counteract the effects of radical chemo-radiotherapy confirms exercise rehabilitation as an important method of reestablishing CRF. The speed of response to exercise after potent chemotherapeutic regimes demonstrated in the present study, with effects shown after just 3 weeks, may suggest a different mechanism of CRF deterioration than simple deconditioning processes, chronic disease, or obesity which often require months of exercise therapy to show significant benefit. $^{18}$

Of course, chemo- and radiotherapy regimes come in many forms and different agents are being constantly developed. For this reason, extrapolation of these findings to other surgical groups may be inappropriate.

And while exercise training is intuitively attractive as a strategy to improve CRF before surgery, it cannot be taken for granted that it always works. Systematic reviews $^{6,7,19}$ reveal a paucity of primary research. While most existing single-centre studies show some improvement in surrogate markers of physical fitness, several highlight practical and response issues related to exercise programmes.

Carli and colleagues’ $^{20}$ randomized clinical trial of prehabilitation in individuals undergoing major colorectal surgery revealed the surprising finding that measurable improvement in physical fitness as expressed by 6 min walking distance (6MWD) was less in a group of patients who were recruited to a home-based, structured cycling and strengthening regimen than in a sham control group who were simply advised to walk for 30 min every day. Further, 6MWD actually deteriorated during the preoperative period in 15 of 36 patients in the prehabilitation group. This may be to do with compliance: over a mean period of 52 days; participants were instructed to perform daily stationary cycling of moderate intensity, along with weight training exercises totalling $\sim 3.5$ h week$^{-1}$. Only 16% fully adhered to the programme, leading the authors to speculate that an excessively demanding exercise schedule is counterproductive. In a follow-up study evaluating the impact of a trimodal prehabilitation package which offered nutritional counselling, anxiety reduction, and protein supplementation along with a less stringent exercise intervention, the same investigators observed considerably better compliance, around half the patients fully adhered. Here, the mean postoperative walking capacity and self-reported physical activity in the group was better than that of historical controls and no patients’ 6MWD deteriorated. $^{21}$
This is why the clinical team reporting the present study should be highly commended in demonstrating the feasibility of developing an intensive, structured exercise training programme within the confines of the colorectal surgical pathway. They achieved an unprecedented adherence rate: 21 of 22 patients in the exercise group completed all 18 sessions.

A dedicated team is required to sustain enthusiasm within the team itself and for the individuals performing the exercise. These two components undoubtedly created levels of compliance to the programme that is a marked contrast to previous in-hospital and community-based exercise therapy studies. In this context, health-care professionals managing the surgical patient would need significant education and training to promote exercise therapy before it could be successfully integrated into clinical practice.

In terms of how widely applicable the current study might be, the non-randomized study design is highly relevant. Eligible patients were allocated to the treatment group by default, unless they opted out. Therefore, the control group, who constituted 37% of those who agreed to participate, were by definition demotivated in performing exercise. They were also older (mean age 72 vs 64 yr), had more comorbidity as expressed by ASA and CR-POSSUM physiological scores, and poorer baseline function as characterized by World Health Organization Performance status. Supplementary material provided reveals that at baseline, they had a lower FEV₁/FVC ratio, lower peak power on CPET, and less efficient pulmonary gas transfer (ventilatory equivalent for carbon dioxide) than their younger counterparts. This is an important group in which to concentrate future efforts.

To get the best from any exercise programme, there has to be an understanding of the complex individualization of behavioural change in this setting and the barriers and facilitators. There may be safety concerns, although studies such as that of West, where no adverse events were reported, go some way towards addressing these. One out of a group of 17 patients with AAAs under surveillance who performed a 6 week regimen of in-hospital supervised moderate intensity cycling suffered a ventricular fibrillation arrest during exercise, requiring immediate cardiac intervention. A recent systematic review of preoperative prehabilitation in mainly high-risk patients included 524 patients from 10 studies—only two adverse events were reported during exercise. Interestingly, 15 adverse events which were not associated with exercise were noted in this cohort—a mix of acute coronary syndromes and chronic obstructive pulmonary disease exacerbations; eight of these were in control patients.

Application of any exercise therapy programme will fail if the motivational, environmental, and socioeconomic factors that encourage engagement, adherence, and therapy completion are not addressed. Surgery that restores quality of life (e.g. knee replacement) may improve engagement. In contrast, patient anxiety around the diagnosis of malignancy, adjuvant chemotherapeutic treatments, or repetitive diagnostic procedures are all potential de-motivating factors that may prevent exercise. These factors may be amplified in demotivated older patients, chronically deconditioned, with low basal activity levels and unaware of the potential benefits of exercise. Their behavioural and psychological requirements for involvement in exercise programmes are extremely different from a motivated younger group.

What is the ideal intervention? Exercise training programmes imply a structured increase in physical activity with the distinct aim of improving measured cardiorespiratory performance and muscle strength. Locomotor and inspiratory muscle power is synergistic with CRF. West and colleagues' team designed for each individual a bespoke regimen of alternating moderate and high-intensity interval training, modified according to their ramped CPET protocol results. This is in line with the observation in elderly heart failure patients that high-intensity interval training is more effective than continuous moderate intensity exercise in improving cardiovascular fitness. It appears that high-intensity exercise improves the oxidative capacity of skeletal muscles, enhances endothelium-dependent relaxation, and causes an acute oxidative stress which promotes protective anti-oxidant mechanisms.

However, there is a differential response to exercise. Around 10% of the population are super-responders to high-intensity exercise. Conversely, some people may see no benefits. Re-analysis of the cohort from the Carli and colleagues study revealed 33% as responders, whose preoperative walking distance improved. In contrast, 29%, whose 6 MWD deteriorated during the prehabilitation phase, had a higher incidence of postoperative complications requiring surgical reintervention or unplanned admission to critical care. A high proportion of the non-responders were aged over 75 yr.

Similarly, in a study of patients with AAA, only six of 17 (all males) participating in a 6 week supervised exercise programme achieved a ‘clinically significant’ improvement in oxygen consumption at lactate threshold (2 ml kg⁻¹ min⁻¹). Much investigation is still required to identify tolerable, optimal interventions to achieve clinically meaningful, timely improvements in fitness across a heterogeneous population of preoperative patients, many of whom are frail. Although the initial thrust of enthusiasm for exercise therapy is likely to come from enlightened clinicians, who believe in the relevance to surgical outcome, responsibilities also lie at the patients’ doorstep. Promotion of the psychological concept of self-efficacy (the extent of a person’s belief in their own ability to complete tasks and reach goals) may be important in this regard. The need for surgery may be used as an important stimulus for behavioural change towards exercise, allowing the preoperative phase to become an important ‘teachable moment’.

Of course, benefits for preoperative aerobic exercise training on health related quality of life and physical fitness are relevant only where they bear predictive relationship to postoperative outcome. The evidence for this is developing. In a separate study, the same authors have demonstrated that postoperative complications after rectal oncological surgery are concentrated in those patients whose oxygen uptake at estimated lactate threshold is <12.0 ml kg⁻¹ min⁻¹ at baseline. On average, these patients’ oxygen uptake at estimated...
lactate threshold had deteriorated to <10.7 ml kg⁻¹ min⁻¹ after NACRT. This has important implications for the timing of surgery, which currently often follows a finite period of ‘recovery’ after chemoradiotherapy. For many patients, including the control group in the current study, surgery probably comes when their CRF is at a nadir, such that they are at a disadvantage in their ability to cope with the physiological stress.

A crucial question is what do we have to show in order to redefine the role of exercise therapy within the confines of current surgical pathways? Times from diagnosis to definitive resection are tight, on the basis that delay promotes tumour spread. What is tantalizing about the current study is the possibility that exercise actually improves tumour regression: response to NACRT (tumour shrinkage) assessed by a multidisciplinary team blinded to group allocation was significantly better in the exercise group. In addition, the exercise regimen demonstrated effects on CRF over and above the detriment caused by NACRT, with CRF being returned beyond baseline levels by 6 weeks. If this is indeed the case, and can be verified in a larger cohort, then by taking time to get fitter while awaiting surgery, patients may be substantially improving their chances of beating cancer.

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C.P.S. and G.M.: conception, drafting, and revision of the article, and final approval.

Declaration of interest
None declared.

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