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REVIEW ARTICLE

Physiological relationship between cardiorespiratory fitness and fitness for surgery: a narrative review

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Summary

Epidemiological evidence has highlighted a strong relationship between cardiorespiratory fitness and surgical outcomes; specifically, fitter patients possess heightened resilience to withstand the surgical stress response. This narrative review draws on exercise and surgical physiology research to discuss and hypothesise the potential mechanisms by which higher fitness affords perioperative benefit. A higher fitness, as indicated by higher peak rate of oxygen consumption and ability to sustain metabolic homeostasis (i.e. higher anaerobic threshold) is beneficial postoperatively when metabolic demands are increased. However, the associated adaptations with higher fitness, and the related participation in regular exercise or physical activity, might also underpin the observed perioperative benefit through a process of hormesis, a protective adaptive response to the moderate and intermittent stress of exercise. Potential mediators discussed include greater antioxidant capacity, metabolic flexibility, glycaemic control, lean body mass, and improved mood.

Keywords: anaerobic threshold; cardiorespiratory fitness; exercise training; hormesis; peak oxygen consumption; perioperative; surgical stress response

Editor's key points

- Major surgery comprises multiple physiological stressors both intraoperatively and postoperatively.
- Impaired cardiorespiratory fitness increases the risk faced by patients undergoing major surgery; however, the physiological mechanisms underpinning this relationship is imperfect.
- In this narrative review, the authors discuss potential factors by which greater fitness provides resilience to surgical stress. Mediators discussed include perioperative oxygen consumption, antioxidant defences, substrate oxidation, glycaemic control, lean body mass and mood.
- Future research must expand from cross-sectional epidemiological research to test specific hypotheses and better understand the relationship between fitness and surgical outcomes.

Participation in regular exercise or physical activity confers many physical and mental health benefits. A common and important benefit is increased cardiorespiratory fitness. Low fitness is independently associated with a higher risk of developing cardiovascular and metabolic diseases, several cancers and psychological disorders such as anxiety and depression, amongst others.[1–6] More recently, it has been

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shown to increase the risk for surgical-related morbidity and mortality.[7–9] Given that low fitness is a modifiable risk factor, preoperative testing of fitness has become an important component of preoperative assessment.[7] Whilst there is extensive literature describing preoperative exercise testing methodology and the prognostic information it offers,[7–14] little attention is given to the physiological underpinnings. This review aims to integrate exercise and surgical physiology research to better understand the role regular exercise training and fitness may play in a patient's fitness for surgery.

What is cardiorespiratory fitness?

Cardiorespiratory fitness refers to the circulatory and respiratory systems' ability to supply tissues with oxygen to generate adenosine triphosphate (ATP) and prevent metabolite accumulation. Maximal rate of oxygen consumption ($\dot{V}_{O_2}$) is an indicator of fitness and is formally defined by the Fick equation, the product of cardiac output and arteriovenous oxygen difference (a–vO_2 difference).[7,15,16] The structures and integrative control processes that contribute to fitness decline with age, which is reflected by reduced peak $\dot{V}_{O_2}$. Similarly, any medical condition that limits pulmonary function, cardiac output, or a–vO_2 difference will limit peak $\dot{V}_{O_2}$. Conversely, peak $\dot{V}_{O_2}$ can be increased and the age-related decline in peak $\dot{V}_{O_2}$ attenuated *via* adaptations to regular exercise.[17]

The anaerobic threshold is another key measure of fitness. The anaerobic threshold represents the physiological demarcation during incremental exercise, where blood lactate concentration or ventilation increases disproportionately, reflecting increased motor unit recruitment, 'anaerobic' glycolysis, and a larger increase in rate of lactate appearance relative to its disposal/disappearance from blood, as the demand for ATP production rises.[7,18] Whilst anaerobic metabolism is valuable initially after increased demand for ATP, these systems are inefficient, have low capacity for energy yield, and accumulation of metabolic by-products (i.e. hydrogen, pyruvate, and lactate) ensues. Anaerobic metabolism, therefore, cannot be sustained.

Why measure cardiorespiratory fitness in the surgical setting?

Cardiopulmonary exercise testing (CPET) is considered the 'gold standard' for measuring fitness; for detailed background and methodology on CPET, refer to consensus guidelines published by Levett and colleagues.[7] Poor performance during CPET is predictive of worse perioperative outcomes for numerous surgery types.[8,9] Peak $\dot{V}_{O_2}$ and anaerobic threshold data may be used to inform the most appropriate postoperative treatment, such as triage to critical care for 'high-risk' patients or ward care for 'low-risk' patients[7]; other CPET indices, such as the efficiency of ventilation ($\dot{V}E/\dot{V}_{CO_2}$), can also enhance risk stratification.[7] Appropriate triage of lower-risk patients has been shown to reduce bed stays in intensive care/higher-dependency units, whilst not increasing cardiovascular mortality in patients triaged to ward care.[19,20] Patients with low fitness (e.g. peak $\dot{V}_{O_2}$ <15 ml min^{-1} kg^{-1} and anaerobic threshold <9–11 ml min^{-1} kg^{-1}) appear to have diminished capacity or physiological reserve to respond to stressors. As a lower peak $\dot{V}_{O_2}$ and anaerobic threshold are associated with a diminished ability to deliver and sustain oxygen uptake and utilisation in metabolically active tissue, it is plausible that this deficiency may be evident in other physiologically stressful conditions, where oxygen (O_2) demand is increased and O_2 deficit occurs, such as surgery.

Physiological stress of surgery

Intraoperative

Like exercise, the surgical stress response is characterised by increased inflammatory and endocrine activity and an upregulation of the hypothalamus–pituitary–adrenal axis and sympathetic nervous system.[21] In a fasted or highly anxious patient, this may start before entering the operating theatre. Inflammatory signalling pathways are activated to limit tissue damage and facilitate repair and to protect against bacterial infection.[22] There is a dose–response increase in inflammatory cytokines in proportion to tissue damage.[22,23]

Intraoperatively, oxygen delivery is reduced, likely because of the anaesthetic agents' effect on myocardial contractility and consequently left ventricular stroke volume and cardiac output.[24–27] General anaesthesia may also affect $\dot{V}_{O_2}$ peripherally, with direct effects on O_2 uptake within skeletal muscle *via* reduced oxidative capacity of mitochondria.[28,29] Reduced $\dot{V}_{O_2}$ is further attributed to reduced muscle tone, reduced cerebral metabolic rate of $\dot{V}_{O_2}$, and hypothermia, whether intentional (e.g. during cardiopulmonary bypass) or secondary (e.g. because of heat loss mechanisms exacerbated during surgery).[30–32] Consequently, intraoperative $\dot{V}_{O_2}$ decreases 25–50% below preoperative levels after general and spinal anaesthesia.[26,27,30,33–36]

Postoperative

Whilst the intraoperative period is unquestionably influential in determining surgical outcomes, more than 99% of in-hospital mortality associated with noncardiac surgery occurs after the patient has left the operating theatre.[37] A major determinant of longer-term outcome appears to be the patient's response in the immediate postoperative period and their physiological reserve to respond to complications (Fig 1).

Research in the 1980's consistently demonstrated that cardiac output and $\dot{V}_{O_2}$ are increased postoperatively.[24,26,38,39] It was hypothesised that because of the reduction in intraoperative $\dot{V}_{O_2}$, tissue hypoxia and ischaemia ensued, triggering a hyperdynamic postoperative response to restore cell homeostasis. Postoperative $\dot{V}_{O_2}$ was reported to be twice that of preoperative values[40,41] but more frequently reported at ~40–50% greater[38,39]; Biccard[42] estimates that patients need to sustain a $\dot{V}_{O_2}$ of 5 ml min^{-1} kg^{-1} postoperatively to withstand the stress response. Unlike for exercise, this postoperative increase in $\dot{V}_{O_2}$ may be sustained for days to facilitate restoration of systemic homeostasis (e.g. substrate mobilisation, wound healing, and restoration of oxygen debt). It remains unclear what effect recent advances in anaesthetic and surgical techniques and in perioperative patient care have had on not only the stress response but specifically on variables related to this review (e.g. perioperative $\dot{V}_{O_2}$). Nevertheless, the stress response (albeit minimised by modern techniques) and restoration of homeostasis increase metabolism and $\dot{V}_{O_2}$ postoperatively. Therefore, it is likely that patients who are

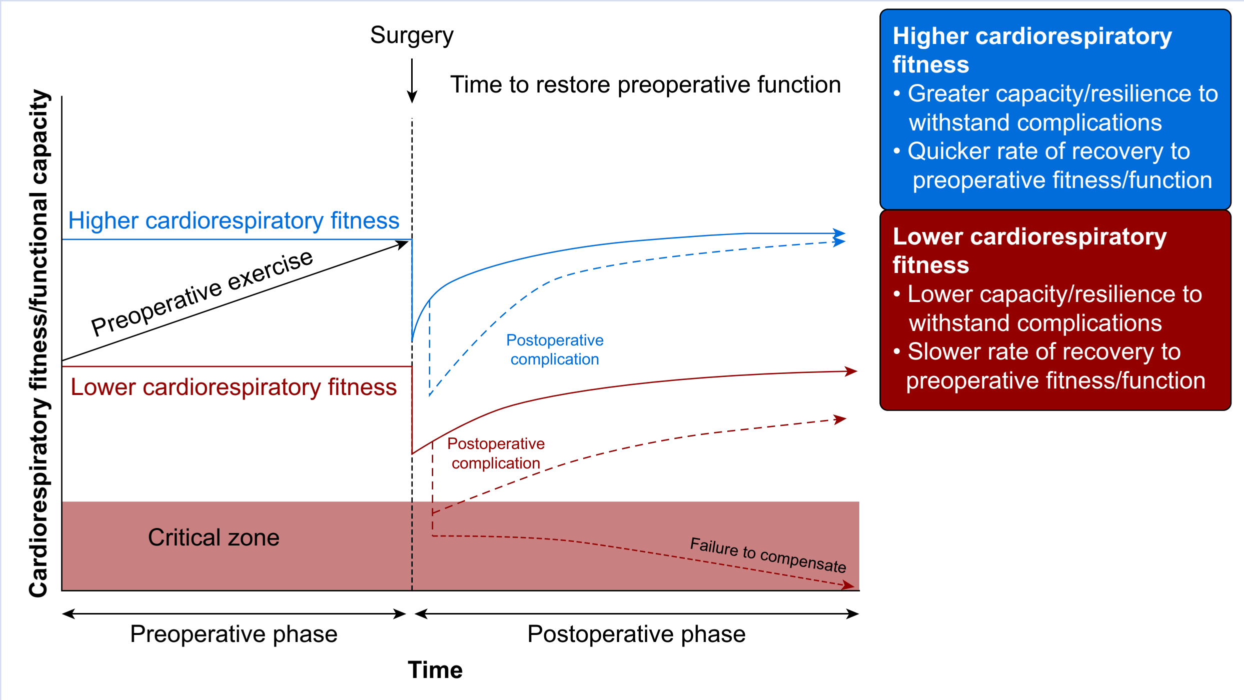

Fig 1. Theoretical model of the effect of higher (blue lines) and lower (red lines) preoperative fitness on recovery from surgery and resilience to postoperative complications (dashed lines). Black line indicates change in fitness with preoperative exercise/prehabilitation. The probability of recovery is greatly diminished in the critical zone.

unable to meet this increased requirement are at increased risk of postoperative complications.[26,38]

How may cardiorespiratory fitness influence fitness for surgery?

Whilst no study has explored the relationship between preoperative fitness and perioperative $\dot{V}_{O_2}$, from a biological plausibility perspective, it is logical that patients who have impaired $\dot{V}_{O_2}$ response during exercise/CPET may also have an impaired response perioperatively. For example, as shown in Fig 2, for patients with low fitness, even small elevations in $\dot{V}_{O_2}$ may exceed their anaerobic threshold. During exercise, the stress is self-regulated, and intensity can be decreased or ceased abruptly such that $\dot{V}_{O_2}$ will reduce below this threshold; however, during and after surgery, this O_2 requirement is often prolonged and cannot be self-regulated. Consequently, as postoperative $\dot{V}_{O_2}$ can be elevated for prolonged periods, and as anaerobic metabolism can supply ATP only short term, further oxygen debt may ensue (rather than restoration) and increase complication risk in those with low fitness.

A greater contribution of anaerobic metabolism in the postoperative period is an indicator of physiological strain; this is not dissimilar to exercise. During a CPET, the ratio of carbon dioxide production to O_2 consumption, formally known as the respiratory exchange ratio (RER), provides insight on energy substrate contribution; a value near 0.70 indicates that lipid is the predominant fuel source, whilst a value near or above 1.00 usually represents almost exclusive oxidative metabolism of carbohydrate along with glycolytic production of lactate. Recent studies have shown RER to be higher in those experiencing postoperative complications during laparoscopic surgery (1.04 *vs* 0.88; $P<0.05$) and major noncardiac surgery (1.06 *vs* 0.81; $P<0.05$) compared with those with no complications.[43,44] Additionally, an RER >0.90 has been shown to be a predictor of tissue hypoperfusion and hyperlactataemia during surgery.[45,46]

Elevated blood lactate (>3 mM) is another indicator of physiological strain and increased anaerobic metabolism in the postoperative period and is associated with greater postoperative morbidity and mortality in haemodynamically stable patients.[47–49] From exercise physiology research, a higher peak $\dot{V}_{O_2}$ is associated with less reliance on glycolytic metabolism during exercise for a given workload; fitter individuals both produce less lactate and have greater clearance from the blood.[50–53] It is possible that patients with a lower peak $\dot{V}_{O_2}$ or anaerobic threshold may rely disproportionally on glycolysis to sustain ATP production in the early postoperative period, and similarly to exercise, an increased RER or blood lactate reflects this.

Whilst an enhanced ability to consume oxygen (and less reliance on anaerobic metabolism) appears to be beneficial in the surgical context, there are several other physiological adaptations associated with higher fitness and participation in physical activity that likely afford perioperative benefit and underpin the importance of preoperative exercise. Conversely, the patient undergoing surgery with low fitness, who relies disproportionately more on anaerobic metabolism and also lacks the cellular defences and physiological reserve to withstand the surgical stress response, is most vulnerable perioperatively.

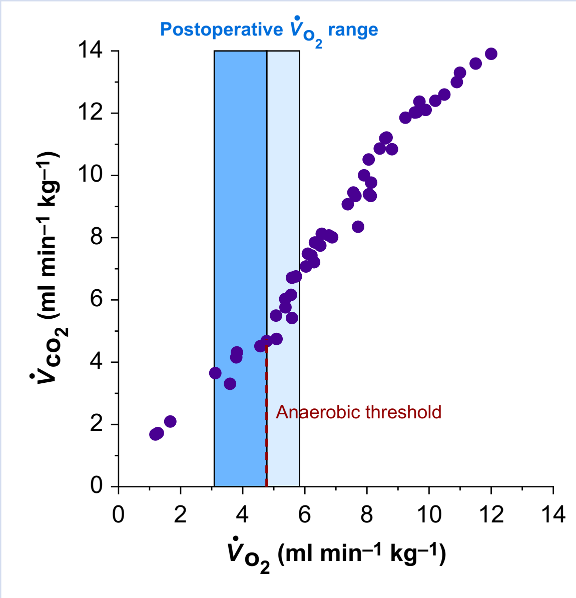

Fig 2. Example cardiopulmonary exercise test output for a patient with low preoperative peak $\dot{V}_{O_2}$ (~12 ml min^{-1} kg^{-1}) and anaerobic threshold (~5 ml min^{-1} kg^{-1}; red dashed line). The blue zone represents a typical range of postoperative $\dot{V}_{O_2}$ values after major surgery; for this patient, the upper limit of this range is above their anaerobic threshold.

Is there more to cardiorespiratory fitness? The role of cross-stressor adaptation

One of the many unique stress-protective aspects of exercise is that it invokes widespread changes in cells, tissues, and organs. The biological mechanisms underpinning fitness and metabolic resilience are complex and multi-factorial, and indices such as peak $\dot{V}_{O_2}$, and the anaerobic threshold may be useful catch-alls, or surrogates of these wider effects (Fig 3). The following sections provide further rationale for the role of fitness and some of the other broader benefits of regular participation in physical activity and exercise.

Acute physical (e.g. exercise and surgery) or psychological stressors trigger an upregulation of the hypothalamus–pituitary–adrenal axis and sympathetic nervous system, in a strongly non-linear dose-related manner.[21,54] This stimulates the cardiopulmonary, immune, musculoskeletal, and metabolic responses.[54] Insufficient activation (e.g. physical inactivity) and prolonged activation (e.g. psychological stress) of these systems negatively affect health. However, isolated or repeated intermittent stress, such as acute exercise, appears to confer an adaptive or training effect, whereby the physiological response to a subsequent given stress is blunted.[54–57] For example, during a given bout of exercise, fitter individuals exhibit less hypothalamus–pituitary–adrenal axis and sympathetic nervous system activation for identical absolute workloads, which also recovers more rapidly.[55] This concept of adapting to moderate and intermittent exposures of a sub-lethal stress is formally known as hormesis.[56]

Research is now revealing that hormetic adaptations may be beneficial not only to the original stressor that the body adapted to but also confers benefits against other stressors. This ‘cross-stressor adaptation’ phenomenon implies that repeated exposure to a discrete stressor of moderate intensity (e.g. exercise), with sufficient time to recover, can increase resilience to other forms of stress (e.g. heat, surgery, psychological, etc.). Cross-sectional studies and some prospective studies have shown that regular exercise training increases not only fitness but also one’s ability to buffer psychological stress.[58,59] For example, fitter individuals exhibit blunted neuroendocrine and inflammatory cytokine responses to acute psychological stress[60–62] and combined exercise and mental stress.[63] Moreover, fitter individuals show greater tolerance to heat stress because of enhanced thermoregulatory and cardiovascular capacities.[64,65] Cross-stressor adaptation plausibly extends to the surgical context in that fitter individuals likely have a blunted neuroendocrine and inflammatory response to a given surgical stress.

Inflammatory and oxidative stress response

Surgery can lead to cellular hypoxia and ensuing oxygen debt.[66,67] Furthermore, certain surgeries often necessitate blood flow occlusion (and ischaemia), such as tourniquet use in arthroplasty and aortic clamping in cardiac and lower-limb vascular surgery. Reperfusion and reoxygenation of ischaemic tissue are associated with oxidative stress, tissue injury, and a large inflammatory response.[68] For example, in the myocardium, reperfusion after ischaemia typically results in myocardial stunning, dysfunction or necrosis.[68]

Because of the self-regulated and progressively incremental nature of exercise, cells are exposed to intermittent hypoxia. With the concept of hormesis in mind, this repeated and transient exposure to cellular hypoxia increases factors that respond to cellular hypoxia and oxidative stress triggered by surgery. For example, exercise training can provide myocardial and neuromuscular protection against ischaemia–reperfusion injury in a rat model.[69–72] Similar work in humans has shown that combined heat and exercise stress before coronary artery bypass surgery reduces susceptibility to ischaemia–reperfusion injury compared with usual care.[73] An inductive increase in heat shock proteins (HSPs), a defence mechanism protecting against excessive cellular stress and hypoxia, may be responsible for some of this heightened resilience.[74]

Heat shock proteins exert potent anti-inflammatory and cytoprotective effects against oxidative,[75] ischaemic,[76] metabolic,[77] and other stressors. Both basal HSP levels and their response to stressors appear to be blunted in age-related chronic diseases, such as coronary artery disease[78] and Type 2 diabetes.[79] Meanwhile, people who are fitter and more active have higher basal skeletal muscle HSP content.[80,81] Patients undergoing thoracotomy exhibit less HSP70 postoperatively, presumably having encountered surgical stress,[82] and patients with the lowest preoperative HSP70 or HSP72 are more likely to experience surgical complications.[70,83,84]

Similarly, exercise training confers stress tolerance by way of antioxidant protection. The potent antioxidant, manganese superoxide dismutase, plays an important role.[81] It is located in mitochondria and upregulated in response to the reactive oxygen species produced during ischaemia and reperfusion.[85] Just three days of exercise training can increase manganese superoxide dismutase in rats and importantly translates to protection against *in vivo* ischaemia–reperfusion injury.[70,86–88] Although translation of animal data to humans is a challenge, the relationship should be explored.

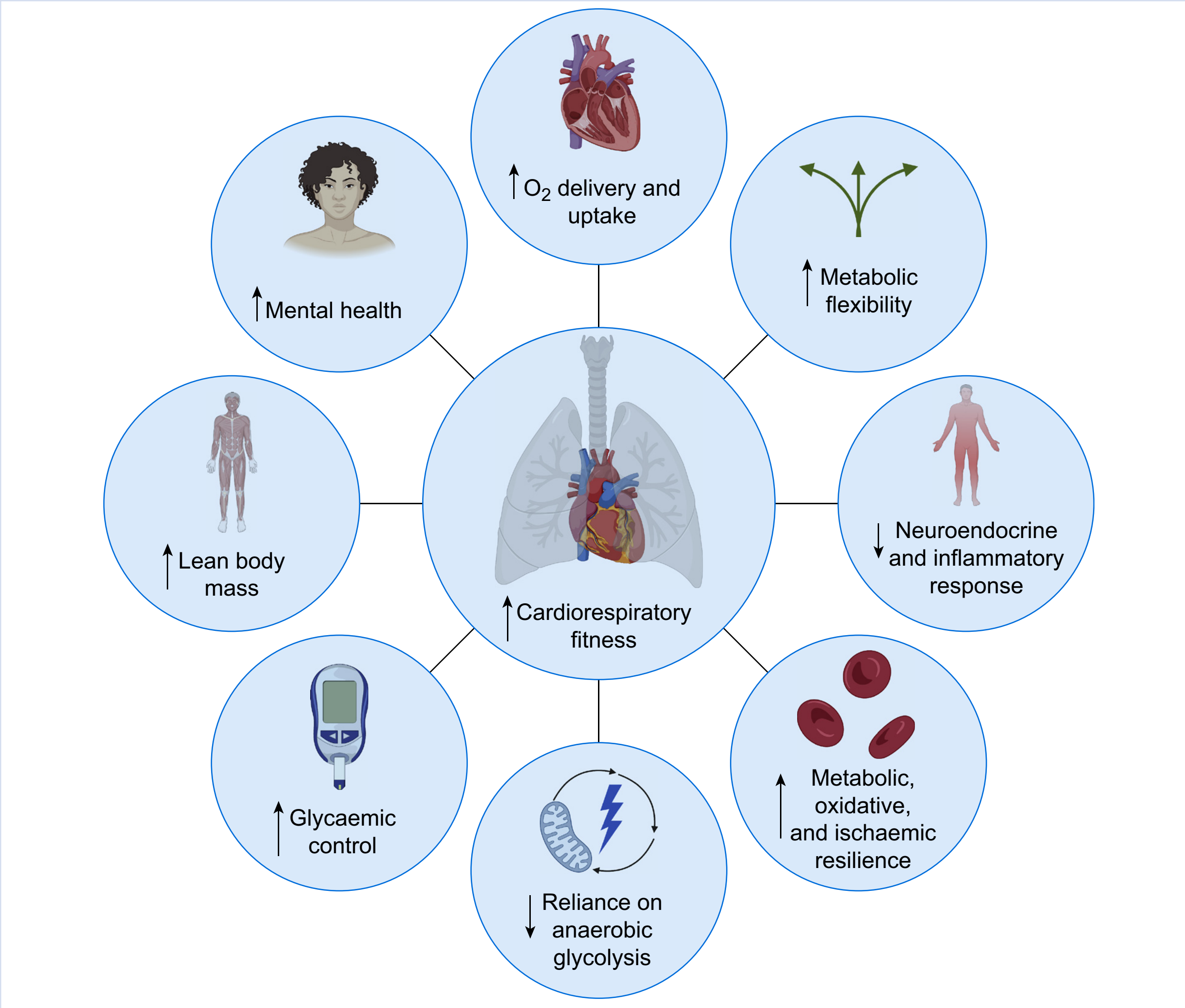

Fig 3. Physiological and psychological effects associated with higher cardiorespiratory fitness that likely improve fitness for surgery.

Metabolic flexibility

Metabolic flexibility reflects an individual's ability to adapt fuel oxidation to meet changes in energetic demands.[89] It is particularly important in patients undergoing surgery because of limited fuel availability and increased substrate demands perioperatively. Furthermore, unlike in a non-operative fasted state where metabolism is decreased, postoperative metabolism and substrate oxidation is markedly increased,[90] as mentioned previously. Because of preoperative fasting or delays in postoperative nutrition, energy stores (i.e. glycogen, body fat, or muscle protein) must be mobilised to supply ATP to facilitate homeostasis restoration. Although humans generally have sufficient muscle protein and body fat stores, glycogen stores are functionally depleted within 12–14 h during rest and much faster during stress.[91] Whilst protein and fat stores are abundant, the process of transforming these stores into usable ATP *via* aerobic metabolism is less efficient than using glycogen. Fatty acids provide the majority of energy requirements at lower intensities *via* aerobic metabolism[92]; however, for an individual with a low peak $\dot{V}_{O_2}$, even small elevations in $\dot{V}_{O_2}$ above resting values (e.g. during exercise or postoperatively) would exceed this threshold. Reassuringly, the alterations in skeletal muscle metabolism induced by regular aerobic exercise enhance fatty acid oxidation when $\dot{V}_{O_2}$ requirements are increased.[93,94] For example, mitochondrial number and size (the main site of fatty acid oxidation) and muscle oxidative enzyme activity are increased, which are limiting factors for lipid oxidation.[93,95] Consequently, fitter individuals are able to oxidise more fat for a given absolute $\dot{V}_{O_2}$ and importantly conserve muscle and liver glycogen.[96] This has relevance to patients undergoing surgery, as a fitter patient will have greater capacity for fatty acid oxidation postoperatively, particularly if $\dot{V}_{O_2}$ requirements are increased.

Glycaemic control

An inverse relationship exists between low fitness and clinical markers of glycaemic control.[97–99] Poor perioperative glycaemic control, as indicated by elevated preoperative glycated haemoglobin, and elevated intraoperative blood glucose concentrations are associated with an increased risk of morbidity and mortality after surgery.[100–102] Intraoperatively, as part of the surgical stress response, upregulated stress hormones, such as cortisol and adrenaline, contribute to increased blood glucose concentrations through increased hepatic glycogenolysis and gluconeogenesis. Insulin sensitivity becomes impaired and insulin secretion is also decreased, contributing to an insulin-resistant state and intraoperative hyperglycaemia.[21] Again, although speculative, a blunted stress hormone response may reduce this impact in fitter people. Interestingly, HSP activation inhibits nuclear factor κB, a major inflammatory mediator that promotes insulin resistance when activated[103]; given that fitness is related to basal HSP content, higher HSP may help preserve perioperative insulin sensitivity.

Fitter individuals have enhanced blood glucose regulation.[97–99] Increased muscle glucose transporter Type 4 (GLUT-4) content and insulin signalling are partly responsible.[104] GLUT-4 is a key glucose transporter responsible for translocating glucose from the bloodstream into muscle and fat cells.[105] Increased GLUT-4 translocation from the cytoplasm to the cell membrane is achieved through both insulin-dependent and insulin-independent mechanisms.[106] This is beneficial for patients with insulin resistance because both pathways are enhanced acutely *via* muscle contraction and persist for 12–48 h,[107–109] thereby again providing complimentary acute and chronic benefits. Therefore, although fitter individuals are more likely to have superior glycaemic control, patients with insulin resistance or diabetes may achieve better perioperative glycaemic control by performing exercise ~24 h before surgery. Future research should confirm if this is true and if a relationship exists between preoperative fitness, incidence of perioperative hyperglycaemia, and postoperative outcomes.

Lean body mass

Catabolism is a consequence of the surgical stress response. In the absence of adequate caloric and protein intake in the perioperative period, substrate availability is compromised. As discussed in earlier sections, when these two factors combine, protein is mobilised from lean body mass. As a result of this catabolism, weight loss is a major side-effect of surgery, with skeletal muscle atrophy during the perioperative process common,[110–112] and it occurs significantly quicker than it can be regained[113]; in fact, it is often never fully recouped.[114] Patients undergoing surgery who are frail or sarcopenic/cachexic have lower lean body mass, thus reduced metabolic reserve and capacity to respond to catabolism, making them more vulnerable to surgical stress.[115–121] The importance of lean body mass is highlighted by the obesity paradox, where patients with obesity have a lower 30 day mortality risk than patients with normal weight after general surgery,[122] likely because of higher lean body mass secondary to having a high fat mass.[123] Furthermore, frail patients and those with lower skeletal muscle mass are at increased risk of postoperative delirium.[124,125] Fitness is inversely related to sarcopenia, independent of age and sex,[126–129] that is, fitter individuals are more likely to have higher lean body mass and be less sarcopenic. Similarly, physically active older adults have higher lean body mass than those who are least active.[130]

Mood

Whilst this review has focused on physiological and metabolic aspects that relate fitness to surgical outcomes, their relationship to psychological disposition is worth considering. Preoperative depression, anxiety, and low self-efficacy independently increase the risk of adverse physiological surgical outcomes.[131,132] It has been shown that anxiety not only alters the surgical stress response,[133] but it is an independent risk factor for greater postoperative pain and analgesic use.[134] Anxiety and depression have also been implicated as negatively affecting wound healing, with preoperative anxiety impairing the early postoperative inflammatory response and matrix degradation processes in the wound.[132,135] Low fitness has been linked with higher incidence of depression and anxiety and reduced ability to cope with exposure to stress.[136–139] Conversely, fitter individuals have less anxiety and depression and generally have greater ability to perform activities of daily living and explore the environment, which are beneficial for psychological health.[6,137] Reassuringly, prospective trials have highlighted the positive effect of exercise interventions on clinical depression and anxiety severity, further reinforcing the utility of exercise as part of multimodal prehabilitation.[140,141]

Perspectives

As researchers and clinicians, we can be motivated to unrealistically discover a single variable to identify ‘high-risk’ patients with as much sensitivity and specificity as possible. Given the complexities of exercise and fitness, by adopting such a narrow-minded focus, we may lose sight of the bigger picture. During exercise and indeed surgery too, multiple systems synergistically work to respond to acute stress. Whilst an enhanced ability to consume oxygen (i.e. higher peak $\dot{V}_{O_2}$) appears to be beneficial in the surgical context, as highlighted in this review, many other hormetic adaptations are associated with a higher fitness that likely afford perioperative benefit. Furthermore, there are indirect social and psychological benefits associated with exercise that influence behaviour and surgical risk and outcomes.

Although some appealing associations are evident between fitness and the physiological response to surgery, it remains unclear whether these are correlational or causational. Future research must expand from simple cross-sectional epidemiological research to better understand the physiological mechanisms for why fitness is beneficial in the surgical context. Importantly, peak $\dot{V}_{O_2}$ or the anaerobic threshold may be merely a surrogate marker for a collection of optimised and enhanced physiological processes that are refined with regular exercise.

Conclusions

The biological mechanisms underpinning cardiorespiratory fitness and metabolic resilience are complex and multifactorial; peak $\dot{V}_{O_2}$ and the anaerobic threshold are prominent indicators or biomarkers of this. We make the case that many parallels exist with the metabolic events of surgery and exercise and a strong association with fitness and surgical outcomes; a patient who can respond metabolically efficiently during exercise appears more likely to do so in the postoperative setting and also possesses heightened resilience to withstand the stress of surgery.

Whilst it is not possible to 'train' for the stress of surgery, the benefits of regular exercise training likely cross over and provide benefit in the perioperative setting. However, it is important to recognise that the benefits of exercise cannot be solely explained through fitness and likely extend to (but are not limited to) the underlying physiological changes of enhanced antioxidant defences and substrate oxidation, improved glycaemic control, greater lean body mass, and improved mood.

Authors' contributions

Drafting of original article: BHR, KNT
Critical revisions of the work for important intellectual content: all authors
Final approval: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

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