**Mechanisms of Multi-modal Prehabilitation Effects on Surgical Complications: A Narrative Review**

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**INTRODUCTION**

The number of surgical procedures performed globally is rising in response to growing rates of chronic disease.1 Increased demand for surgical services will be met by a proportional increase in surgical complications, resulting in compromised patient health and healthcare system burden.2 Approximately 14% of all surgical patients experience one or more complications,3 and this proportion increases to 43.5% among patients with underlying frailty.4,5 Meta-analyses have established an inverse relationship between preoperative functional status and surgical complications.6–8 Given that preoperative functional status is a modifiable surgical risk factor, preoperative interventions aimed at improving functional status may improve surgical outcomes.9 Such interventions are known as ‘prehabilitation’ and involve screening patients for impairments and delivering a multi-modal intervention to improve physiological and psychological resilience to surgery.9 Continuous advances in prehabilitation research over the past several decades have clarified its role in improving preoperative risk factors such as low functional capacity,10 frailty,11 and malnutrition.12 However, the evidence for the role of prehabilitation to reduce surgical complications is of low certainty.13

While there is some evidence of benefits to surgical outcomes afforded by prehabilitation, the underlying biological mechanisms have yet to be thoroughly explored. Clarifying mechanistic relationships between prehabilitation and surgical complications represents an important basis for establishing biological plausibility, developing targeted therapies, generating hypotheses for future research, and contributing to the rationale for implementation into the standard of care.14,15 Biological plausibility is particularly important as it is one component of the causal pathway that also includes temporality (e.g., does the intervention precede the desired effect?) and consistency (e.g., does the intervention produce the desired effect when replicated?).16 The findings of interventions with coherent biological plausibility are at decreased risk to be misled by “third variable effects” (i.e., mediators, moderators, and confounders).17 Previous research has called for mechanistic studies to establish the biological plausibility of prehabilitation and identify preoperative modifiers of the surgical stress response.18 In this narrative review, we discuss and synthesize the current evidence base for the biological plausibility of multimodal prehabilitation to reduce surgical complications. The goal of this review is to aid future prehabilitation interventions more effectively target surgical outcomes by outlining biologically plausible mechanisms of benefit and generating hypotheses for future research.

**METHODS**

**Defining Surgical Complications**

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) provided a framework for classifying surgical complications. This allowed a review of mechanisms for complications routinely assessed at 706 participating sites.19,20 Table 1 provides an overview and definition of ACS-NSQIP complications.21–23

Table 1. ACS-NSQIP Complications

|  |  |
| --- | --- |
| ACS-NSQIP Complication | Definition |
| **Pulmonary Complications** | |
| Pneumonia | An infection of one or both lungs caused by bacteria, viruses, fungi, or aspiration. |
| On Ventilator > 48 hours | Total cumulative time of ventilator-assisted respirations exceeding 48 hours. |
| Unplanned Intubation | The placement of an endotracheal tube or (other similar breathing tube) and ventilator support. |
| **Cardiac Complications** |  |
| Myocardial Infarction | Ischemia to the heart causing damage or death to part of the heart muscle**.** |
| Cardiac Arrest Requiring Cardiopulmonary Resuscitation | The initiation of cardiopulmonary resuscitation following an absent cardiac rhythm. |
| **Infectious Complications** | |
| Surgical Site Infection (SSI) | An infection that occurs within 30 days after the primary procedure including superficial, deep, and organ/space SSI. |
| Urinary Tract Infection | An infection in the kidneys, ureters, bladder, or urethra). |
| Clostridioides difficile | Colonization by C. diff. releases toxins (A&B) that cause mucosal inflammation and damage, disturbing normal bacterial flora of the colon. |
| **Renal Complications** |  |
| Progressive Renal Insufficiency | The reduced capacity of the kidney(s) to function in comparison to the preoperative state. |
| Acute Renal Failure Requiring Dialysis | Significant decline of kidney function in comparison to the preoperative state. |
| **Venous thromboembolism** (VTE) | New diagnosis of blood clot or thrombus within the venous system (superficial or deep) which may be coupled with inflammation and requires treatment. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are classified as VTE. |
| **Ischemic Stroke** | Disrupted blood supply to the brain resulting in motor, sensory, or cognitive dysfunction. |
| **Other Complications** |  |
| Sepsis/Septic Shock. | A generalized response to infection (e.g., bacterial, fungal, viral). Septic shock is a more severe form of sepsis resulting in organ and/or circulatory dysfunction |
| Wound disruption | Spontaneous dehiscence of a surgically closed wound**.** |
| Blood transfusion | Transfusion of blood including red blood cells and cell-saver products |

*Notes*: Definitions adapted from the ACS NSQIP Operations Manual24

**Search Strategy**

Although this was not a systematic review of the current evidence, this narrative review reports the search strategy and study eligibility used to enhance transparency and replicability. Studies that contributed to the purpose of this review were identified usingOvid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, PEDro (Physiotherapy Evidence database), and Google Scholar. The search was limited to articles published prior to January 2022 and in English. Searches were conducted using component blocks of terms: for instance: “mechanisms” and “preoperative” and “exercise” or “nutrition” or “psychological intervention.” Each component was fleshed out with both controlled vocabulary and text word terms and synonyms. Reference lists of relevant studies were also reviewed.

**Study Eligibility**

All study designs were considered for this review. Studies were included if they reported on a prehabilitation intervention modality among adults (≥ 18 years old). For the purposes of this review, prehabilitation modalities were broadly defined as an exercise, nutrition, or psychological intervention. Briefly, exercise encompassed aerobic, resistance, stretching, or inspiratory muscle training (IMT). Other exercise modalities, such as locoregional exercises or yoga, were also considered. Nutrition interventions encompassed personalized nutrition counselling and supplementation of energy (i.e., increased caloric intake), macronutrients (e.g., protein), micronutrients (e.g., vitamins) and other compounds (e.g., polyphenols). Psychological intervention included any non-pharmacologic intervention with the goal of stress reduction, such as guided imagery, progressive muscle relaxation, or psychotherapy.25 Interventions initiated > 24 hours preoperatively (or could reasonably be implemented within this window) to improve postoperative outcomes were included.26 For example, when evidence was limited, we expanded our search to interventions initiated postoperatively or among non-surgical, clinical, and healthy populations. Pre-clinical interventions were also included. Studies were excluded if the sample was not comprised solely of adults. Studies reporting on interventions specific to the surgical procedure (e.g., osteopathic knee manipulation prior to total knee arthroplasty) or surgical sub-group (e.g., anemia correction for anemic patients) were also excluded.

Mechanisms that could be achieved within a typical prehabilitation window (< 8 weeks) were prioritized over those that require longer intervention periods. Differences in the quantity of content across various surgical complications and prehabilitation modalities reflect discrepancies in the available evidence generated by our search strategy. First, we summarized the biological rationale and existing evidence supporting the implementation of a prehabilitation intervention to reduce each surgical complication. We then synthesized the existing evidence for the biological mechanisms of exercise, nutrition, and psychological intervention to reduce each surgical complication.

**SYNTHESIS**

**Pulmonary Complications**

Postoperative pulmonary complications (PPCs) are one of the most common surgical complications (Figure 1). Patients develop PPCs due to impaired pulmonary mechanics, use of anesthetics, excess mucous production/impaired mucous clearance, diminished respiratory drive (including the ability to cough), and impairment of the pulmonary immune response.27 Many of the causal mechanisms of PPCs, such as respiratory muscle weakness and an impaired immune response, are amenable to preoperative intervention.28 In a meta-analysis of exercise prehabilitation versus usual care, Assouline and colleagues found that prehabilitation significantly reduced PPCs (RR: 0.52, 95% CI: 0.41, 0.66).29

**Figure 1**. The proportion of surgical complications in 2020 as reported by ACS-NSQIP across 706 sites.

*Notes:* Data reflects 86 977 cases of surgical morbidity. VTE = venous thromboembolism. Stroke, wound disruption, and blood transfusion are not modeled in the ACS NSQIP report. The constituents of each complication can be found in Table 1.

*Exercise*

Prehabilitation may capitalize on established pulmonary adaptations of exercise to reduce PPCs, including improving functional residual capacity, vital capacity, and forced expired volume. Surgery impairs pulmonary function, which is linked to increased susceptibility to PPCs.30 Mechanistically, improvement of breathing performance preoperatively may prevent PPCs through increases in surfactant production, lung immunity, and alveolar-arterial gas exchange. Primarily composed of phospholipids, surfactant is responsible for preventing alveolar collapse by decreasing alveolar surface tension.31 Surfactant also has an immunological role through interaction with pathogens and modulation of the pulmonary immune response.31 Consequently, an inadequate supply of pulmonary surfactant is a risk factor for PPCs through the promotion of atelectasis and bacterial growth.32 Increases in tidal volume with exercise upregulate the production of surfactant from alveolar type IIa cells and modifies its composition.33,34 This increases the availability of surfactant to bind to alveolar macrophages, which attack invading micro-organisms as a first-line defence to inhaled pathogens. The binding of surfactant to macrophages enhances their phagocytotic activity, as was demonstrated in a pre-clinical study.35 By understanding the role of preoperative surfactant deficiency on the surgical stress response, targeted therapies such as prehabilitation may be better equipped to decrease the risk of PPCs. cells.33–35

Aerobic exercise also leads to adaptations to lung immunity independent of surfactant, including anti-inflammatory, pro-oxidative, and bacterial clearing responses to pathogens.36 Mechanisms include decreased interleukin (IL)-1β, IL-6, CXCL1, and TNF-α as well as upregulation of the anti-inflammatory cytokine IL-10 from pulmonary leukocytes and airway epithelial cells.36 By reducing low-grade, chronic inflammation preoperatively with exercise, there exists the potential for an enhanced immune response to nosocomial infection.36 Antimicrobial peptides, such as α- and β-defensins, also play important roles in lung immunity. Directly, defensins can destroy microbes through membrane permeation or electrostatic interaction.37 Indirectly, defensins modulate the immune response through interactions with toll-like receptors and chemokines. Importantly, defensins are upregulated following a single exercise bout and are increased further with sustained exercise regimens.37,38

Patients are exposed to the risk of PPCs due to respiratory drive impairment from surgery. For example, respiratory muscle impairment from surgery alters ventilation perfusion (V̇/Q̇) relationships that contribute to alveolar deadspace and impaired oxygenation.39 This impairment is amenable to intervention: 1 to 10 weeks of inspiratory muscle training (IMT) has been shown to improve respiratory strength and respiratory endurance by 18% and 15% respectively among high risk patients undergoing coronary artery bypass graft (CABG) surgery. As a result, PPCs were reduced by 17% compared to usual care.40 The diaphragm, the primary respiratory muscle, is responsible for creating intrathoracic pressure during inspiration and is dysregulated with surgery.41 Diaphragm displacement during surgery and weakness following surgery are key antecedents of atelectasis and PPCs, respectively.39 Pre-clinical models show ≤ 4 weeks of exercise training significantly improves diaphragmatic function through increases in diaphragmatic capillary density and oxidative capacity.42

Enhanced respiratory muscle function with exercise reduces the alveolar-arterial oxygen difference and contributes to a higher lung diffusing capacity for oxygen, improving pulmonary gas exchange and oxygen transport. The resulting increase in respiratory drive attenuates the impact of acute alveolar hypoxia on the partial pressure of oxygen and pulmonary arterial pressure.43 Attenuation of acute hypoxia may prevent the need for mechanical ventialitation.44 Independent of respiratory muscle function, exercise may also improve alveolar-to-arterial oxygen exchange via capillary blood volume, Hb concentration, and pulmonary membrane diffusing capacity.43,45 For example, a study comparing athletes and non-athletes demonstrated that athletes had larger alveoli and greater pulmonary capillary recruitment as mechanisms for increased membrane diffusion capacity.45 Indeed, elevated pulmonary arterial pressure during exercise increases capillary distension and recruitment, improving membrane diffusing capacity and pulmonary perfusion.45 If elicited preoperatively, such adaptations may mitigate the risk of PPCs from surgically induced respiratory dysfunction. Unfortunately, the volume of exercise required to elicit the mechanisms mentioned above nor their durability can be stated with certainty. This remains an important undertaking for future research.

*Nutrition*

Prevention or correction of preoperative malnutrition (i.e., nutritional prehabilitation) may also contribute to reduced risk of PPCs by supporting optimal immune and respiratory function. The surgical insult is marked by skeletal muscle catabolism (including skeletal, gut, and respiratory tissues) through proteolysis, increased respiratory rate, and an innate inflammatory response.46 For patients with malnutrition or reduced muscle mass, without sufficient perioperative nutritional support, the resultant immunosuppression and respiratory muscle catabolism leave patients vulnerable to PPCs.47 Traditional markers of cell-mediated immunity such as macrophages, phagocytosis, and cytotoxic CD8+ cells are impaired in malnourished patients.48 For example, malnutrition can result in decreased levels of alveolar macrophages by 40%.49 Immunosuppression secondary to malnutrition is modifiable: a 10-day nutritional prehabilitation randomized controlled trial (RCT) targeting the postoperative decline in serum albumin reduced the incidence of surgical complications (unspecified) compared with controls.50 This intervention established a risk threshold for preoperative serum albumin (4 mg/dl) that predicts postoperative complications.50 Establishing biologically plausible biomarkers of PPCs that are modifiable preoperatively represents an opportunity to increase the certainty of evidence demonstrating prehabilitation improves surgical outcomes.

Impairment in cell-mediated immunity due to malnutrition may be explained in part by dysregulated energetics in serum mononuclear cells.51 Complex I is a mitochondrial enzyme contributing to proton gradient creation to drive aerobic ATP synthesis. Complex I is impaired in mononuclear cells proportionally to the degree of malnutrition.52 However, Complex I function responds rapidly to nutrition intervention within 1 week, and normalizes within 1 month.53 The resulting improvement in cellular energetics and consequently, cell-mediated immunity, is a potential mechanism for the prevention of PPCs. Improved mitochondrial ATP production may also have important implications for improving overall muscle function. This may facilitate early mobilization, a PPC prevention strategy with “good” strength of supporting evidence.54

There is a significant relationship between muscle function, mobility, and pulmonary function that can be addressed preoperatively via nutrition.55 Diaphragmatic atrophy and weakness predispose patients to PPCs.56,57 Malnutrition impairs oxygen consumption, minute ventilation, and the ventilatory response to hypoxia, suggesting an influence on both pulmonary musculature and autonomic nervous system regulation.58–60 Initiated postoperatively, nutrition support may significantly increase the likelihood of being weaned off a ventilator.61 Prior to surgery, nutritional support may increase muscular reserve and improve respiratory muscle function.12,50 For example, by supporting caloric requirements preoperatively, insulin growth factor-1 (IGF-1) is sustained, supporting respiratory muscle maintenance and synthesis via the IGF-1-mTOR pathway.62 In addition, adequate caloric intake averts mitochondrial oxygen consumption deficits that predispose patients to PPCs.63 For instance, when 8 healthy participants were subjected to 7 days of a hypocaloric dextrose infusion, resting energy expenditure and ventilatory measurements (e.g., mean inspiratory flow) were significantly depressed; improvement was noted within 4 hours of initiating an amino acid infusion (providing approximately 465 additional kcal) and normalized within 24 hours .60

*Psychological Intervention*

Several trials have demonstrated that preoperative psychological intervention can significantly reduce the anxiety of surgical patients.64–66 Zhang and colleagues’ preoperative education intervention of 40 CABG patients 3 days before surgery demonstrated a significant reduction in respiratory infections versus usual care (12 vs. 1; *p* = 0.009).64 Psychological distress prior to surgery poses a challenge for postoperative recovery and may increase the risk of PPCs. The growth of psychoneuroimmunology research has implicated the principal role of chronic stress in hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) dysregulation, immune dysfunction, and the pathogenesis of physical diseases.67 Stress-induced chronic increased glucocorticoid and epinephrine secretion can lead to immune suppression and ultimately increase risk of PPCs.68,69 Peptidergic nerve fibres across the body close neuroeffector junctions with lymphocytes and macrophages. Neurotransmitters released from these nerves are received by lymphocytes, macrophages, and granulocytes.70 Attenuation of stress-related SNS activity may enhance preoperative immune function via this innervation of lymphoid tissue by the central nervous system.71 This neural-immune interaction is a plausible mechanism for psychological prehabilitation and reduced PPCs.72–74

**Cardiac Complications**

As an area of research, prehabilitation to reduce cardiac complications is in its early stages. For instance, in a previous systematic review of 61 uni- and multi-modal prehabilitation studies in cardiothoracic and major abdominal surgery, only 4 studies reported on cardiac complications.72 Notwithstanding the limited attention paid, a significant reduction in cardiac complications was shown (OR 0.46, 95% CI 0.22-0.96, p = .044).72 With regards to multimodal prehabilitation among elective cardiac surgery patients, a previous historical control trial and retrospective cohort trial demonstrated an 8% and 11% reduction in cardiac complications, respectively.75,76

*Exercise*

Exercise prehabilitation may contribute to reduced cardiac complications through several mechanisms, including ischemic preconditioning, improved autonomic modulation of cardiac tissue, antioxidant buffering capacity, cardiac remodeling, and natriuretic peptides. Regarding preconditioning, brief and reversible periods of exercise-induced ischemia may protect the heart from infarction following longer periods of ischemia, as well as subsequent reperfusion injury.77 Indeed, the cardioprotective benefit of exercise has been demonstrated in pre-clinical and clinical models.78–80 Protective adaptations, described below, can occur in as little as one bout of exercise.80

Cardioprotective adaptations to exercise include upregulated adenosine receptors, endogenous opioids, AMPK, and reactive oxygen species (ROS).80 For example, adenosine and opioid receptors are activated following exercise and act on protein kinase C (PKC)-dependant mechanisms.80 When PKC-δ isoforms are blocked, preconditioning cardioprotection is nullified, suggesting this is a crucial protective mechanism.81 Zdrenghea and colleagues showed that performing a single bout of exercise increased plasma nitric oxide (NO) that decreased myocardial ischemia during a subsequent exercise bout.78 Transient protective benefit to subsequent ischemic events and reperfusion injury may persist for at least 9 days following the cessation of exercise.82

Exercise-induced modulation of heart rate variability (HRV) may also elicit cardioprotection. Defined as the time-variation between consecutive heartbeats, HRV is a marker of autonomic function.83 Depressed HRV is an independent predictor of cardiac mortality.84 In a pre-clinical study, 6-weeks of daily aerobic training led to a 74% increase in HRV.85 Exercising subjects experienced 100% protection against ventricular fibrillation compared to cage rest during a submaximal exercise test.85 Measured through heart rate variability and baroreflex activity 12 and 14 weeks of aerobic exercise was shown to improve parasympathetic nervous system activity among older adult males and patients who recently suffered a coronary event, respectively,.86,87 Exercise-induced improvement of vagal modulation is mediated by nitric oxide and angiotensin II.88,89 The result is decreased contractility and workload of cardiac tissues, such as the sinus node and myocardium. Improved cardiac efficiency, as indicated by increased vagal tone and HRV, reduces myocardial oxygen demand, inhibits prolonged sympathetic nervous system activity, and reduces the susceptibility of the heart to arrythmia.89 Accordingly, increased HRV is a potential mechanism of cardioprotection from surgical stress.

Exercise prehabilitation may also exert cardioprotection through an increase in antioxidant buffering capacity. Oxidative stress, measured through ROS production, is predictive of the severity of the surgical stress response, recovery time, and development of severe postoperative complications.90,91 Patients who are frail experience a blunted response to oxidative stress, mediated by nuclear erythroid factor erythroid 2- related factor 2 (Nrf2) and antioxidant response element.92 The result is increased susceptibility to oxidative stress and myocardial dysfunction. Within 6 weeks in pre-clinical models, moderate exercise has been shown to protect against cardiac damage by upholding the expression of NrF2.93

Acute bouts of exercise also upregulate the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase.94 Although strenuous exercise increases oxidant production, the resulting perturbations in ROS homeostasis facilitate an adaptive response, increasing antioxidant enzyme activity.95 In fact, exercise-induced increases in antioxidant buffering capacity is posed as the primary mechanism for cardioprotection against doxorubicin-induced cardiotoxicity.96 Here, cardioprotection may occur via reduced apoptotic ubiquitin-proteasome pathway activation, preserved contractile power of cardiac proteins, and upregulating heat shock proteins.97,98 Importantly, increases in antioxidant buffering capacity are achievable with five days of aerobic exercise.94,99

Left-ventricular remodeling comprises pathological dilation and altered geometry of the left ventricle in response to mechanical stress or myocardial injury.100 Following single bouts of exercise, the initiation of a reversal of left ventricular remodeling may occur through improved hemodynamic loading and a reduction in shear wall stress. Aerobic exercise may also reverse left ventricular remodeling through improvements in ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV).101,102 However, these adaptations require at least 8 weeks of exercise training.101 Other biomarkers of cardiac function, such as atrial natriuretic peptide (ANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are improved in shorter timeframes. Protective against cardiac remodeling, ANP is increased in a single 30 minute bout of exercise through cGMP-dependent protein kinases (PKG).103 As an endogenous peptide released as a result of ventricular wall stress and myocardial ischemia, NT-proBNP is a powerful prognostic biomarker for heart failure and an independent predictor of cardiac complications following surgery.104,105 Exercise modulation of ANP and NT-proBNP demonstrates reduced cardiac complication risk via i) vasodilation and natriuresis; ii) counter-activation of the sympathetic nervous system; and iii) counter-activation of the renin-angiotensin-aldosterone system.

*Nutrition*

Nutritional intervention is also emerging as a promising strategy to reduce cardiac complications.106,107 Abnormal nutritional biomarkers, such as albumin, transferrin, and hyperglycemia, are predictive of postoperative cardiac events.108,109 Markers of malnutrition are associated with electrophysiologic dysregulation, sympathoadrenal activation, hemodynamic dysfunction, and cardiac tissue hypoxia.110,111 Poor nutrition is also linked to cardiac complications through systemic inflammation.112 Cytokine-induced inflammation is associated with high-fat, high-sugar, and gut microbiota dysbiosis contributing to the pathophysiology of atherosclerosis and vessel rupture.113–115 Anti-inflammatory nutrients such as polyunsaturated fatty acids, ω-3 fatty acids, and fibre may underlie the previously documented effect of prehabilitation for reducing cardiovascular complication risk.76,116 For example, one RCT using a 3-diet crossover design among hypercholesterolemic and overweight/obese adults compared 6 weeks of diets high in polyunsaturated fatty acids and either linoleic acid or α-linolenic acid versus a usual care control.117 Within the 6-week period, α-linolenic acid demonstrated a 75% reduction in the inflammatory cytokine CRP. In cancer patients, randomized trials (≥ 4 weeks) of fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) versus control provides a blunted or reduced inflammatory response, measured through CRP.118,119 Through vascular endothelial growth factor (VEG-F), CRP leads to downstream vascular permeability to low-density cholesterol.120 Preoperative reductions in CRP may therefore reduce atherosclerotic plaque buildup and decrease cardiac complication risk.121 Based on previous positive findings for the role of prehabilitation to reduce cardiac complications,75,76 anti-inflammation may represent a potential mechanism and thus should be tested in future prehabilitation trials.

Preoperative insulin resistance is a particularly salient marker of cardiac risk. Surgery results in impairment of both peripheral and central insulin sensitivity by disturbing insulin-mediated glucose uptake into cells via defects in the phosphoinositide-3-kinase–protein kinase (P13K) signalling pathway and glucose transporter type 4 (GLUT4) translocation.46 There is evidence to support reduced insulin resistance perioperatively and postoperatively through preoperative carbohydrate loading. Indeed, clinical trials in cardiac patients have found a reduced need for perioperative inotropic agents,122 lower incidence of postoperative hypotension, and reduced severity of cardiac arrythmia following preoperative carbohydrate loading.123 Despite traditionally being incorporated in enhanced recovery after surgery (ERAS) protocols, the success of diabetes management and oral carbohydrate supplementation prior to the day of surgery provides a strong biological rationale for attenuating insulin resistance using prehabilitation.122,124

Whether nutritional prehabilitation can affect gut microbiota is an emerging area of research following evidence that gut health is related to the risk of cardiac events.125 Although not yet established as a preoperative risk factor for cardiac complications, gut microbiota is a determinant of inflammation and oxidative stress.126 Diets abundant in red meat lead to excess consumption of L-carnitine and choline, precursors to trimethylamine N-oxide (TMAO).126 Studies of TMAO, a microbiota-related metabolite, indicate its role in the expression of heat shock proteins, such as GRP94 and HSP70, that bind to endothelial walls and promote inflammation and atherosclerotic plaque.127 Consequently, gut microbiota and related metabolites are increasingly targeted for their potential therapeutic impact on cardiovascular risk. A 4-week randomized controlled trial of the prebiotic arabinoxylan oligosaccharides versus a placebo control significantly reduced TMAO among chronic kidney disease (CKD) patients.128 Within the first 30 days of an RCT among patients with high cardiovascular risk, polyphenols and probiotics significantly decreased TMAO by 59% and 23%, respectively.129 The direct impact on cardiovascular risk afforded by this inexpensive and expeditious intervention makes TMAO reduction a potential mechanism for reducing cardiac complications.

*Psychological Intervention*

Psychological prehabilitation may improve several risk factors underlying the pathogenesis of cardiac complications.130 During the preoperative phase, psychological distress, anxiety, and depression are risk factors for postoperative complications and prolonged recovery.131,132 Surgery is associated with increased SNS activity, tachycardia, hypercoagulability, bleeding, and inflammation.133 The physiological stress of surgery leaves patients prone to cardiac complications, particularly when there is hemodynamic compromise and decoupling between oxygen supply and demand.134

Preoperative psychological distress is amenable to intervention and can improve surgical outcomes.135 For example, two preoperative educational stress management trials delivered 3 days before surgery successfully reduced postoperative stress and anxiety in patients undergoing cardiac surgery.64,65 One trial reported significantly reduced cardiovascular complications (dysrhythmia and deep vein thrombosis).64 Psychological prehabilitation interventions may contribute to reducing chronic hyperactivation of the general stress response and in turn, reduce hypertension, inflammatory system activation, and vascular constriction.136 For example, cortisol is an anti-inflammatory hormone that, when elevated chronically through prolonged stress responses, produces IL-6, IL-1β, and TNF-α and a state of chronic inflammation.137 Serum cortisol is closely related to troponin and predicts cardiac risk among non-cardiac surgeries.138 Importantly, a 20-minute psychological intervention has been shown to significantly reduce cortisol levels prior to surgery,139 possibly as a result of decreased adrenocorticotropic hormone.140 Reductions in cortisol were mirrored by self-reported anxiety. There are clear physiologic links between psychological stress and surgical cardiac risk; such stress can be improved with preoperative psychological intervention. Whether this reduction in stress improves cardiac complications remains an important area for future trials.

**Infectious Complications**

Surgery predisposes patients with underlying frailty and comorbidities to increased risk of infection due to antibiotic-resistant nosocomial pathogens, and immunosuppression.141 For the purposes of this review, infectious complications are consolidated due to overlapping risk factors, etiology, and prevention strategies.141,142 In addition, consolidating these complications aligns with previous prehabilitation trials that have considered infectious complications in aggregate.143 Prehabilitation is a potential prevention strategy to attenuate the surgical stress response and target modifiable risk factors for infection including low preoperative functional capacity, excess visceral adiposity, malnutrition, and anxiety.144–146

*Exercise*

The immunological impact of exercise is complex. Exercise at high intensities and prolonged durations ( > 90 minutes) can increase susceptibility to infection.147 However, exercise at light and moderate intensities upregulate immune function, mediated by inflammatory cytokines, metabolic markers, and pathogen clearing processes (e.g., phagocytosis).148 For example, a 4-week multi-modal prehabilitation intervention by Cho and colleagues among stage I gastric cancer patients with metabolic syndrome resulted in 0 cases of postoperative SSI (n = 18) versus 9 cases in the control group (n = 54), attributed to significant reductions in visceral fat.149

Visceral fat reduction and skeletal muscle improvement achieved with exercise (and/or nutrition) may reduce susceptibility to infection due to an endocrine influence on NK cell activation, insulin resistance, and metabolism.150 Both visceral adiposity and skeletal muscle mass regulate inflammation via adipokines and myokines, respectively.151 For example, visceral adiposity is negatively correlated with NK cell activity, mediated by adipose release of the pro-inflammatory cytokines TNF-α and IL-6.151 Adiponectin, an anti-inflammatory adipokine, is downregulated in individuals with increased visceral fat, inhibiting its regulation of immune function through macrophages, monocytes, and dendritic cells.152 The myokine IL-15, produced in skeletal muscle and upregulated with exercise, is a requirement for NK cell function and thus, overall immunity.151 Enhanced endocrine function of adipose tissue and skeletal muscle through regulation of body composition is an important mechanism for reducing infectious complication risk with prehabilitation.153–155

Exercise may also boost immune function through direct upregulation of lymphocytes, an independent predictor of infectious complications following surgery.156,157 Exercise bouts lasting less than 60 minutes result in a transient mobilization of NK cells and CD8+ T cells independent of visceral fat.158 Repeated bouts can lead to a clinically important lymphocyte reserve in the bloodstream and uptake into tissues.159 For example, a 6-week supine exercise intervention among patients awaiting allogeneic bone marrow transplantation resulted in a small increase in lymphocyte count, contrasting the significant decrease observed in the control group.160

Glycemic control and insulin sensitivity also represent potential mechanisms underlying reduced incidence and severity of postoperative infectious disease following prehabilitation. The physiologic stress of surgery upregulates glucose production through catecholamines and cortisol, antagonizes insulin action through hormonal and inflammatory markers, and can cause immunosupression.161 Insulin resistance impairs immunity through alterations in chemotaxis, phagocytosis, and oxidative burst which reduce the effectiveness of neutrophils and leukocytes.144,162–164 Visceral adiposity and insulin resistance are interrelated through cell-autonomous mechanisms and adipocyte interactions with inflammatory cytokines.165 Reduced insulin resistance through reductions in visceral adiposity has been postulated to explain the protection from postoperative infection.149

Meaningful reductions in insulin resistance through exercise can also occur independently of adiposity and in as little as 8 weeks.166 Exercise increases insulin sensitivity in a single bout by activating AMPK, and in repeated bouts by upregulating GLUT4 expression, a protein responsible for insulin-mediated glucose transport into muscle.167 Repeated exercise bouts further decrease insulin resistance by increasing capillarization of muscle and reducing the diffusion distance of insulin into muscle.168 Therefore, the attenuation of insulin resistance and metabolic control associated with surgical stress is a possible mechanism for the prevention of infectious complications.

*Nutrition*

With regards to nutritional prehabilitation, a 2020 systematic review of 860 oesophageal or gastric patients showed preoperative dietary counselling and supplementary enteral feeding for at least 10 days significantly reduced SSI.169 Another systematic review of prehabilitation RCTs delivering immunonutrition to 609 major elective surgery patients significantly reduced infectious complications by 36% (RR 0.64, 95% CI 0.40 to 1.01, I2=56%) compared to usual care. Mechanisms for the role of nutritional prehabilitation in reducing infectious complications include attenuating surgical catabolism, enhancing immune function, and normalizing blood glucose.143,170–172

Adequate nutritional status is necessary for cell-mediated and humoral immune responses to surgical wounds and nosocomial pathogens.173–177 Surgery induces a state of systemic catabolism, impairing proteoglycan and collagen synthesis that contribute to wound healing.144 Malnourished individuals may not have the physiologic reserve to withstand catabolism associated with a prolonged surgical stress response.178 Supplementation of ω-3 fatty acids or amino acids preoperatively serve to activate the mTOR-p70s6k pathway through upstream insulin growth factor (IGF-1), a signalling pathway that promotes muscle synthesis.62,179 This promotes the synthesis of collagen, proteoglycan, and lymphocytes that mediate wound healing and the immune response to pathogens.180 Improved IGF-1 activation may contribute to the reduced incidence of infectious complications found among abdominal surgery patients at nutritional risk following preoperative nutrition support initiated at least 7 days prior to surgery.181 Accordingly, attenuating perioperative catabolism and promoting preoperative anabolism through nutritional support may underpin the reduction of infectious complications following prehabilitation.182,183

Immunonutrition refers to the provision of nutrients to promote improved immune function. Preoperative immunonutrition has been shown to decrease hyperinflammation, improve wound healing, and enhance gut barrier function.184 For example, preoperative supplementation of L-arginine and ω-3 fatty acids are associated with increased postoperative lymphocyte and NK cell activity, resulting in resistance to bacterial infection and wound healing.185,186 Previous evidence suggests the benefit of immunonutrition may take 7 days to be fully realized.187 In addition, there are several barriers to nutrition interventions delivered postoperatively, including nausea and ileus.188 Accordingly, preoperative initiation of immunonutrition may be a mechanism for infectious complication reduction.142 Given that preoperative immunonutrition interventions are often compared to usual care, it is unclear whether the observed reduction in infectious complications is due to general preoperative nutrition support or the provision of immune-enhancing nutrients. Future research comparing preoperative immunonutrition to isocaloric and isonitrogenous nutrition may further elucidate the mechanisms proposed in this review.

*Psychological Intervention*

Concerning stress-reduction components of prehabilitation, a previous RCT of preoperative nurse-led education emphasizing anxiety control techniques (i.e., deep breathing, music therapy, mediation, sleep and rest) 3-4 days before cardiac surgery significantly decreased anxiety compared to usual care.66 Another RCT found decreased respiratory infections following the reduction of preoperative anxiety.64 However, these results are contested by previous findings.189,190

Chronic psychological distress or anxiety preoperatively may exacerbate the effect of surgical stress and healing of surgical wounds.191 Delayed wound healing increases the amount of time for opportunistic pathogens and infectious complications following surgery.68 Psychological stressors, depression, and anxiety are associated with delayed wound healing following surgery.192–194 Stress-mediated physiological cascades involving prolonged surges in glucocorticoid secretion, such as cortisol and corticosterone, and concurrent blunted pro-inflammatory cytokines (IL-1ß, IL-1a, IL-6, IL-8, TNF-α) are considered the principal physiological mechanisms underlying the stress and wound healing relationship.193

Psychological prehabilitation in cancer patients has demonstrated significant decreases in preoperative stress, increased circulating inflammatory cytokines (e.g., IL- 1β, IL-12p70, TNF-α), and higher IFN-γ compared to usual care.195,196 These improvements facilitate recruitment of neutrophils and NK cells, enhancing innate immunity.197 Attenuating chronic HPA axis activation and associated glucocorticoid secretion during the preoperative window may lead to reduced downstream catabolic and immunosuppressive wound dynamics, potentially reducing infection.198,199 Psychoneuroimmunological pathways remain a promising and plausible mechanism for infectious complication prevention.193

**Renal Complications**

Hypertension, decreased renal function, and decreased physiologic reserve are key antecedents to renal complications that can be addressed preoperatively.200,201 Over 80% of renal oxygen extraction occurs in the renal medulla despite 10% of renal blood flow directed to this region.202 The low oxygen tension required for homeostatic renal medulla perfusion underlies the kidneys’ susceptibility to hypoxic injury.202 Clinical evidence of prehabilitation and risk for renal failure remains scarce. To date, evidence is restricted to pilot and feasibility trials prior to kidney transplantation and dialysis.203–205 Yet, the interrelatedness of cardiac and renal health implicates prehabilitation as a promising strategy to reduce renal failure.206

*Exercise*

Surgical stress elicits a state of hypoperfusion that constricts afferent arterioles via angiotensin II, endothelins, and catecholamines. If prolonged, this process can lead to ischemic renal failure.207 Exercise training has been shown to significantly reduce blood pressure, oxidative stress, and arterial stiffness — tenets of renal failure pathophysiology.208,209 For example, exercise promotes a state of balance between vasoconstriction and vasodilation in renal arterioles, evident through improvements in glomerular filtration rate (GFR).210 Mechanistically, exercise impedes vasoconstriction by repressing angiotensin II and catecholamines. Exercise also promotes vasodilation through prostaglandins and NO.211 Furthermore, exercise stimulates adenosine release from ATP.212 Adenosine is a medullary dilator with a role in attenuating renal hypoxia.213 When vasodilatory mechanisms fail and afferent arterioles constrict, NADPH oxidases release ROS, resulting in oxidative damage.214 Oxidative stress further contributes to renal failure and heart failure.214 Accordingly, increases in antioxidant buffering capacity following exercise, as described in cardiac complications, in addition to vasodilation of renal arterioles, are two mechanisms by which prehabilitation may reduce postoperative renal failure.

*Nutrition*

Commonly conducted among CKD patients, dietary interventions, such as the Mediterranean diet, carbohydrate-restricted low-iron diets, and polyphenol enriched diets, have shown to improve risk factors for factors for renal complications.215 Hypertension causes arteries surrounding the kidney to narrow, weaken, or harden, reducing blood flow to nephrons. This results in reduced kidney function to filter blood and produce aldosterone, further increasing blood pressure, a positive feedback loop implicated in renal complications.216 Therefore, interventions that lower blood pressure and improve endothelial function are crucial for improving renal outcomes.

Beets and leafy greens are natural sources of NO with anti-hypertensive effects in as little as 30 minutes.217 In pre-clinical trials, NO supplementation reduced proteinuria, inflammation, glomerular decline, and arterio-arteriolar decline. These mechanisms prevented renal complications from sodium-induced hypertension.218 Other than through blood pressure, supplementation of NO may also maintain renal homeostasis through scavenging of superoxide and protection against ischemia-reperfusion injury.219,220 In states of ischemia-reperfusion, the vasodilatory effects of NO have been shown to protect rats from renal complications by decreasing the production of superoxide anion and other ROS molecules compared to controls.221 In humans, increases in NO formation via L-arginine supplementation 2 hours prior to and 3 days following surgery increased GFR and renal plasma flow in kidney transplantation recipients.222 Given that the protective benefit persisted 7 days following the cessation of L-arginine supplementation, prehabilitation-related increases in NO production may be a potential mechanism for the prevention of renal complications.

*Psychological Intervention*

Limited research has directly investigated psychological prehabilitation and renal complications. For instance, Yau and colleagues’ meta-analysis of multimodal prehabilitation prior to cardiac surgery found only one study reporting unclear results regarding the risk of acute kidney injury (AKI) following prehabilitation (RR 2.60, 95% CI 0.12-58.48) with very low-certainty evidence.74 However, there are several mechanisms by which psychological prehabilitation may induce surgical nephroprotection. The kidneys are innervated by sympathetic nerves and both sodium and water retention are regulated by neuroendocrine mechanisms.223 Psychological distress may negatively impact kidney function by upregulating the HPA axis, increasing SNS activity, and prolonging glucocorticoid secretion.223 These physiological responses have a known deleterious impact on several known risk factors for postoperative renal injury including heart rate, blood pressure, vascular reactivity, and insulin resistance.224–228 Future research investigating such pathways may necessary clarify the role of psychological prehabilitation in postoperative renal complication prevention.

**Venous Thromboembolism (VTE)**

Venous stasis, vascular injury, and hypercoagulability (also known as Virchow’s Triad) represent three clinical conditions that predispose an individual to VTE.229 To our knowledge, no prehabilitation trial to date has demonstrated improved VTE following prehabilitation. Yet, improvement of VTE risk factors such as metabolic disturbance, pulmonary function and immobility provide promising evidence for the role of prehabilitation to reduce this complication.230 This opportunity must be considered alongside VTE risk factors that are not amenable to intervention, such as previous VTE, varicose veins, and presenting for major surgery.230

*Exercise*

Preoperative exercise directly influences the clinical events that precede VTE —Virchow’s triad. Regarding hypercoagulability, fibrinolysis is a process of plasmin generation to digest fibrin and maintain vascular patency. Surgically induced impairment of fibrinolysis is implicated in VTE.231 A single bout of moderate or maximal exercise has been shown to improve fibrinolysis,232 which may be linked to i) the upregulation of tissue plasminogen activator (tPA), a rate limiting factor for fibrinolysis and ii) downregulation of plasminogen activator inhibitor-1, a tPA inhibitor.233,234 Transient increases in pro-thrombotic processes with exercise may be justified by longer-lasting upregulation of anti-thrombotic processes.235,236 This may be particularly pertinent in patients with impaired fibrinolytic activity due to metabolic and endothelial dysfunction.237–239

Endothelial function, implicated in the risk of VTE, is impaired due to the trauma of surgery. The surgical stress response increases blood pressure resulting in reduced synthesis of the vasodilator, NO, as well as an increase in the vasoconstricting endothelin-1.240 In as little as 1 bout of submaximal exercise, laminar shear stress stimulates platelet L-arginine transport of NO into smooth muscle.241,242 Thus, exercise-induced vasodilation attenuates endothelial dysfunction and platelet aggregation by stimulating platelet L-arginine transport and NO.243,244 Early mobilization, a strategy used in ERAS protocol, is recommended for the prevention of VTE.236,245 Early mobilization operates through similar mechanisms as preoperative exercise, increasing lower limb circulation to prevent venous stasis.246 Given that multi-modal prehabilitation improves functional recovery, postoperative mobilization may begin earlier, mitigating the risk of venous stasis associated with prolonged postoperative immobilization.247 Therefore, prehabilitation may reduce VTE via improvements in fibrinolysis, endothelial function, and venous stasis.

*Nutrition*

As previously mentioned, metabolic disturbances have pro-thrombotic consequences including abnormal platelet activity, endothelial dysfunction, and reduced fibrinolysis.248 Strattman and Tschoepe summarize the complex interaction between insulin resistance and platelet activity, including amplified agonist-receptor coupling and increased binding of fibrinogen.249 Ultimately, prehabilitation trials that improve metabolic control and endothelial function (as described throughout this review), mediated by insulin resistance, dyslipidemia, and hyperactive platelets, may attenuate an exaggerated-thrombotic response to surgery and reduce VTE risk.

The mechanistic link of nutrition to reduce VTE formation may also be attributed to the antioxidant properties of polyphenols, abundant in fruits, vegetables, and cocoa. Polyphenols, (especially flavonols) have been found to inhibit primary hemostasis, platelet hyperactivity and adhesion, and eliminate free radicals that contribute to thrombus formation.250–252 For example, metabolic disturbances such as excess visceral fat, dyslipidemia, and insulin resistance activate GPIIb/IIIa receptors on platelets, allowing them to bind and aggregate to endothelial walls through fibrinogen and von Willebrand factor.251 Once activated, platelets release factors that promote clotting and vasoconstriction, such as the ROS molecule hydrogen peroxide. Polyphenols counteract this pathological process by increasing vasodilation through NO. Polyphenols also act directly on platelets by inhibiting the expression of GPIIb/IIIa, impeding fibrinogen and von Willebrand factor binding.253 These mechanisms may explain Flammer and colleagues’ findings in a double-blind RCT using dark chocolate, a flavonoid-rich potent antioxidant, versus a cocoa-free control.254 Results showed coronary artery vasodilation and decreased platelet adhesion among heart transplant recipients 2 hours after ingestion.254 Although no trials have specifically examined the clinical application of preoperative polyphenol supplementation and postoperative VTE incidence, supplementing platelet-inhibiting dietary polyphenols is a potential mechanism for reduced VTE with prehabilitation.255

*Psychological Intervention*

Mechanisms by which prehabilitation may reduce VTE, as well as other surgical complications, are summarized in Figure 2. There exists limited clinical evidence directly relating psychological interventions to reduced VTE. However, one nurse-led education intervention aimed at reducing anxiety significantly decreased deep venous thrombosis.64 Psychological prehabilitation may attenuate the thrombosis-forming processes that result from stress and anxiety. Accumulating evidence suggests inflammatory responses, such as those caused by psychological stress, are a cause of VTE.256–258 Inflammation of the vessel wall may initiate thrombosis by activating a prothrombotic cascade mediated by endothelial cells, platelets, leukocytes, microparticles, and procoagulant extracellular matrix materials.67

The hemodynamic response to psychological stress is an adaptive survival mechanism that results in mobilization of pro- and anti-coagulant factors that favour the former, resulting in a net blood thickening that leaves patients susceptible to VTE.259 For example, stress causes a transient influx in procoagulant processes mediated by fibrinogen, Von Willebrand factor, as well as clotting factors VII, and XII.239 As a result, platelet count and aggregation are increased.260,261 Psychological stress also elevates hydrostatic pressure via circulating catecholamines, this releases fluid outside of the plasma and increases blood viscosity.262 By attenuating psychological stress with prehabilitation, thrombus formation is potentially reduced via these mechanisms.

**Ischemic Stroke**

Prehabilitation to reduce ischemic stroke (referred to as stroke hereafter) is an emerging area of study.263 Deficits pertaining to cardiovascular and renal function considerably increase a patient’s susceptibility to ischemic and hemorrhagic injury, the two main etiology of stroke.264 Stroke is often included in reports of overall surgical complications with multimodal prehabilitation protocols; however, primary evidence of reduced stroke following psychological prehabilitation is limited. For instance, a previous umbrella review of 55 systematic reviews of multimodal prehabilitation suggested reduced overall surgical complications including but not differentiating stroke in mixed surgeries, non-oncological abdominal surgeries, and cardiovascular surgeries.265 A systematic review that assessed stroke in isolation did not find significantly reduced risk following multimodal prehabilitation prior to cardiac surgery (RR 0.59; 95% CI 0.08-4.56; 230 patients).74

*Exercise*

The neuroprotective effect of exercise prior to stroke is well-documented and may be attributed to cerebral angiogenesis, an increase in brain-derived neurotrophic factor (BDNF), and a reduction in the blood-brain barrier disruption.266,267 For example, in a pre-clinical trial, Ding et al. noted significant neuroprotection from 3 weeks of exercise prior to stroke.268 BDNF is a neurotrophin that promotes cerebral plasticity due to its role in angiogenesis, cell survival, synaptic consolidation, and NMDARs.269 Neurotrophins such as BDNF and nerve growth factor are significantly increased in as little as 3 weeks of exercise.268 The result is an increase in cerebral angiogenesis.270 Exercise-induced angiogenesis exerts a clear benefit for the prevention of stroke by protecting against states of ischemia or increased oxygen utilization incurred with surgery.271 Mechanisms include increases in capillaries and capillary density, as well as improved coronary blood flow.271 When stroke cannot be prevented, the neuroprotective effect of 3 weeks of exercise can decrease the infarct size and edema from cerebrovascular occlusion.268 This benefit is mediated by BDNF, which promotes the survival of cortical neurons.268

Along with a reduction in blood flow, increased permeability in the blood-brain barrier is a pathophysiological mechanism of stroke.272 The tight junction integrity of the blood-brain barrier is compromised by neuroinflammation mediated by cytokines, chemokines, ROS, and adhesion molecules.273 For example, IL-6 is a biomarker of stroke severity and disrupts the permeability of the blood-brain barrier by reducing the expression of endothelial tight junction proteins.274 In pre-clinical models, 3 weeks of exercise has also been shown to ameliorate blood-brain barrier dysfunction following the induction of stroke.275 Therefore, decreasing blood-brain barrier permeability represents a mechanism for stroke prevention with exercise prehabilitation. Other, mechanisms of exercise-induced neuroprotection have also been proposed, such as a reduction in glutamate and caspase activity as well as increases in cerebral integrins and VEG-F.266

*Nutrition*

Regarding nutritional prehabilitation, several pathophysiological mechanisms of stroke that can be targeted preoperatively include hyperglycemia, hypertension, inflammation and endothelial function.276 Preoperative hyperglycemia is an independent risk factor for stroke through increases in ROS and NADPH. In addition, hyperglycemia upregulates nuclear factor kappa B (NF-κB), a transcription factor resulting in downstream inflammation and blood-brain barrier disruption.276,277 As previously discussed, preoperative nutrition intervention has successfully improved peri- and post-operative glycemic control.171 In addition, an RCT of a low-fat diet nutritional prehabilitation intervention versus a usual care control among 145 men with prostate cancer found significant decreases in 6 proinflammatory cytokines and angiogenic factors that are regulated by NF-κB.278 This RCT also demonstrated a trend towards reduced NF-κB, highlighting a plausible mechanism for stroke prevention with nutritional prehabilitation.

Serum potassium is a dietary component related to the risk of stroke that can be targeted preoperatively.279 For example, potassium, consumed mainly from fruits and vegetables, suppresses the formation of free radicals and promotes a healthy endothelium by reducing macrophage adherence to the vascular wall.280,281 Given that hypertension is a principal pathophysiological mechanism for stroke, the blood pressure-lowering effect of potassium for both systolic (-3.11 mm Hg; 95% CI: -1.91 to -4.31) and diastolic (-1.97 mm Hg, 95% CI: -0.52 to -3.42) blood pressure may be essential for prevention.282 Such benefits may explain the significant inverse epidemiological relationship between potassium consumption and stroke.279 An RCT of serum potassium monitoring and intervention of dyskalemia (<3.5 mmol/L and >5.5 mmol/L) among 104 abdominal surgery patients demonstrated improvement in hypokalemia and subsequent reductions in infectious and cardiac complications — stroke was not assessed.283 Accordingly, the mechanistic link between potassium and stroke warrants further study.

*Psychological Intervention*

Psychological prehabilitation may attenuate major risk factors of occluded or hemorrhaged vasculature implicated in stroke, such as stress, hypertension, and atherosclerosis.284 Stress-related inflammatory and oxidative processes are considered to contribute to cerebrovascular endothelial dysfunction and the pathogenesis of atherosclerotic lesions that may become prothrombotic during the surgical stress response leading to stroke.194,285 Interventions including mindfulness-based stress reduction, cognitive behavioural therapy, Transcendental Meditation, and progressive muscle relaxation may reduce prothrombotic consequences of stress among clinical populations primarily by regulating the HPA axis and ANS activity and associated glucocorticoid and catecholamine related endothelial dysfunction.286,287 Although the current evidence base is equivocal, it does suggest psychological prehabilitation may improve the psychological stress-related dimension of the risk factor profile for stroke.

**Other Surgical Complications**

A detailed synthesis of prehabilitation mechanisms underlying other ACS-NSQIP defined surgical complications such as sepsis, blood transfusion, and wound disruption was out of the scope of this review given etiological heterogeneity and a corresponding dearth of evidence of preoperative risk attenuation. However, since surgical candidates are generally considered at increased risk of surgical complications when in a physiological or psychological state that is sub-optimally prepared to accommodate the stresses of surgery and recovery, these other surgical complications share common risk factors that prehabilitation may improve such as insulin resistance, systemic inflammation, and decreased physiologic reserve.288 Addressing these factors may improve the pathogenesis of sepsis, blood transfusion, and wound disruption. For example, immunonutrition that has reduced the incidence of infectious complications has also demonstrated reduced duration of systemic inflammatory response syndrome.186 Though related to sepsis, research examining the role of prehabilitation to reduce sepsis specifically, as well as blood transfusion and wound healing remain an endeavour for future research.

Diagram

Description automatically generated**Figure 2.** Key mechanisms for the role of prehabilitation to reduce surgical complications.

*Notes:* EF = ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume; AMPK = AMP-activated protein kinase; ROS = reactive oxygen species; ANP = atrial natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAI-1 = plasminogen activator inhibitor-1; VWF = von Willebrand factor tPA = tissue plasminogen activator; NK = natural killer cells; TNF-α = tumour necrosis factor alpha; IL = interleukin.

**PRACTICAL CONSIDERATIONS AND FUTURE DIRECTIONS**

In view of the growing clinical role of prehabilitation in the surgical context,289,290 this review represents the first to synthesize evidence concerning the mechanisms of prehabilitation to reduce various surgical complications. This is accomplished by outlining the pathophysiology of ACS-NSQIP complications and the potential biological pathways by which they may be prevented or mitigated by exercise, nutrition, and psychological intervention. Despite empirical evidence supporting the use of prehabilitation to reduce postoperative complications,29,291 the biological plausibility of this relationship remains a high priority research area.292

Biological plausibility applied to prehabilitation research: i) informs how prehabilitation may achieve its desired benefit; ii) aids clinical decisions regarding the intervention with greatest therapeutic benefit; and iii) outlines an opportunity for the improvement of contemporary prehabilitation designs. For example, the current review highlights the role of prehabilitation to enhance natural immunity as a mechanism for preventing multiple surgical complications. Sleep health is a well-established determinant of immune function and is protective against acquiring infectious diseases.293,294 Though not yet included as a traditional prehabilitation modality, preoperative sleep intervention remains a promising avenue for future research.

A surgical database, such as the ACS-NSQIP, is particularly useful to address contextual needs related to prehabilitation as it reports the incidence of each postoperative complication compared to the median score of all participating hospitals and assigns a quality score (e.g., “as expected” or “needs improvement”). Accordingly, the mechanisms highlighted in this review can be used to implement strategies to effectively meet the needs of medical institutions with higher-than-average rates of a surgical complication. For example, an institution shown through NSQIP to have higher than average rates of pulmonary complications may prioritize intervention strategies that have the greatest biological plausibility to improve this complication (e.g., aerobic exercise, IMT, or malnutrition intervention).

The present review also reveals discrepancies between biological plausibility and clinical evidence. In some cases, clinical trials of prehabilitation do not assess the reduction in surgical complications despite a strong biological rationale to do so. Studies that do measure surgical complications may be limited by sample size, finite resources, and follow-up to detect the full benefit of prehabilitation. For example, the ‘prehabilitation window’ may not present sufficient time to create a physiologic buffer large enough to prevent the occurrence of a surgical complication amidst the immense physiologic stress undertaken during surgery. In lieu of *incidence,* trials that assess the *duration* and *severity* of complications may be better suited to establish the clinical effectiveness of prehabilitation.

**Limitations**

There are several important limitations with this review. The ACS-NSQIP was used as a framework for surgical complication reporting. However, this is not an all-encompassing framework of surgical morbidity. Some complications, such as sepsis, blood transfusion, and wound healing, are not modeled across all participating sites. In addition, some postoperative complications, such as delirium and cognitive dysfunction, are not routinely assessed. Delirium is a prevalent surgical complication that can be prevented with the emerging use of cognitive prehabilitation.295 Smoking cessation was also not included despite its presence in many multi-modal prehabilitation programs. Despite a preference for using mechanistic evidence from randomized controlled trials initiated preoperatively, this was not always possible. A noteworthy proportion of evidence used in this review was derived from pre-clinical studies. Such mechanisms remain speculative until they are supported by large scale trials among humans. Finally, although the complications included in this review were organized based on previous research and to increase parsimony, this taxonomy has limitations. For example, pneumonia was classified as a respiratory complication despite both an infectious and respiratory etiology.

**Conclusion**

The current review summarizes the available evidence pertaining to the mechanisms of prehabilitation to prevent postoperative complications. Importantly, this review is not an exhaustive synthesis of the literature and serves as hypothesis-generating rather than hypothesis-testing. Future prehabilitation trials, equipped with the relevant biomarkers to reduce surgical complications, may seek to test the hypotheses generated by this review and establish targeted interventions tailored to individual patient needs.

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