You Are Only as Frail as Your Arteries: Prehabilitation of Elderly Surgical Patients

Matthew J. Durand\textsuperscript{1,2} · Angela K. Beckert\textsuperscript{3} · Carrie Y. Peterson\textsuperscript{4} · Kirk A. Ludwig\textsuperscript{4} · Timothy J. Ridolfi\textsuperscript{4} · Kathryn K. Lauer\textsuperscript{5} · Julie K. Freed\textsuperscript{2,5}

Abstract

Purpose of Review To discuss the concept of prehabilitation for the elderly frail surgical patient as well as strategies to improve preoperative functional capacity and vascular function to decrease postoperative complications.

Recent Findings Frailty is associated with poor surgical outcomes yet there is no consensus on how frailty should be measured or mitigated in the preoperative period. Prehabilitation, or improving functional capacity prior to surgery typically through exercise, has been shown to be an effective strategy to decrease preoperative frailty and improves surgical outcomes. Use of remote ischemic preconditioning (RIPC) may serve as an alternative to exercise in this fragile patient population.

Summary Prehabilitation programs using strategies targeted at improving vascular function may decrease frailty in the preoperative period and improve surgical outcomes in the elderly population.

Keywords Prehabilitation · Ischemic preconditioning · Frail · Endothelial dysfunction

Introduction

The geriatric population undergoing surgery is on the rise. According to the US Census Bureau, the fastest growing age group consists of individuals over the age of 55 [1]. Currently, this age group comprises approximately one-third of the total surgical population; therefore, this demographic shift is causing an increase in the number of surgical procedures performed annually on the elderly. This creates a substantial challenge for our healthcare system, as elderly surgical patients often have multiple co-morbidities, disabilities, and decreased physiological reserve leading to increased hospital stays and higher rates of postoperative complications [2]. Although generally speaking, elderly patients have higher rates of adverse events postoperatively, the majority of complications arise from elderly frail patients [3]. “Frailty” defines a syndrome of decreased physiological reserve and the decline of multiple physiologic systems. Measures of frailty include strength, endurance, walking performance, and activity level [4]. Compared with disability, or the impaired ability to carry out a functional task, frailty is a geriatric biologic syndrome in which there is a loss of resiliency to stressors [5]. In addition to growth of the elderly population, the incidence of cancer is also expected to rise [6]. Cancer is considered a “frailty accelerator” and neoadjuvant chemotherapy is known to further decrease physical fitness and increase mortality following surgery [7]. Since elderly individuals have a disproportionate risk of developing cancer, there will be a significant increase in the number of older cancer patients requiring surgical treatment who are at increased risk for morbidity and mortality in the postoperative period [8].

Surgery is known to induce a strong stress response resulting in varied hormonal changes, an increase in catabolism of stored body fuels, and an elevation of inflammatory substances, such as cytokines [9]. Enhanced recovery after surgery (ERAS) protocols were created in an attempt to...
attenuate the stress response to surgery and circumvent the decline in functional capacity following surgical procedures. This strategy primarily includes preoperative counseling and changes to bowel preparation as well as anesthetic technique. While the ERAS pathway has been shown to reduce length of hospital stay and complication rates in patients undergoing major colorectal surgery, no significant differences in readmission rates or mortality have been found [10]. However, the concept of “prehabilitation,” or improving functional capacity and decreasing frailty prior to surgical stress, has been shown to improve survival in some post-surgical patients [11]. Decreasing baseline frailty and increasing functional capacity in the preoperative period may have a significant impact on postoperative recovery; therefore, methods in which to accomplish these goals need to be developed. This brief review will discuss preoperative prehabilitation of the elderly surgical patient including the concept of frailty, as well as methods of assessment. Alterations within the vasculature associated with aging will be highlighted as well as how prehabilitation may mitigate these changes. Finally, strategies to improve functional capacity by targeting the vasculature will be debated.

The Elderly Frail Surgical Patient

Frailty is considered a state of vulnerability. Following a stressful event, such as surgery, frailty has been shown to be associated with adverse outcomes such as cognitive dysfunction and disability [4, 12]. The decreased physiological reserve observed in frail individuals is due to a combination of age-related changes. For instance, structural changes in the aging brain likely contribute to the increased incidence of postoperative delirium associated with the elderly patient [13]. The immune system is also the culprit to decline with aging and often becomes senescent and unable to appropriately mount a proper immune response during the stress of acute inflammation [14]. Surgical site infections were found to be the most common postoperative complication for both colorectal and cardiac surgeries in a 2013 analysis linking frailty to adverse surgical outcomes [15]. With age, muscle mass and strength decrease, leading to poor functional capacity and a lowered quality of life [16]. In 2015, Reisinger et al. demonstrated that decreased functional capacity and muscle mass (sarcopenia) were both associated with an increased incidence of post-surgical sepsis [17]. All in all, it is widely accepted that elderly frail surgical patients are prone to prolonged hospital stays, are more likely to be discharged to long-term care facilities, and experience higher mortality rates compared with the non-frail patient population [18].

Frailty can be conceptualized into two different domains, phenotypic frailty and deficit-driven frailty. Phenotypic frailty, also known as physical frailty, is defined by decline in skeletal muscle strength, energy, and nutrition [4]. Measurements of phenotypic frailty typically examine unintentional weight loss, grip strength, activity levels, and gait speed [4]. Alternatively, the frailty index defines frailty as an accumulation of medical, functional, and social deficits which can be measured via reporting of symptoms, functional disabilities, lab abnormalities, and medical diagnoses [19]. While there is a growing consensus about the definition of frailty, no single operational measurement has emerged [20]. Despite the fact that nearly 70 frailty instruments have been identified [21], frailty indices and measures continue to be developed. Collectively, these frailty measures have significant heterogeneity and vary in their domains assessed, variables examined, administration time, and underlying conceptual framework.

In surgical patients, both models of frailty, phenotypic frailty and deficit-driven frailty, have been predictive of poor surgical outcomes including post-operative complications, length of stay, and discharge institutionalization. Other frailty measures have also been useful in preoperative assessment including the Edmonton Frail Scale which assesses patients across nine frailty domains and takes less than 5 min. Frailty scales have also been developed focused on surgical subspecialities including the comprehensive assessment of frailty (cardiac surgery) and trauma-specific frail scale (trauma surgery). Surgeons wishing to measure frailty may choose a measure based on specialty or availability of resources, or based on their goal for measurement such as preoperative risk assessment or identification of modifiable risk factors. Because of the wide heterogeneity of frailty measures, broad recommendations and conclusions are difficult to draw. Despite these shortcomings, preoperative frailty measurement is recommended as best practice for the geriatric surgical patient [11].

The Frail Vasculature

Most organ systems experience a functional decline with aging. The human vasculature is no exception where two significant age-associated changes occur: (1) endothelial dysfunction [22], and (2) a decrease in large artery compliance, known as arterial stiffening [23]. The loss of artery elasticity over time ultimately results in hypertension, left ventricular hypertrophy, and subendocardial ischemia [24]. Increased large artery stiffness also results in elevated pressure along the arterial tree down to the resistance vessels which initiates an inflammatory response through formation of reactive oxygen species [25]. Increased intraluminal pressure within the microcirculation will also impair autoregulatory processes and therefore may prove to be detrimental to cerebral, coronary, and renal perfusion [26, 27]. Likewise, the endothelium within resistance vessels plays a critical role maintaining vascular homeostasis by generating and releasing various mediators that act in an autocrine or paracrine fashion to other surrounding tissues [28, 29].
produced to control vascular tone and maintain balance between anti-inflammatory and proinflammatory pathways will not be discussed in this review; however, it should be noted that the predominant mediator produced in healthy adult humans is nitric oxide (NO) and loss of the ability to vasodilate to this compound is referred to as endothelial dysfunction. Increased age strongly correlates to endothelial dysfunction and results in a proinflammatory state [30]. While arterial stiffening and endothelial dysfunction are presented here as two distinct age-related phenotypes, it should be noted that each can contribute to the other. For instance, increased arterial stiffness may cause endothelial dysfunction and impaired endothelial function may, through release of proinflammatory mediators, augment arterial stiffening [31••].

The aging vasculature is at least partly responsible for the decreased functional capacity associated with frailty in elderly individuals. Sarcopenia, or the decrease in muscle mass observed in older patients, has been linked to increased frailty scores [32]. Ochi and colleagues found in men of middle-age, thigh muscle cross-sectional area was negatively associated with arterial stiffness as measured by brachial-ankle pulse wave velocity [33]. More recently, using carotid-femoral pulse wave velocity, it was shown that increased arterial stiffness highly correlates to frailty in adults over the age of 60 [34••]. It is widely accepted that endothelial dysfunction, non-invasively measured by brachial artery flow-mediated dilation (FMD), correlates with advanced age [35]; however, the link between frailty and endothelial dysfunction has not been thoroughly examined.

Prehabilitation Versus Rehabilitation

The goals of rehabilitation and prehabilitation in the surgical patient are the same—to improve postoperative recovery. As the name suggests, the difference is that prehabilitation occurs in the preoperative period whereas rehabilitation occurs postoperatively. This concept is nicely illustrated in a study by Gillis et al. which compared the efficacy of an identical program designed to improve functional capacity in cancer patients, but the program was administered either in the preoperative versus the postoperative period (i.e., prehabilitation vs. rehabilitation) [36]. In that randomized, controlled trial, 77 elderly patients with colon cancer performed 4 weeks of home-based, moderate intensity aerobic and resistance exercise, coupled with nutritional consulting and protein supplementation, either prior to- or post-surgery. Interestingly, at postoperative week 8, the patients who received the intervention in the presurgical period had an increased functional capacity (as assessed by the distance walked during the 6-min walk test) compared with those who received the intervention postoperatively. These results would suggest that increasing an individual’s functional capacity with a prehabilitation program could be a more effective strategy to improve postoperative recovery and function than traditional rehabilitation alone, a concept which is illustrated in Fig. 1. The additive effects of combining a structured prehabilitation program with intensive rehabilitation are still largely unknown. Although prehabilitation has been shown to improve walking distance during the 6-min walk test (6MWT) [37••] and increase cardiopulmonary function [38], as well as reduce hospital length of stay [39] and morbidity following surgery [38], to date, there is no precise definition of what a prehabilitation program should consist of, and how prehabilitation programs should be tailored to the needs of specific patient populations. For example, would an elderly patient scheduled for a knee replacement have the same prehabilitative needs as a patient with colon cancer scheduled for curative bowel resection?

Exercise Prehabilitation and the Vasculature

Similar to there being no established measure of frailty, there is also no standardized prehabilitation program that exists across healthcare systems. Current prehabilitation strategies are generally multimodal and include exercise regimens, nutritional advice and/or supplementation, and psychosocial/health educational components. The exercise component typically consists of both aerobic and resistance training which has been shown to improve postoperative functional capacity.
For instance, the aforementioned study by Gillis et al. demonstrated that 4 weeks of combined aerobic (jogging, walking, swimming, or cycling) and resistance exercise (15 repetitions using resistance bands) in the preoperative period increased walking capacity leading up to surgery as expected. Importantly, this approach was superior to standard rehabilitation in the postoperative period, as quantified by increased walking distance during the 6MWT in the prehabilitation group, 8 weeks postoperatively [36]. More recently, this same group extended this study and showed that the 4-week preoperative exercise regimen, when done under supervision, was capable of further improving functional capacity compared with the non-supervised group, and decreased overall hospital length of stay by 1 day [40].

The decline in exercise capacity due to age is attributed to both a decrease in cardiac output and skeletal muscle blood flow. Age-induced endothelial dysfunction contributes to the lack of skeletal muscle blood flow; however, aerobic exercise is capable of reversing this. Spier and colleagues have demonstrated using a rat model that 10–12 weeks of aerobic exercise improves endothelium-dependent dilation by increasing both microRNA and protein levels of endothelial nitric oxide synthase (eNOS) [41••]. These findings have been translated to the humans as well. Using brachial artery flow-mediated dilation, Black et al. showed that 12 weeks of moderate (30% of heart rate reserve) exercise performed three times per week improved endothelium-dependent vasodilation in older sedentary adults [42]. Of note, the greatest increase in dilation was observed in older, sedentary women.

While the exercise component of these programs may be critical to their overall success, geriatric patients, particularly those with cancer, may be disabled, weak, and unable to exercise at an intensity which would cause physiological benefit. Furthermore, adherence to exercise recommendations during the preoperative period in individuals that are capable is low [43], creating a further challenge to prehabilitating this patient population. Supervised exercise may be a solution to the low compliance; however, this strategy may not be feasible due to cost, adequate staffing, and overall inconvenience for the patient. The length of the prescribed exercise regimen also has to be considered. The majority of exercise prehabilitation studies have examined the effects following training protocols which range from 4 to 8 weeks [38, 39], which to some may be a considerable amount of time to wait for surgery, especially when just diagnosed with cancer. Thus, alternative approaches to exercise that may offer similar benefits should be explored.

Remote Ischemic Preconditioning as an Alternative to Exercise in Prehabilitation

Ischemic preconditioning (IPC) was first described in 1986 as a vascular stimulus to protect vital organs from ischemic injury and has been extensively studied in animal models and humans for its potential to promote cardioprotection from ischemia (see review by Heusch et al. [44]). Since IPC was first described over three decades ago, other groups have shown that IPC, when applied to the arm or leg (known as remote ischemic preconditioning, or RIPC) of healthy individuals with a standard blood pressure cuff inflated to 225 mmHg for 5 min on-off intervals, can promote muscle fatigue resistance [45], increase athletic performance [46–49], and promote motor learning [50]. It is important to note that in most of these studies, the effect sizes of RIPC to promote athletic performance are relatively small (improvements between 2 and 5%); however, these studies were performed in young, healthy individuals; thus, a ceiling effect likely exists. Recently, the effects of RIPC on motor function and muscle performance in patient populations with reduced physical capacity (chronic stroke survivors) were examined for the first time, and those studies showed the positive effects of RIPC to promote strength [51••] and reduce neuromuscular fatigue [52••] far exceed those reported in healthy volunteers and occur in as little as 2 weeks [52••]. Furthermore, in chronic stroke, individuals with the slowest self-selected walking speed and largest strength deficits tended to show the most improvement in muscle strength following RIPC [51•]. Despite these promising results, the effects of RIPC on physical function and measures of frailty in the elderly population are still largely unknown. However, these previous findings, coupled with the fact that RIPC is low risk, low cost, easy to perform, and well tolerated makes RIPC an attractive alternative to traditional aerobic exercise to improve functional capacity in the frail patient in the preoperative period.

The underlying mechanisms of RIPC are inherently complex and involve neuronal, humoral, and local pathways [53, 54]. It is accepted that ischemia and subsequent reperfusion of a remote limb causes the release of cardioprotective substances, as evidenced by the fact that organ protection is observed in animals that have received blood transfusions from preconditioned donors [55]. It is hypothesized that organ protection from RIPC may depend on improvements in vascular function as RIPC has been shown to improve brachial artery flow-mediated dilation (FMD) in humans [56] and our own preliminary data shows that RIPC improves brachial artery FMD in chronic stroke survivors. Further, RIPC has been demonstrated to reduce the rate of acute kidney injury following cardiac surgery [57]; therefore, RIPC may not only decrease frailty and improve postoperative physical function but may also have more broad beneficial effects on cardiovascular health as well. Although it is well established that RIPC improves vascular endothelial function (FMD) and prevents end-organ damage in the perioperative period, whether preoperative RIPC can prevent postoperative vascular dysfunction or increase functional capacity remains unknown.
Conclusions

The rise in the elderly population, combined with the expected increase in cancer diagnoses, has caused a substantial increase in the number of surgical procedures performed annually in elderly patients and continues to put stress on our healthcare system. The majority of these patients will present as frail, weak, and with decreased physiologic reserve. This vulnerable population is at risk for postoperative complications which may lead to long-term impairments and even death. However, with proper proactive approaches, these complications and their associated burden can partly be mitigated. Preoperative exercise programs are an effective strategy to decrease the morbidity and mortality associated with elderly frail surgical patients; however, limitations such as compliance, lack of capacity to exercise, cost, and time required for effect are all significant limitations. Vascular function improves greatly with exercise leading to increases in skeletal muscle blood flow and reversal of age-induced endothelial dysfunction. RIPC may offer the same vascular benefits as exercise and therefore serve as a low-cost alternative to physical training. The correlation between vascular function and age has long been known, as the seventeenth century English physician Thomas Sydenham stated, “Man is as old as his arteries.” In order to provide the best possible surgical outcomes for the elderly population, the link between vascular function and frailty needs further exploration as well as development of exciting new therapies in which to improve vascular function prior to the day of surgery.

Compliance with Ethical Standards

Conflict of Interest Matthew J. Durand, Angela K. Beckert, Carrie Y. Peterson, Kirk A. Ludwig, Timothy J. Ridolfi, Kathryn K. Lauer, and Julie K. Freed declare they have no conflict of interest. Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

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