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Reducing Elective Vascular Surgery Perioperative Risk With Brief Preoperative Dietary Restriction

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Introduction

Vascular surgery patients face a heightened risk of peri-procedural cardiovascular complications including heart attack, stroke, and death [1]. Effective therapies to mitigate risk of complications or ameliorate their severity are lacking. Rising health care expenditures, the aging population, and the increasing incidence of diabetes all point to a dire need for affordable and feasible strategies to improve outcomes in vascular procedures. Dietary restriction (DR), defined as reduced food intake without malnutrition, is best known for extending lifespan in a variety of species including non-human primates. It is also an established method of reducing surgical stress in preclinical models. Clinical applications of DR have never been considered feasible because of practical difficulties associated with voluntary food restriction and a long-held assumption that DR benefits take a long time to accrue. Recent studies suggest DR benefits against surgical stress and trauma may, in fact, occur in a clinically relevant time frame. Herein, we discuss our novel hypothesis that reduced food intake in the preoperative period may be a feasible, inexpensive, and effective method of preconditioning the body against surgical stress. Specifically, we will consider the potential of "dietary preconditioning" to reduce the onset and severity of complications arising in the context of vascular surgery.

High Risk of Morbidity and Mortality in Vascular Surgery

Vascular surgery causes among the highest rates of perioperative cardiovascular and cerebrovascular events, leading to considerable morbidity and mortality and heavy tolls on individuals and society alike. Significant effort has been expended in assessing and modifying the risk of perioperative myocardial infarction, the predominant cause of mortality in high-risk vascular surgery [1]. Codification of these best practices has resulted in modest improvements in outcome over the past several decades [2]. However, the aging population, rising incidence of the metabolic syndrome and increasing access of vascular surgery to higher-risk patients populations may threaten this incremental progress. Compounding these problems, there is now evidence that the rates of cardiac injury after vascular surgery are far higher than previously recognized. Novel markers of myocardial injury have shifted the focus of postoperative events from perioperative myocardial infarction to myocardial injury.

Basic Mechanisms Underlying Vascular Surgical Complications Are Known

Surgical trauma engenders both a local inflammatory response as well a systemic neuroendocrine response via stimulation of local sympathetic afferent neurons controlling release of stress hormones, including glucocorticoids and catecholamines from the adrenal glands. Hyperactivation of three key elements of this stress response - the sympathetic nervous system, inflammation and oxidative stress - is associated with adverse cardiovascular events. Vascular surgery increases catecholamine release from the adrenal medulla, resulting in constriction of blood vessels and heightened risk of occlusive events. Several clinical trials have demonstrated that antagonism of this system with beta adrenergic blocking agents reduces the risk of perioperative cardiovascular events. However, because optimal methods of administration have not yet been made clear, no clear consensus yet exists about the benefit of this class of medication in perioperative care [3].

Inflammation is recognized as a causative mechanism underlying atherogenesis and acute clinical events related to atherosclerosis. In the surgical setting, inflammation increases the risk of plaque rupture, which can lead to thrombus formation, vessel occlusion and ischemic injury. Elevated markers of inflammation are predictive of both first and recurrent cardiovascular events, as well as cardiovascular events associated with vascular surgery. In support of the role of systemic inflammation in cardiovascular complications, anti-inflammatory drugs such as statins have been shown to reduce postoperative cardiac events in patients undergoing vascular surgery [4].

Oxidative stress, defined as an imbalance between pro-oxidants such as reactive oxygen species (ROS) and antioxidant capacity, participates in the stress response through both chronic and acute mechanisms. Oxidation of LDL and lipoprotein in the vascular wall results in plaque formation and chronic activation of the inflammatory response, while surgical trauma or infection activate acute inflammation. Inflammatory cells such as macrophages and granulocytes are major producers of ROS and oxidative stress in both acute and chronic inflammation. Oxidative stress is also associated with reduced bioavailability of nitric oxide (NO), a risk factor for cardiac injury during vascular surgery.

Ischemia reperfusion injury, a multifactorial insult involving components of both inflammation and oxidative stress and exacerbated by vasoconstriction, is likely a fundamental mechanism underlying vascular surgical complications. Hypoxia, nutrient deprivation and waste buildup occur upon lack of blood flow, resulting in cellular dysfunction and death. This occurs particularly rapidly in the brain, which has a very low tolerance for oxygen or nutrient deprivation. Reperfusion is necessary for cell survival, but also allows recruitment of inflammatory mediators to locally damaged tissues and propagation of oxidative stress and byproducts of metabolism to remote parts of the body, promoting both local and systemic injury. In some surgeries, ischemia and reperfusion are necessary and intentional, for example in coronary artery bypass grafting and open aortic arch reconstruction. Ischemia can also result indirectly from inadvertent atherosclerotic plaque rupture, microembolization of plaque material or other thrombo-embolic events associated with vascular interventions. Even less invasive procedures, including arthroscopic knee surgery, share these risks to varying degrees.

In conclusion, major surgery is a stress to which the body can overreact via highly evolved mechanisms such as increased sympathetic tone, inflammation and oxidative stress. These pathways increase the likelihood of mal-perfusion syndromes and atherosclerotic plaque rupture and subsequent vessel occlusion. Any modifications that can abrogate these adverse events and/or reduce the severity of the resulting ischemic damage could be useful at reducing morbidity and mortality associated with vascular surgery. Dietary restriction has the potential to address all of them in a single intervention as discussed below.

Benefits and Mechanisms of Dietary Restriction in Preclinical Models

DR was recognized nearly a century ago to prevent the incidence and severity of cancer in laboratory rodents [5]. In the ensuing decades, evolutionarily conserved benefits of DR have been recognized in a wide variety of metabolic and stress-related endpoints relevant to protection from surgical stress. For example, DR is anti-inflammatory in a number of different contexts ranging from sterile inflammation induced by LPS to experimental autoimmune encephalomyelitis. DR protects against acute oxidative stress and forestalls the age-dependent increase in markers of chronic oxidative stress. It increases parasympathetic tone through vagal stimulation and reduces sympathetic tone through upregulation of eNOS gene expression [6]. DR also protects against damage from ischemia reperfusion injury to a number of organs, including brain, heart, liver and kidney [7].

A leading molecular hypothesis regarding the mechanism underlying pleiotropic DR benefits, including stress resistance, is known as the hormesis hypothesis. Hormesis describes a common phenomenon in which low doses of a given toxin can have beneficial biological effects, for example stimulation of cell growth at low doses of radiation. The hormesis hypothesis of DR posits that nutrient/energy deprivation is a mild stress to which the body responds by activating stress response genes [8]. In support of this model, genetic deletion of an evolutionarily conserved transcription factor responsible for the adaptive response to oxidative stress in worms (Skn1) and mice (Nrf2) abrogates benefits of DR in both organisms (lifespan extension and protection from tumorigenesis in worms and mice, respectively). Nrf2 is activated by oxidative stress, whereupon it translocates to the nucleus and rapidly turns up expression of genes involved in cytoprotection and redox status. DR may actually transiently increase oxidative stress due to increased mitochondrial respiration, thus activating Nrf2 and turning on cytoprotective mechanisms. The role of better-known mediators in DR and longevity, namely the AMP-dependent protein kinase (AMPK), NAD+-dependent deacetylases (sirtuins) and the growth factor/nutrient/amino acid sensor Target of Rapamycin (TOR), may be in sensing changes in nutrient/energy status upon DR and executing the metabolic shift toward increased mitochondrial respiration upstream of Nrf2 activation. A slight but significant increase in cortisol levels by DR also supports the model of DR as a mild stressor. However, improved energy efficiency through increased mitochondrial respiration and vasodilation through increased NO production are also plausible, non-mutually exclusive mechanisms underlying pleiotropic DR benefits in the context of surgical stress resistance.

Benefits of Dietary Restriction in Humans

A number of clinical trials have confirmed that humans on DR respond similarly to experimental animals on DR [9]. For example, 6 months of 20% reduced calorie intake improved measures of cardiovascular health, serum lipids and blood pressure. Recent data also suggest that adverse post-operative outcomes linked to oxidative stress, inflammation and stress hormones may be modified by DR. DR reduces oxidative stress in both chronic and acute settings, and may decrease stress hormone release, including circulating supine norepinephrine levels. DR reduces markers of inflammation, including hs-CRP and IL-6. DR also appears to work rapidly even in obese individuals or critically ill individuals. For example, two weeks of pre-operative DR can reduce the risk of postoperative complications in laparoscopic gastric bypass surgery as well as the perceived difficulty of the procedure [10]. DR can also reduce hospital mortality in ICU patients. In terms of efficacy, DR may thus create a relatively protected vascular and systemic environment for the planned stress of surgery, even in obese or critically ill patients.

Feasibility of Preoperative Dietary Restriction

Elective surgery presents a situation unique in medicine: the planned stressful event. Thus, dietary preconditioning could be tailored to maximize benefits against potential surgical complications in the minimal time possible. What would such a regimen look like, and would it be feasible? Two key issues inform the choice of pre-operative diet to test for benefits against surgical stress: composition and duration. Together, these will influence the feasibility of any proposed preoperative dietary regimen.

Composition

In model organisms such as fruit flies, reduction of calories derived from protein yields greater benefits than from fat or carbohydrate. Restriction of even a single essential amino acid, methionine, can confer longevity benefits. In rodents, methionine or tryptophan restriction extends lifespan and increases stress resistance without enforced dietary restriction. Complete removal of protein or individual essential amino acids from the diet rapidly confers benefits against surgical stress associated with renal and hepatic ischemia reperfusion injury [11]. These benefits depend in part on the conserved amino acid deprivation sensor Gcn2. The other major known amino acid sensing pathway in mammals is controlled by the signal transducing kinase mTOR. Inhibition of mTOR by rapamycin, even in the absence of dietary changes, increases longevity in rodents, possibly by mimicking nutrient deprivation. Furthermore, three days on a glucose water-only diet, the equivalent of a protein-free juice fast, has similar efficacy as water-only fasting against renal ischemic injury in mice without the reduction in subjective well being associated with total food deprivation [12]. Collectively, these studies point to benefits of a diet limited in protein or essential amino acids, but do not rule out the potential additive or synergistic effects of reducing both protein and calories at the same time.

Duration

In lower organisms (fruit flies, nematode worms) the onset of DR benefits is rapid, reaching full effect on mortality risk within 2-3 days. In rodents, surgical stress resistance also occurs rapidly –within a period of days [7, 11]. Because the evolutionary distance between fruit flies or nematodes and rodents is much greater than among mammals, we expect the rapid onset of DR benefits to be conserved in higher mammals as well, including humans. A reasonable explanation for this rapid activation of DR benefits lies in the nature of the protection itself. To the degree that DR is an adaptive response to stress [8], the mechanisms that activate it involve changes in signal transduction, gene expression and protein stability that can act in rapid time frames requiring only hours to days, rather than months to years.

Would a diet found to be maximally beneficial against surgical stress in a minimal time be considered feasible by physicians and their patients? This depends on the combination of duration and severity of the dietary intervention leading to benefits, which is currently not known in humans. However, we can speculate that minimal food restriction deemed feasible for up to a week would be considered impractical if required for three months or more, a time frame routinely leading to benefits in experimental rodents. Similarly, severe food restriction, such as water-only fasting, that might be very effective within a period of a few days may not be deemed practical by physicians and/or their patients. Ergo, based on our current state of knowledge, including rapid onset of benefits and predominant role of dietary amino acid deprivation, we predict that a reduced calorie, protein-free diet such as a juice-only fast for a period of up to one week will be safe, well-tolerated and efficacious.

We recognize that what is considered “feasible” by doctors and their patients is largely a subjective matter, but even here the existing literature is encouraging. It appears that brief (4 days to 2 weeks) pre-operative dietary interventions are both feasible and safe in the context of different patient groups, ranging from obese candidates for laparoscopic surgery to living organ donors. Most patients and their physicians recognize that vascular surgery is a significant stressor with risk for morbidity and mortality. If preoperative DR proves to be effective in modulating the response to stress and reducing postoperative complications, then patients and their providers will have greater incentive to incorporate DR into current operative preparation practices. Carefully monitored DR is distinct from starvation, as patients with malnutrition or other existing metabolic deficiencies would be exempt from DR. Additional investigation into the mechanisms of DR may allow further refinements in preoperative dietary management, leading to more specific restrictions and the addition of beneficial dietary supplements.

Conclusions

Dietary restriction represents a well-known, pleiotropic intervention with a wide range of benefits including those against surgical stress in experimental rodents. Dietary restriction produces many of the same metabolic changes in people, increasing the likelihood that DR would work against surgical stress as well.

Mechanistically, DR likely works by activating adaptive mechanisms in response to the relatively mild stress of nutrient/energy deprivation leading to reductions in sympathetic tone, inflammation and oxidative stress. Only recently has it been recognized that the benefits of DR accrue rapidly. This short time frame makes it possible to test in the clinic. We propose that vascular surgery, with its relatively high rates of perioperative complications and inadequate preventative measures, represents a unique opportunity to test the hypothesis that brief periods of clinically practical preoperative DR will reduce incidence and severity of surgical complications. If successful, such an intervention could stimulate research into evidence-based guidelines for preoperative nutrition and spawn interest in an inexpensive and readily accessible intervention to enhance outcomes in the planned acute stress in vascular surgery and beyond.

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Hypothesis

Brief preoperative dietary interventions emphasizing reduced calorie and protein intake will reduce perioperative morbidity and mortality associated with vascular surgical procedures by modulating the body's maladaptive response to surgical stress.