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Abstract

Impaired microcirculation secondary to underlying vascular endothelial dysfunction is increasingly recognized to play a central role in the pathophysiology associated with numerous postoperative complications. Noxious stimuli, including direct injury from surgical trauma and hypoxia (e.g., ischemia-reperfusion injury), trigger adrenergic-inflammatory-thrombotic-immune cascades to impair the microcirculation, with consequent perfusion-related postoperative complications. The endothelium, characterized by exquisite sensitivity to inflammation and low proliferative potential, has limited self-repair capacity that is dependent on circulating bone marrow-derived endothelial progenitor cells for regeneration. As such, the extent to which the endothelial physical and functional integrity is preserved mirrors not only underlying cardiovascular health but is also an important factor in susceptibility to postoperative morbidity. This review explores the effect of perioperative inflammation on the microcirculation and some of the current protective strategies available to clinicians. “Prehabilitation,” with preoperative exercise to improve the underlying endothelial function and bone marrow responsiveness for endogenous endothelial repair mechanisms, and anti-inflammatory strategies to limit activation of the endothelial-thrombotic-inflammatory cascades may provide clinical strategies to preserve the microcirculation to engender optimal surgical outcomes.

Keywords: microcirculation, endothelial dysfunction, inflammation, perioperative, surgery
1. Introduction

With an estimated 234 million operations performed annually, surgical care is an integral part of health care throughout the world [1]. Furthermore, the World Health Organization (WHO) estimates that the incidence of trauma, predominantly requiring surgery, accounts for 10% of deaths and 16% of disabilities worldwide—considerably more than malaria, tuberculosis, and HIV/AIDS combined [2].

Confounding the underlying comorbidities that patients present with during surgery, patients also suffer a significant biologic perturbation—the “surgical stress response”—a significant stressor to the human body during the perioperative period. A variety of systems are involved in this stress response, including the sympathetic autonomic nervous system, endocrine system, and immune system [3]. Inflammatory mechanisms are intimately tied to the immune system and contribute to direct defense against infection and promote postoperative wound healing. This physiological reaction of the human body can be exaggerated by a systemic inflammatory response syndrome (SIRS) [4]. SIRS results from the release of endogenous factors such as damage-associated molecular patterns (DAMPs) or alarmins [4, 5] after surgical tissue injury [6]. DAMPs activate the complement system, leading to a rapid generation of C3a and C5a [7–9] and initiation of the release of a myriad of inflammatory mediators such as adiponectin, leptin, C-reactive protein, interleukins (IL-8, IL-10, etc.), soluble tumor necrosis factor-receptor 1 (sTNF-R1), and 8-isoprostane.

Figure 1. The surgical pro-inflammatory and pro-oxidant milieu may result in both functional and structural alterations in the endothelium, resulting in hemostatic dysregulation and impaired microcirculation with consequent microvascular-related postoperative complications (Illustration courtesy of Dr Marissa Ferguson).

Interestingly, these inflammatory mediators, described as a systemic “inflammmome,” are increased in obese patients presenting for bariatric surgery [10]. Hence, this suggests that a
significant number of patients may present to surgery with an underlying pro-inflammatory state and is also seen in patients with inflammatory comorbidities, such as rheumatoid disease, inflammatory bowel disease, and diabetes mellitus [11, 12]. This inflammatory burden activates cellular processes at affected sites within tissues, with enhanced capillary permeability to soluble mediators, particles, and cellular trafficking. These systems are in a delicate balance, which can be easily disrupted to exacerbate disease or organ dysfunction [13].

Impaired microcirculation, largely driven by vascular endothelial dysfunction, is increasingly implicated as a central pathophysiological feature of postoperative morbidity. Microcirculation is affected by certain noxious stimuli, many of which are common to the perioperative period, including direct injury from surgical manipulation or hemodynamic shear stress, hypoxia (e.g., ischemia-reperfusion injury), and through exposure to inflammatory cytokines and endotoxins. Perioperative inflammation caused in reaction to surgical trauma causes a pro-inflammatory and pro-oxidant milieu that results in both functional and structural alterations in the endothelium. This may lead to microcirculation hemostatic dysregulation with impaired local tissue perfusion and consequent micro- and macrovascular-related postoperative complications (Figure 1) [14, 15].

2. Physiology of the endothelium

The endothelial “organ” is estimated to weigh approximately 1 kg in adults and covers the entire vasculature with a single layer of cells, covering a surface area of approximately 100–150 m² and comprising 10–60 trillion cells in a single layer.

For a long time, the endothelium was considered to be inert, tasked with passive maintenance of a non-thrombogenic blood-tissue interface. In 1980, however, Furchgott and Zawadzki [16] discovered the endothelium-derived relaxing factor (nitric oxide), and since then our understanding of the importance of the vascular endothelium has undergone a dramatic evolution.

The endothelium is now recognized as a complex tissue composed of key immunoreactive cells that respond to environmental conditions. Sandwiched between the blood compartment and the vascular smooth muscle cells, the single layered endothelium is ideally located to act as a dynamic sensor-effector organ. Most of the endothelial cell mass is found in the endothelial lining of the resistance vessels and capillaries, thereby exposing a relatively large endothelial surface to a small volume of blood (up to 5000 cm²/ml). This facilitates the exchange of nutrients and metabolic products [17], and thus allows the endothelium to exert significant autocrine, paracrine, and endocrine actions on smooth muscle cells, platelets, and peripheral leukocytes. Endothelial cells, thereby, participate actively and reactively in the regulation of a number of key physiological processes, including vascular tone, vascular permeability, hemostasis (thrombosis, fibrinolysis, and platelet adherence), immune and inflammatory (leukocyte adherence) reactions, angiogenesis, and maintenance of the basement membrane. This dynamic “gate keeping” role of the endothelium, modulated through its metabolic and synthetic functions (such as production of nitric oxide, endothelin, prostaglandins, cytokines, growth factors, and adhesion molecules) and through the expression of endothelial cell
3. Pathophysiology of the endothelium

In contrast, endothelial dysfunction, activation, and injury are characterized by inhibition of vasodilation, promotion of a pro-thrombotic/anti-fibrinolytic state, and promotion of platelet and leukocyte adhesion. Altered release of endothelium-derived factors appears to be pivotal in pathophysiological changes that occur in disease states, such as atherosclerosis, thrombosis, hypertension, pulmonary hypertension, eclampsia, hyperglycemia, diabetes, metastatic disease, immune diseases, inflammatory syndromes, infectious processes, and sepsis. Indeed, there is increasing evidence that perturbations in the vascular endothelium are directly or indirectly involved in the pathophysiology of numerous disease processes, including postoperative morbid events.

Figure 2. The phenotypic expression of the endothelium can be described as a dynamic “set point” that ranges between a quiescent, activated, or dysfunctional state. Endothelial cell (EC) dysfunction caused by perioperative inflammation in response to an acute stressor (surgery, critical illness) is accompanied by microcirculatory hypoperfusion that can lead to end-organ dysfunction.

The crucial step in the progression of perioperative endothelial dysfunction is the change of the endothelium from a quiescent into an active state. The endothelium, activated by exposure to inflammatory cytokines, becomes prothrombotic, prone to vasoconstriction instead of vasodilation, and more porous with increased fluid extravasation and increased cellular trafficking to the intercellular space. A systemic response to major trauma, associated with a
lowered ability to fight infection and susceptibility to sepsis, will further activate the destructive inflammatory response [19].

In those patients presenting with underlying impaired preoperative microcirculatory function now confounded by the pathophysiologic changes to the endothelium that accompanies the surgical stress response will be at higher risk of deterioration of the endothelial reserve below a critical “physiologic threshold” required to sustain microvascular integrity and perfusion (Figure 2).

4. Endothelial regeneration

Through reconstitution of the endothelial layer, which generally occurs in the presence of angiogenesis and vasculogenesis, endothelial function can be restored. Neovascularization is mediated through migration and proliferation of endothelial cells within the vasculature. Endothelial colony-forming cells (CFCs) developing endothelial progeny is the key factor in order for mature endothelial cells to proliferate and restore endothelial function [20–22]. For adult vasculogenesis, endothelial progenitor cells (EPCs) play an important role for the de novo formation of blood vessels. Historically, the presence of circulating blood cells with the ability to promote vascular repair and regeneration was first described in 1997 [23]. A variety of seemingly endothelial-specific cell surface antigens were displayed on the cells identified as EPCs. Subsequently, numerous experimental studies have assessed the mechanism induced by tissue ischemia, vascular trauma, tumor growth, and inflammation by which EPC are released from the bone marrow, travel to the sites of active neovascularization, and initiate the homing process in the endothelial layer. Furthermore, some studies suggest EPCs as a biomarker for clinical disorders, such as cardiovascular disease [24], cerebrovascular disease [25, 26], sepsis [27], and numerous types of cancer [28, 29]. Interestingly, there is an inverse correlation between the number of bone marrow released, circulating EPC and the postoperative complication risk. Subsequent experimental data from marrow transplantation demonstrated that these stem cells are recruited to sites of active neovascularization and differentiate into vascular cells in-situ. However, the frequency of this occurrence and the identification of the cell type involved need to be fully determined [30].

5. Endothelial progenitor cell populations

A major limitation in this field has been the lack of specific markers and different methods used to identify circulating EPCs. Different methods included flow cytometry, cell culture methods, immunostaining, and consequently render comparison difficult. Three functional populations of EPCs have generally been well defined. A cellular population that expresses the phenotype CD34+ AC133+ KDR+ has gained wide acceptance as a measure of circulating EPC in human subjects [31]. These cells, while being recruited to denuded vessels in ischemic sites, do not become persistent vascular endothelial cells or display de novo in-vivo vasculo-
genic potential, but rather exhibit potent paracrine properties to regulate new vessel formation through angiogenesis [32, 33]. These cells are referred to as proangiogenic hematopoietic cells [22, 34, 35]. Colony-forming assays, in which plated human CD34+ peripheral blood cells form cellular clusters on fibronectin-coated dishes in-vitro, have identified other populations of EPC. Asahara et al. [23] described that CD34+ peripheral blood cells form clusters, bind acetylated low-density protein (acLDL) and differentiate into spindle-shaped endothelial cells. These cell clusters are referred to as EPC colony-forming units (CFU). A third population of EPCs, identified as yet another type of cell colony emerging from plated peripheral blood mononuclear cells, form tightly adherent cells with a cobblestone appearance and are referred to as endothelial colony-forming cells (ECFC), late outgrowth cells (OEC), or blood outgrowth endothelial cells (BOEC). These cells become part of the systemic circulation of the host and have vessel-forming ability [36]. These ECFCs, with in vivo human vessel-forming ability, exhibit the greatest features consistent with human postnatal vasculogenic cells [37].

EPC enumeration correlates with cardiovascular risk factors, extent of coronary disease, and risk of future cardiovascular events [24]. EPC enumeration and functional characterization assess the reparative ability and propensity to cardiovascular injury, and thus greatly improves the risk stratification of patients for postoperative morbidity. Given that peripherally circulating EPCs and intrinsic stem cells play an important role in accelerating endothelialization and tissue remodeling following vascular damage from both disease and toxic insults, we anticipate that therapeutic attempts to stimulate mobilization and homing of bone marrow-derived EPC or exogenous administration of cell-based (progenitor) therapies will likely emerge in clinical medicine over the next decade [38–40]. Comorbid disease states and aging associate with decreased regenerative ability by EPCs and may underlie the etiology of postoperative complications and delayed recovery following surgery. For example, diabetes is characterized by poor bone marrow mobilization and decreased proliferation and survival of EPCs [41]. Inhibiting oxidative stress has been shown to modulate EPCs and normalize post-ischemic neovascularization in diabetics. Similarly, EPC mobilization is also reported to improve with insulin therapy in diabetic rats [42]. Whether this effect is mediated by insulin itself or through improved glucose control needs to be clarified.

6. Impaired endothelium-dependent vascular function in the clinical setting

An intact microcirculation is key for the functional success of the cardiovascular system and end-organ perfusion. In the perioperative period, a wide range of microcirculatory alterations associated with surgery itself, including factors such as anesthesia type, hypothermia, hemodilution, inflammatory reaction, and microemboli formation [43,44], impair endothelium-dependent vascular function to decrease blood flow and oxygen supply to the parenchymal cells. An improved understanding of the different types of microcirculatory alterations may also contribute to reducing perioperative complications. Variants of impaired microcirculation include impaired microcirculatory perfusion where obstructed capillaries are observed next to capillaries with flow, often seen in clinical conditions such as sepsis or
reperfusion injury; microcirculatory alterations characterized by increased diffusion distance between oxygen-carrying red blood cells and tissue cells, often seen in hemodilution that accompanies cardiopulmonary bypass; microcirculatory tamponade, often associated with excessive use of vasopressors and/or increased venous pressure. This fluid overload causes tissue edema that consequently leads to a damage of endothelial cells and losses of hemodynamic coherence, glycocalyx barriers, and/or the compromise of adherence and tight junctions [45].

7. Impaired microcirculation during critical illness

Alterations of the cerebral microcirculation may represent a key component for the development of postoperative sepsis-associated encephalopathy. Cerebral hypoperfusion is a common complication of sepsis and its pathophysiology is complex and related to numerous processes and pathways, while the exact mechanisms producing neurological impairment such as delirium in septic patients is not fully understood. Cerebral hypoperfusion is caused by vasoconstriction that may be induced by inflammation and hypocapnia. The underlying endothelial dysfunction in sepsis leads to impairment of microcirculation and cerebral metabolic uncoupling that may further reduce brain perfusion. The natural autoregulatory mechanisms that protect the brain from reduced/inadequate cerebral perfusion can be impaired in septic patients, especially in those with shock or delirium, and this further contributes to cerebral ischemia if blood pressure drops below critical thresholds [46].

Postoperative brain dysfunction (delirium and coma) may relate to impaired microcirculation following surgical trauma and the associated inflammation seen in the postoperative period. Postoperative neurocognitive dysfunction is very prevalent, especially in the elderly surgical patient population. It has been reported to independently associate with prolonged mechanical ventilation, longer and more costly hospitalizations, delayed cognitive dysfunction that persists for months after hospital discharge, and increased mortality [47–53]. Factors implicated in the pathogenesis of acute brain dysfunction, such as inflammation, abnormal cerebral blood flow, and increased blood-brain barrier permeability [54, 55], are known to impact endothelial function. Similarly, critical illnesses, such as sepsis and multiple organ dysfunction syndrome, states that circulating inflammatory cytokines affect endothelial nitric oxide production and expression of adhesion molecules [56, 57]. This results in coagulation system activation, altered perfusion, distorted permeability, and decreased ability for vascular repair [58, 59]. In the brain specifically, structural and functional alterations of blood–brain barrier endothelial cells secondary to inflammatory states have been associated with increased microvascular permeability and impaired microcirculatory blood flow [60–63]. This relationship between endothelial dysfunction and brain dysfunction during critical illness is increasingly reported in critically ill patients. The observed impact of endothelial dysfunction and injury on brain function will also likely reflect that seen in other end organs, including acute lung injury following surgery [64] or during critical illness [65].
8. Therapeutic options to improve perioperative endothelial dysfunction

Therapeutic modulation of underlying subclinical microvascular endothelial dysfunction holds promise for a significant reduction in perioperative morbidity and specifically for complications such as impaired wound healing and end-organ dysfunction related to impaired microcirculation following surgery. Perioperative inflammation can be targeted with non-steroidal anti-inflammatory drugs to limit activation of the endothelial-thrombotic-inflammatory cascades with potential to improve perioperative outcomes [66–68]. Other therapeutic interventions, including preoperative exercise capacity, which aim to improve endothelial-dependent vascular function before surgery in order to cope with the inflammatory burden are currently under investigation in clinical studies [69, 70].

9. Mobilizing of endothelial progenitor cells with preoperative exercise

Numerous factors have an important role in the mobilization of EPCs [71, 72]. These include growth factors (e.g., GM-CSF, GCSF, VEGF, placental growth factor, erythropoietin, and angiopoietin-1), pro-inflammatory cytokines, chemokines (e.g., stromal cell-derived factor-1), hormones (e.g., estrogens, and lipid lowering and antidiabetic drugs), and physical activity [73]. The stimulatory effect of exercise on EPC has been shown in highly trained athletes [74], healthy subjects [71], and importantly also in patients with cardiovascular disease [75]. However, further research is required to understand the potential benefit of exercise to endothelial health in patients with subclinical cardiovascular disease characterized by endothelial dysfunction secondary to comorbidities, including metabolic syndrome or in patients subjected to the acute inflammatory insult of surgery.

Exercise has been shown to improve exercise capacity, specifically the anaerobic threshold (AT) and the maximum oxygen consumption (pVO2), and underlying endothelial reserve. In healthy subjects, Laufs et al. [76] showed that moderate and intense running for 30 min (80–100% velocity of individuals’ AT) increased circulating EPC levels, but this was not seen with running occurred at short intervals (10 minutes). In elderly patients with coronary artery disease, a 4-week exercise program achieved significant upregulation of circulating EPCs. More recently, this was achieved after an even shorter (15 days) cardiac rehabilitation program, with an increase in EPCs that correlated with improved exercise capacity [73]. Other markers of improved endothelial function from a cardiac rehabilitation program included: a two-fold increase in EPCs, a three-fold increase in CFU, increased blood nitrite concentration, and reduced EPC apoptosis [75]. The duration and the intensity of exercise that are needed to adequately stimulate EPC mobilization and improve endothelial function require further investigation [77]. Surgical injury induces the mobilization of EPCs, with significantly higher circulating EPC and bone marrow EPC levels observed 24 hours after surgery in an animal model [78]. The ability to mount an EPC response is also seen in critical illness, and the response is significantly greater in patients that survive sepsis [27], and recover from illness, for example, without fibrotic changes after pneumonia [40].
Given that “responders” who mount a “cellular” stress response to injury, with increased EPC mobilization, have improved organ recovery [40] and improved survival [27], it is increasingly clear that a bone marrow-derived cellular component must follow the surgical “stress response” to facilitate repair processes. In a recent pilot study, we were able to demonstrate that patients scheduled for major surgery that exhibited an EPC response to the stressor of preoperative exhaustive exercise with a single cardiopulmonary exercise test up to pVO2 suffered significantly fewer postoperative complications [69]. Whether strategies to improve bone marrow capacity and responsiveness will influence a patient’s ability to withstand surgical injury remains to be investigated. Increasing this bone marrow-derived regenerative response through preoperative exercise training may be one potential therapeutic option to optimize patients’ health status prior to surgery.

However, discovering an inadequate EPC response during acute illness, such as impaired wound healing, pneumonia, acute lung injury [64], or sepsis [65], is likely too late. Hence, using a surrogate stressor, for example, exercise, to allow for early identification of at-risk patients prior to surgery will enable timely strategies to improve bone marrow responsiveness to be implemented. Importantly, some of the endothelial dysfunction, particularly that acquired in the perioperative period, may be transient or reversible and may not actually involve structural change in the cells of the vascular endothelium, but more likely potentially reversible alterations in function—so these would not require new cells, just repair of a damaged process. Importantly, whether this lack of EPC response is an epiphenomenon, a surrogate marker, or indeed causative of increased postoperative complications, requires further study. The causative nature is supported by animal studies that suggest that exogenous EPC administration can rescue endotoxin-induced acute respiratory distress syndrome (ARDS), with reduced inflammation, improved oxygenation, and improved survival [38, 39].

Jeong et al. [79], investigating whether diabetic neuropathy could be reversed by local transplantation of EPCs, reported that motor and sensory nerve conduction velocities, blood flow, and capillary density were reduced in sciatic nerves of streptozotocin-induced diabetic mice; with recovery after hindlimb injection of bone marrow-derived EPCs that were shown to engraft in close proximity to the vasa nervorum. This study demonstrated that bone marrow-derived EPCs could reverse manifestations of diabetic neuropathy, and that cell-based translational approaches may provide a novel and valid therapeutic alternative in the future.

Exercise [80] and tissue insult from surgery [78] are known to increase the mobilization of EPC. In this manner, cardiopulmonary exercise testing (CPET) can be used as a catalyst to increase the circulating population of EPCs and as a diagnostic tool of a patient’s ability to mount an EPC response preoperatively. Additional gas exchange parameters obtained during a diagnostic CPET (anaerobic threshold and peak VO2) can be used to determine patients’ individual physiologic capacity and the amount of exercise needed in order to stimulate the population of EPC. Preoperative exercise training could condition patients’ individual functional capacity and to improve endothelial reserve by affecting EPC responsiveness. As such, Cesari et al. [73] reported a significant increase in circulating EPCs in those patients that improved their exercise capacity by more than 23%, as assessed by a six-minute walk test, after completion of a rehabilitation program.
10. Exercise and inflammation

Regular exercise has been described to be involved in risk reduction of many chronic pathological alterations such as cancer, cardiovascular, and neurodegenerative diseases. One key mechanism, which is frequently discussed in this context, is that exercise contributes to an anti-inflammatory environment, thereby counteracting a major risk factor of those diseases [81–83]. This hypothesis is supported by a vast body of literature, indicating that acute exercise induces a short-term strong increase in the pro-inflammatory cytokine interleukin-6, which in turn induces a long-term depression of TNF-α and the expression of anti-inflammatory mediators, such as interleukin-10 and soluble receptors of interleukin-1 [84]. Furthermore, recent research suggests that regular exercise suppresses over a life-span the permanent expression of inflammatory cytokines via epigenetic mechanisms. Nakajima et al. [85] showed that the DNA-methylation in the promoter region of the ASC gene, the products of which induce inflammation, is decreased in older subjects. An intermediate exercise intervention resulted in a re-methylation of this region; hence, the methylation pattern of 60- to 70-year old was corrected to those of 30- to 40-year-old study participants.

The anti-inflammatory effect of exercise is mediated by cells which secrete protective cytokines, such as interleukin-6, which is expressed by skeletal muscle-tissue during physical activity. However, little is known about the exact mechanism in which exercise triggers the anti-inflammatory component. Evidence rises that regular exercise and higher levels of cardiovascular fitness are related to an increased number of regulatory T-cells. Since these cells have strong anti-inflammatory properties (e.g., by secreting Interleukin-10), they may contribute to the intermediate anti-inflammatory effect of exercise [86].

Exercise is involved in multiple processes establishing an anti-inflammatory environment, which counteracts with perioperative inflammatory stress. Therefore, preoperative exercise, which is feasible over a 1-month time period, may contribute to a reduction of the inflammatory burden that is present in patients undergoing surgery.

11. Other aspects of exercise promoting endothelium-dependent vascular function

Besides the mobilization of EPCs and its anti-inflammatory properties, exercise is known to regulate key factors of vascular functioning. Furthermore, exercise induces the expression of the endothelial nitric oxide synthase (eNOS) and increases the levels of VEGF [87–89]. The first studies revealed that the regulation of these factors is at least partially driven by epigenetic mechanisms. Wu et al. [90] revealed that exercise in rats results in a downregulation of the microRNA155. Interestingly, the messenger RNA of eNOS is known to be inhibited by microRNA155. One essential mediator may be displayed by shear-stress which is also associated with epigenetic modifications of the chromatin (histone modifications) in the eNOS gene region [91, 92]. Fernandes et al. [93] found reduced levels of microRNA126 and 16 in exercising animals. Both microRNAs were previously described to inhibit the expression of
VEGF. Although the previous studies give a premature insight into the underlying mechanism, they display that exercise truly contributes to the improvement of vascular function and regeneration on the molecular level. Further research, especially in humans, is warranted to get more information about the mechanism and dose–response relationship of exercise contributing to endothelial and vascular regeneration.

12. Conclusion/Summary

Impaired microcirculation secondary to underlying vascular endothelial dysfunction is increasingly recognized to play a central role in the pathophysiology associated with numerous postoperative complications. Noxious stimuli, including direct injury from surgical trauma and hypoxia (e.g., ischemia-reperfusion injury), trigger adrenergic-inflammatory-thrombotic-immune cascades to impair the microcirculation, with consequent perfusion-related postoperative complications.

The endothelium, characterized by exquisite sensitivity to inflammation and low proliferative potential, has limited self-repair capacity that is dependent on circulating bone marrow-derived endothelial progenitor cells for regeneration. As such, the extent to which the endothelial physical and functional integrity and bone marrow responsiveness, for the circulating progenitor pool, is preserved mirrors not only underlying cardiovascular health but also as an important factor in susceptibility to postoperative morbidity.

This review explores the effect of perioperative inflammation on the microcirculation and some of the current protective strategies available to clinicians. “Prehabilitation,” with preoperative exercise to improve underlying endothelial function and bone marrow responsiveness for endogenous endothelial repair mechanisms, and anti-inflammatory strategies to limit activation of the endothelial-thrombotic-inflammatory cascades may provide clinical strategies to preserve the microcirculation to engender optimal surgical outcomes.

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