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Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention

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van Wijck K, Lenaerts K, Grootjans J, Wijnands KA, Poeze M, van Loon LJ, Dejong CH, Buurman WA. Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. Am J Physiol Gastrointest Liver Physiol 303: G155–G168, 2012. First published April 19, 2012; doi:10.1152/ajpgi.00066.2012.—Physical exercise places high demands on the adaptive capacity of the human body. Strenuous physical performance increases the blood supply to active muscles, cardiopulmonary system, and skin to meet the altered demands for oxygen and nutrients. The redistribution of blood flow, necessary for such an increased blood supply to the periphery, significantly reduces blood flow to the gut, leading to hypoperfusion and gastrointestinal (GI) compromise. A compromised GI system can have a negative impact on exercise performance and subsequent postexercise recovery due to abdominal distress and impairments in the uptake of fluid, electrolytes, and nutrients. In addition, strenuous physical exercise leads to loss of epithelial integrity, which may give rise to increased intestinal permeability with bacterial translocation and inflammation. Ultimately, these effects can deteriorate postexercise recovery and disrupt exercise training routine. This review provides an overview on the recent advances in our understanding of GI physiology and pathophysiology in relation to strenuous exercise. Various approaches to determine the impact of exercise on the individual athlete’s GI tract are discussed. In addition, we elaborate on several promising components that could be exploited for preventive interventions.

athletes; gastrointestinal compromise; strenuous exercise

THE GASTROINTESTINAL (GI) system plays an important role in the athlete’s ability to perform strenuous exercise (24). Proper GI function enables endurance performance and promotes early recovery. In contrast, a compromised GI system will likely impair performance and subsequent recovery and may give rise to serious GI problems, such as nausea, vomiting, abdominal angina, and bloody diarrhea (102, 124). Such symptoms, manifestations of a compromised GI system, are experienced by 25–70% of endurance athletes (102, 124). Among the reported deleterious manifestations of strenuous exercise are mucosal erosions and ischemic colitis, both observed after long-distance running (4, 21, 25, 54, 90, 95). Although the etiology of exercise-induced GI distress is multifactorial, GI ischemia is often acknowledged as the main pathophysiologic mechanism for the emergence of such distress (29, 90, 123, 124).

This review provides an overview on the current understanding of GI physiology and pathophysiology during and after exercise. Strategies will be discussed that may be used by athletes to determine the impact of exercise on the GI tract. Ultimately, we will provide insight into some promising resources that may be used to prevent exercise-induced abdominal distress.

Gastrointestinal Perfusion

The arterial blood supply of the GI tract consists of three main afferent routes: the celiac trunk and the superior and inferior mesenteric artery (81). These three main arteries ramify into three dense vascular plexuses, the serosal, submucosal, and mucosal plexuses, of which the latter shoots the microcircular capillary network that irrigates the intestinal mucosa. Drainage of the splanchnic area is covered by the superior mesenteric vein, inferior mesenteric vein, and the portal vein,
which return the venous blood to the heart via the liver and subsequently the inferior vena cava (81). The splanchnic vasculature constitutes a system with a remarkable capacity to adapt to physiological stressors promoting vasodilatation or constriction via regulation of the mesenteric vascular resistance by neuroendocrine, humoral, and paracrine mechanisms (79). During strenuous physical activity or exercise, the release of norepinephrine near the α-adrenoreceptors of the sympathetic nervous system induces splanchnic vasoconstriction, thereby increasing total splanchnic vascular resistance (41, 81, 140). The blood is rapidly redistributed from the splanchnic area to be used for the perfusion of tissues with increased activity during exercise, such as heart, lungs, active muscle, and skin (Fig. 1) (98, 109). Although Doppler ultrasound and contrast extraction studies in the 1950s had already revealed a vast reduction in hepatosplanchnic blood flow during exercise (14, 110a), it was the technique of gastric tonometry that revealed that strenuous physical exercise results in splanchnic hypoperfusion and mucosal acidosis in healthy individuals (92, 98). Tonometry is a functional test that relies on the principle that inadequate tissue perfusion and tissue hypoxia lead to mucosal accumulation of carbon dioxide (CO₂). The exact working mechanism of gastric tonometry during exercise is depicted in Fig. 2. In short, the accumulated CO₂ increases the gastric CO₂ tonus (P₇CO₂), which is measured by the tonometer (67), and the gap between gastric and systemic P₇CO₂ reflects the adequacy of splanchnic perfusion. Gastric exercise tonometry revealed a rapid onset of splanchnic hypoperfusion, with the most pronounced changes in splanchnic perfusion occurring in the first 10 min of strenuous exercise (134) (Fig. 3A), indicating a rapid response of the splanchnic vascular bed. In addition, a rapid restoration of splanchnic blood flow was observed in the first 10 min of postexercise recovery, suggesting rapid reperfusion of the splanchnic area (134) (Figs. 1 and 3A).

Tonometry also demonstrated that the severity of splanchnic hypoperfusion was proportional to exercise intensity as assessed by increasing blood lactate levels (123), without a critical reduction in splanchnic perfusion during submaximal exercise in healthy individuals (98, 123). The majority of symptomatic athletes, however, already developed splanchnic hypoperfusion during submaximal exercise (123), suggesting vascular hyperresponsiveness to exercise. In addition, early studies have pointed out that there is a clear relationship between the reduction in splanchnic blood flow and relative workload (23), suggesting that regular training has an impact on the sensitivity of the splanchnic vascular responsiveness to exercise. However, data comparing trained and untrained subjects are required to verify whether this is true.

Age has also been suggested to affect blood flow redistribution during exercise, since the vascular system in elderly may be less responsive to catecholamines (68), whereas atherosclerotic plaques and vascular stenosis associated with aging of the vascular system may also play a role. Reductions in splanchnic blood flow were indeed reported to be less pronounced in elderly (mean age 64 years) compared with their younger counterparts, who were closely matched with respect to maximal oxygen uptake capacity, when exercise intensities exceeded 60% of peak oxygen consumption (65). These observations corroborate the higher frequency of exercise-induced abdominal complaints in young athletes that may be hypoperfusion related (41, 124), although the latter may of course also be related to the fact that in general, absolute workloads of young athletes are substantially higher than for the elderly, leading to more profound circulatory changes.

Fig. 1. Schematic overview of the processes proposed to play a role in the development of exercise-induced gastrointestinal injury. Strenuous physical exercise leads to redistribution of blood, shunting blood away from the splanchnic area, thereby significantly reducing splanchnic blood flow. The ensuing ischemia leads to tissue hypoxia, local depletion of ATP, and acidosis. After exercise, when splanchnic circulation is restored, reperfusion injury may develop, characterized by local inflammation and formation of reactive oxygen species. Both ischemia and reperfusion sequela lead to mucosal damage and gut wall integrity loss, which is accompanied by increased permeability, bacterial translocation, and intestinal inflammation. It remains to be clarified whether the exercise-induced mucosal injury impairs nutrient uptake, potentially decreasing athletic performance and delaying postexercise recovery. Adapted from Van Wijck K, Buurman WA. Exercise-induced splanchnic ischemia/reperfusion injury. In: Encyclopedia of Exercise Medicine in Health and Disease, edited by Mooren F-C. New York: Springer, 2012.
Another explanation for the less extensive splanchnic hypoperfusion observed in the elderly is their reduced muscle mass.

In conclusion, exercise leads to redistribution of blood away from the splanchnic area, resulting in intestinal hypoperfusion and rapid reperfusion, which may contribute to GI distress in symptomatic athletes.

GI Function: Exercise-Induced Loss of Epithelial Integrity and Barrier Function

Decreased oxygenation of the intestinal epithelium may lead to damage at the intestinal villus tips (Fig. 1) (30, 49). In line with this, exercise-induced hypoperfusion leads to loss of cellular integrity in the intestine of young, healthy individuals during strenuous exercise, which is reflected by significantly increased plasma levels of intestinal fatty acid binding protein (I-FABP) (Fig. 3B) (134). I-FABP is a small, cytosolic protein present in mature enterocytes at the upper half of the small intestinal villi and is rapidly released into the circulation upon cellular injury (30, 101, 127). The susceptibility of the mature enterocyte population to low-flow states and ischemic events is explained by the countercurrent exchange mechanism of the villus (10, 11) that creates a constant low-oxygen, hyperosmolar environment at the villus tip (51). Reduced splanchnic perfusion deteriorates the physiological low-oxygen state.
which is characterized by complement activation, production
contributing to intestinal barrier function loss. Additionally, strenuous
exercise may induce Paneth cell dysfunction, thereby possibly
influencing Paneth cell apoptosis, and loss of these cells was indeed associated
with exercise-induced hemorrhagic colitis requiring surgery, a condition particularly described in marathon runners (107, 115).

Exercise-induced intestinal injury may be the result of either hypoperfusion only or a combination of ischemia with subsequent reperfusion, since restoration of the splanchnic blood flow can further compromise epithelial integrity due to oxidative stress and inflammation (Fig. 1) (36, 49). Loss of epithelial integrity is associated with increased GI permeability, bacterial translocation, and intestinal inflammation (Fig. 1) (7, 36). Such barrier integrity loss includes disruption of the tight junctions interconnecting the intestinal epithelial cells, either by alteration of the epithelial cytoskeleton or by loss of tight junction proteins (59, 125, 126). Increased permeability and bacterial translocation may occur (7), and tight junction proteins are rapidly redistributed to quickly restore an effective intestinal barrier (77).

Increased intestinal permeability after strenuous exercise was confirmed by increased urinary excretion of orally ingested permeability probes such as chromium-51 ethylenediaminetetraacetic acid (51Cr EDTA) (95) and sugar permeability probes (76, 99). Sugar-based permeability analysis relies on the permeation of large and small sugar probes through GI mucosa, which provides a specific index of GI permeability (9). An increase in this permeability index was also observed in plasma samples of young athletes, reflecting a transient increase in GI permeability after 1 h of vigorous cycling, indicating disruption of the GI barrier (134). Although healthy individuals are well able to cope with a transient increase in GI permeability, in case of prolonged, vigorous exercise, more profound increases in intestinal permeability lead to translocation of luminal endotoxins, resulting in endotoxemia (13, 64).

Another important line of defense in the small intestine that is worth mentioning in the setting of intestinal ischemia is the immunological barrier formed by the Paneth cells. These cells, located in the crypts of the intestine in between the stem cells, continuously produce and secrete antimicrobial proteins into the intestinal lumen to prevent bacterial translocation. In addition, they directly sense and respond to bacterial threats (1, 129). Recent studies have shown that intestinal ischemia-reperfusion in the human intestine is associated with Paneth cell apoptosis, and loss of these cells was indeed associated with increased bacterial translocation and inflammation (48). Although never investigated in the setting of physical activity or exercise, the involvement of Paneth cell dysfunction in the intestine of endurance athletes is tempting to speculate on. During prolonged, vigorous exercise, splanchic hypoperfusion may induce Paneth cell dysfunction, thereby possibly contributing to intestinal barrier function loss.

Loss of epithelial integrity, increased GI permeability, and bacterial translocation induce a strong inflammatory response, which is characterized by complement activation, production and release of cytokines, endothelial activation, and local neutrophil influx in the intestinal mucosa (30). Indeed, circulating levels of mannose-binding lectin (MBL), a player of innate immunity and an important initiating complement component (31), increased after 1 h of vigorous cycling in healthy, young athletes (unpublished data), suggesting activation of the complement system. Furthermore, exercise led to elevated cytokine levels and an increase in endothelium-derived factors and acute-phase proteins (17, 100). Although these inflammatory markers may originate from skeletal muscle (17, 100), increased fecal levels of neutrophil-derived calprotectin and bacterial translocation suggest an additional role for the intestinal mucosa as a contributor to the inflammatory response after strenuous exercise (13, 64, 69, 134).

In short, splanchic hypoperfusion during exercise leads to loss of intestinal epithelial integrity, which may be accompanied by intestinal blood loss. Additionally, strenuous exercise results in loss of intestinal barrier integrity, reflected by increased permeability, bacterial translocation, and intestinal inflammation (Fig. 1).

GI Function: Exercise-Induced Changes in Digestion and Absorption

The consequences of vigorous exercise on GI function are diverse and many aspects remain to be clarified. For example, the effect of exercise on gastric emptying is very heterogeneous. Although exercise at the individual’s maximum capacity has been reported to delay gastric emptying in some studies (16, 38), the majority of studies fail to report any major changes in gastric emptying, even during more vigorous physical exercise (43, 120, 131). On the basis of the current literature, it seems fair to conclude that gastric emptying is not limiting the speed of nutritional uptake during exercise when appropriate measures are taken regarding the volume, composition, temperature, and osmolality of the ingested drinks (42, 110, 113).

After gastric emptying, the luminal content enters the small intestine, the principal site of nutrient digestion and absorption. The latter is highly important with respect to digestive tolerance during exercise and determines the rate of nutrient supply to the active muscles (15). It is tempting to assume that GI function is reduced during vigorous physical exercise, and several authors have prompted that decreases in splanchic perfusion and oxygen supply up to 80% reduce nutrient digestion and absorption (15, 29, 131). In line with this, several studies have demonstrated that, whereas glucose absorption is unaffected by exercise at low and moderate intensity levels, it is decreased during strenuous physical exercise (71, 131). Yet corroborative evidence supporting the theory that splanchic hypoperfusion accounts for this decrease in absorption is still lacking. In addition to a putative effect of hypoperfusion on metabolic function, mucosal injury and local inflammation may exert negative metabolic effects during exercise. On the other hand, specific nutritional strategies may be able to preserve sufficient splanchic flow during and after exercise. The latter contributes to the maintenance of a positive energy balance necessary to ensure optimal metabolic recovery and to promote optimal muscular regeneration processes (119).

Other factors that may contribute to decreased GI metabolic function are altered neurohormonal levels, altered secretary AJP-Gastrointest Liver Physiol · doi:10.1152/ajpgi.00066.2012 · www.ajpgi.org
activities, and disturbances in the electrolyte and acid-base balance (91). Last of all, inadequate fluid intake during strenuous exercise in a hot environment, leading to hypohydration of 3% of body weight, did not interfere with digestion and absorption (111) but may impair intestinal barrier maintenance (69, 70).

In short, on the basis of the available data, we consider that if strenuous exercise is prolonged, the need for energy substitution increases, whereas the absorptive capacity of the gut may decrease.

**Individual Predisposition**

There is large heterogeneity in the response of the GI system to exercise. Splanchnic hypoperfusion during exercise ranges from mild circulatory changes to profound GI ischemia (Fig. 3, A and C). In line with this, the consequences of hypoperfusion within the GI tract, i.e., epithelial injury and changes in GI permeability and epithelial barrier function, greatly differ between individuals (Fig. 3, B and D). Ultimately, the presence and nature of abdominal symptoms experienced by athletes vary from mild, exercise-related discomfort to severe ischemic colitis and diarrhea (88). A number of factors contributing to the pathophysiology of exercise-related abdominal distress have been identified, such as age, female sex, medication, dehydration, food intake, a hot humid environment, type of exercise, exercise duration, and exercise intensity (29, 41, 102, 124). Another factor that may contribute to the differences in the hypoperfusion sequelae is genetic background; e.g., previously, carriers of a homozygous MBL2 genotype were reported to have significantly lower levels of plasma I-FABP after intestinal ischemia (80), indicating that MBL-deficient individuals may be protected against ischemia/reperfusion-induced intestinal epithelial injury. An unfavorable combination of factors places the individual at risk of developing GI problems. Exercise-induced GI ischemia has been reported to occur in 50% of symptomatic athletes at submaximal exercise intensities, whereas asymptomatic athletes do not display intestinal ischemia during exercise at that level of intensity (123).

Importantly, specific underlying pathology may also give rise to GI problems during or shortly after physical exercise, and exercise-related symptoms may represent an early sign of such pathology. Vascular conditions known to cause exercise-related complaints can be classified as nonocclusive or occlusive disease, affecting single or multiple vessels. The main cause of single artery stenosis is celiac artery compression, in which extrinsic compression of the celiac artery by the median arcuate ligament of the diaphragm hampers the inflow of blood (82, 118). Critically reduced perfusion through the celiac artery is thought to produce upper abdominal pain in a similar fashion as exercise leads to ischemia-associated abdominal discomfort. This also explains why the pain in celiac artery compression syndrome (CACS) is typically experienced postprandially and during exercise, since a combination of ischemic factors leads to a greater perfusion mismatch within the splanchnic area. Although the prevalence of CACS in the general population is still unclear, Mensink et al. (82) found a prevalence of 13.4% in 320 patients with suspected chronic GI ischemia. Other conditions such as splanchnic atherosclerosis may also cause nonocclusive mesenteric ischemia, classically leading to postprandial abdominal pain and exercise-induced symptoms. In addition, patients with compromised cardiac and/or pulmonary function, e.g., chronic heart failure or chronic obstructive pulmonary disease are suggested to be at risk of developing splanchnic hypoperfusion and the associated intestinal injury, barrier dysfunction, and inflammation (112). Since intestinal inflammation may contribute to the state of chronic inflammation that is often seen in these patients, it is essential to avoid an excessive splanchnic response. On the other hand, regular physical exercise in these chronic patients is of important clinical relevance, since it helps to maintain muscle mass and strength, improves cardiovascular fitness, and increases quality of life.

**Evaluation of Splanchnic Perfusion in Athletes**

The currently available clinical tools that may be used to identify whether disproportional splanchnic hypoperfusion or ischemia is present during exercise are tonometry and techniques to evaluate the intestinal microcirculation. An overview of the available tools is depicted in Table 1.

Exercise tonometry enables detection of GI ischemia in all symptomatic athletes during 10 min of maximal exercise (plasma lactate > 5.5 mmol/l). About 50% of these asymptomatic athletes also showed signs of GI ischemia during 10 min of exercise at submaximal workload (3 < lactate < 5.5 mmol/l) (123). Criteria for positive tonometry outcomes generally differ between centers. Otto et al. (97) considered tonometry to be positive in symptomatic athletes in case of increased luminal PCO2 compared with baseline values, in combination with a gastric-arterial gap (gapg·a) PCO2 > 0.8 kPa, or for jejunal tonometry a jejunal-arterial gap PCO2 > 1.4 kPa. Ter Steege et al. (123) used the same criteria to identify ischemia during exercise tonometry, and found gapg·a PCO2 levels of 1.1 and 0.5 kPa during 10 min of submaximal exercise in symptomatic and asymptomatic athletes, respectively, and 2.5 and 1.7 kPa during 10-min exercise increasing to maximum intensity. We observed increased gapg·a PCO2 levels from −0.85 in rest to 0.85 kPa after 1 h of cycling at 70% of the individual athlete’s maximal workload capacity (Wmax) without major abdominal complaints (Fig. 3A) (134). An alternative way to evaluate exercise-induced ischemia may be to consider the increase in gapg·a PCO2 from baseline, since physiological baseline differences are common, and cutoff points for ischemia may also be individually determined. We propose to include markers of ischemia-related epithelial injury and GI compromise such as I-FABP and permeability ratios, respectively, to improve the diagnosis of exercise-induced ischemia. The diagnosis of CACS is largely similar to the multidisciplinary workup of GI ischemia, including gastric exercise tonometry and visualization of the stenosis, and is described in detail by Mensink et al. (82).

Novel techniques introduced to evaluate the intestinal microcirculation are orthogonal polarization spectral imaging (44, 47), sidestream dark-field imaging (58), near-infrared spectroscopy, and visible light spectroscopy. These techniques provide information on the mucosal oxygen saturation of hemoglobin in red blood cells of the intestinal microcirculation by emission and detection of backscattered light during endoscopy (5, 81, 133). This provides a direct measurement of mucosal microcirculatory saturation and simultaneous macroscopic evaluation of the mucosa during upper endoscopy in clinical settings.
Analysis of the sublingual microcirculation using the same techniques provides an indirect, less invasive alternative that may prove useful for athletes to monitor the effects of training on GI function. Measurements must be performed before and directly after cessation of exercise, since movement of the diagnostic probe during exercise interferes with the quality of microcirculatory imaging. Data on the use of these techniques in athletes are not yet available. Studies in patients suspected of chronic GI ischemia are promising (133), and sublingual microcirculation measurements were reported to correlate closely with measurements of the intestinal microcirculation in animal studies (138).

If vascular abnormalities or vascular occlusion are considered to explain existing abdominal symptoms that present either at rest or during exercise, imaging of the abdominal vasculature may be useful to exclude vascular abnormalities. To evaluate intestinal microcirculation, and imaging of the splanchnic vasculature may be useful to exclude vascular abnormalities.

Evaluation of Compromised Epithelial Integrity in Athletes

Circulating plasma I-FABP levels, determined by an ELISA, can be used during and after exercise to obtain information on intestinal injury (127, 134). In healthy, trained individuals, plasma I-FABP levels doubled from ~300 to over 600 pg/ml during 1 h of cycling at 70% $W_{max}$ (134). In addition, plasma I-FABP levels were found to correlate with exercise-induced splanchnic hypoperfusion determined 20 min earlier, emphasizing the suitability of I-FABP as a marker of ischemia-related intestinal injury in athletes (134). Cutoff points for differentiation of normal and abnormal circulating I-FABP levels depend on the sensitivity of the test that is used. Ideally, the athlete’s baseline I-FABP level is determined (at rest) and subsequent levels measured during exercise should be expressed accordingly. The change in I-FABP levels (i.e., the delta) likely represents a more reliable measure to reflect GI homeostasis during exercise and subsequent postexercise recovery. The development of a reliable quick test to evaluate circulating I-FABP levels in capillary blood obtained from a fingertip or earlobe would greatly increase the applicability of I-FABP as marker of ischemia-related injury. In addition to the analysis of plasma and urinary I-FABP levels for early detec-
fication of exercise-induced intestinal injury, intestinal bile-acid binding protein may be used to provide site-specific information on the ileum (134).

In addition, plasma citrulline level before and after exercise may be determined by HPLC as a marker of remaining enterocyte mass (27). Similar to I-FABP, the delta of such plasma levels may be used as a parameter of intestinal integrity. Alternatively, the citrulline generation test has been suggested to assess enterocyte function and may be used in athletes during exercise and postexercise recovery. The citrulline generation test is based on the oral ingestion of a bolus (20 g) of alanine-glutamine and determination of plasma citrulline levels that may change in relation to villous atrophy (104). It remains to be determined whether these tests are useful to assess in exercise-related epithelial injury.

Occult GI blood loss is another feature of exercise-induced intestinal compromise (8, 132), and therefore, FOBT may also be used to determine intestinal integrity during and/or immediately after exercise. The most common commercially available FOBT is the Hemoccult test (Beckman Coulter). A “positive” test result is obtained if the tested stool sample contains over 2–4 ml of blood per 100 g feces, owing to any process that may induce intestinal bleeding, ranging from physical exercise to colorectal carcinoma (128). To avoid false-positive results, it is important that subjects adhere to dietary recommendations such as avoiding intake of red meat, raw peroxide-like fruits and vegetables, or vitamin C supplements, which may generate false-positive outcomes (128). However, it should be noted that the latest FOBTs no longer require such dietary protocols.

Furthermore, among the tests that may be used to assess the impact of exercise on the GI system are tests that aim to assess gut barrier loss. An elegant test to determine the gut barrier function is the sugar-based permeability test, in which the individual drinks a test solution composed of small (<200 kDa) and large (>200 kDa) sugar probes. Preferably, the test drink is ingested during or just after exercise. Urinary and/or plasma concentrations are obtained by use of HPLC-MS (135). The urinary excretion of single sugars and the ratio of large and small sugars can be used to assess GI permeability. The advantage of plasma-based permeability analysis is the ability to detect smaller and transient permeability changes that may not be found on urinary analysis (134). The timing of urinary collections and the selection of the sugar probes depend on the specific area of interest. If small intestinal permeability is to be tested, urine should be collected over 0–3 or 0–5 h, by use of the sugar probes lactulose and l-rhamnose. In contrast, for large intestinal permeability 3–24 or 5–24 h urinary collections are used, in combination with two sugar probes such as sucralose and erythritol that are nondegradable by bacteria in the colon (9) (van Wijck et al., unpublished observations). A classic alternative for intestinal permeability assessment is the use of $^{38}$Cr EDTA (95), but since this technique is dependent on renal function, which may be changed during strenuous exercise, and because of its radioactivity (32), its use for exercise-induced changes is not recommended.

In addition to permeability tests, loss of intestinal barrier function after strenuous exercise may be determined by analysis of circulating endotoxin levels (64). High levels indicate that the GI mucosa was unable to preserve an effective barrier function, resulting in bacterial translocation from the gut lumen to the circulation. Techniques that may be used to determine whether translocation has occurred are the limulus amoebocyte lysate assays, quantifying endotoxin levels in plasma samples, and a test that measures the concentration of endotoxin core antibodies, with reduced antibody levels reflecting antibody consumption by increased circulating endotoxin. Both assays require sampling prior to exercise and postexercise to detect changes in endotoxin or antibody levels, respectively. However, both assays may be influenced by confounding factors such as previous endotoxin exposure, and fungi or polynucleotides that may produce false-positive results (50, 64).

Loss of epithelial integrity in the gut is also reflected by the secretion of inflammatory markers. Although determination of circulatory C-reactive protein, white blood cell counts, and neutrophil products may be useful to estimate the whole body response to exercise, no gut-specific information can be derived from such measurements, since other tissues such as muscles are also known to produce proinflammatory cytokines during exercise (100). Mucosal injury triggers neutrophils and other inflammatory cells to migrate toward the site of injury, where the neutrophils are activated and release their antimicrobial peptides (26, 33, 34, 37). Hence, more specific information on intestinal inflammation may be obtained from quantification of fecal levels of peptides such as calprotectin, a 36-kDa protein with antimicrobial and immunomodulating ability (37, 121, 122).

Changes in the uptake of nutrients, both during strenuous exercise and in the acute recovery period, remain to be clarified. Active sugar uptake during exercise may be analyzed using 3-O-methyl-glucose, e.g., during permeability analysis (94). In addition, stable isotope studies may help to reveal changes in nutrient uptake and possible correlations with exercise-induced intestinal compromise. The latter enable the use of dietary products present in an average everyday diet, thereby providing safe and very relevant information on digestion and absorption of these products (35).

The main features of compromised epithelial integrity during and after exercise are small intestinal injury and increased permeability, which may be determined by analysis of plasma I-FABP levels and permeability analysis. An overview of the available tools to assess intestinal compromise in athletes is presented in Table 1.

Evaluation of the splanchnic response to exercise in asymptomatic athletes. Usually, only symptomatic athletes who are limited by GI symptoms during exercise seek help to identify the origin of their symptoms and consequently may adjust their training and feeding strategies on the basis of recommendations provided by the gastroenterologist. However, others may also benefit from increasing their knowledge of the capacities and limitations of the GI system, especially professional athletes and individuals with compromised cardiovascular and/or pulmonary capacity. Individualized information on GI function may be used to modulate the exercise training program, improve feeding strategy, and prevent adverse effects on GI level. Splanchnic responses to exercise may be different in women compared with men (53). Therefore, individualized information could also be used to design training strategies and recommendations for nutritional strategies specifically for female athletes (53).
Solutions to Prevent Intestinal Compromise During Exercise

Training strategies. Better monitoring of the GI system during training may improve gut function and diminish abdominal discomfort during exercise in symptomatic athletes if training strategies are adapted to GI capacity (123). One of the training adaptations may be to reduce exercise intensity, either temporarily or for a longer period of time depending on the individual’s outcome, and to maintain heart rates below the level at which symptoms generally seem to occur. It will be interesting to find out whether the application of such a strategy in symptomatic athletes will bring elevated I-FABP levels back to physiological levels. If the latter is true, exercise intensity may be adjusted according to the level of I-FABP, and if levels rise above the individual’s predetermined threshold, training intensity may be reduced. It may also be possible to precondition or train the gut to withstand prolonged episodes of physical exercise. If the latter is true, athletes may benefit by gradually increasing exercise intensity during a single training session, creating opportunity to establish an equilibrium that fits the altered physiological situation. Studies that include data on specific adaptations of the gut to training show that gastric emptying and intestinal transit are increased in highly active individuals compared with less active people (18) and that individuals that practice the intake of food and fluids in training sessions experience significantly less GI distress during competition (124), suggesting that adaptation of the GI tract to physical exercise is possible.

Feeding strategies. Optimization of feeding strategies reduces abdominal distress in symptomatic athletes (60, 123). In addition to a well-balanced everyday diet, it is recommended to avoid large meals and the intake of nutritional products that are not easily digested in the 2–3 h prior to strenuous physical exercise, such as foods with a high fiber, protein, or fat content (63, 110). The reason for this may be that postprandially splanchnic blood flow increases significantly (141). The ingestion of these specific foods is associated with larger decreases in splanchnic vascular resistance compared with easily digestible foods (66, 87), which may result in more pronounced splanchnic vasodilatation and increased splanchnic flow. In fact, the ingestion of a liquid test meal [390 kcal, 21.6 g protein, 15.4 g fat, 41.3 g carbohydrate (CHO)] during the first 10 min of a 15-min exercise bout on a treadmill at 20% incline was reported to increase splanchnic blood flow (109), suggesting that oral intake may overrule the exercise-induced decrease in splanchnic circulation. However, the moderate intensity level in this study may explain why exercise-induced hypoperfusion did not overrule the increase in blood flow induced by this large food bolus. Future studies are needed to clarify whether the ingestion of food also interferes with exercise-induced vasoconstriction at higher intensity levels and whether a mismatch in blood flow gives rise to abdominal distress. Currently, athletes are recommended to use small amounts of easily digestible foods in the hours before and during exercise while maintaining euhydration (29). During exercise, CHO ingestion is recommended, since it improves endurance capacity and performance (60, 61). In highly active athletes, the combination of glucose and fructose may be beneficial since it resulted in higher CHO oxidation rates than the ingestion of a single CHO (62), attenuating the depletion of endogenous energy stores during exercise and stimulating repletion of these stores during acute postexercise recovery. However, care should be taken to avoid the intake of hyperosmolar fluids, since these have been associated with abdominal distress and hyperosmolar diarrhea during exercise (110).

Although the intake of high-fat products is not recommended in the 2–3 h prior to and during strenuous physical exercise, lipid-enriched nutrition has been described to attenuate intestinal inflammation, bacterial translocation, and intestinal injury following intestinal hypoperfusion (28). These effects have been assigned to the activation of the autonomic nervous system that increases the splanchnic blood flow via activation of cholecystokinin receptors (28, 117). In line with this, lipid-enriched nutrition ingested in the postexercise period may improve GI function and reduce the flulike condition associated with endotoxemia after strenuous physical exercise by improving postexercise splanchnic flow.

Nutritional strategies prior to, during, and after exercise should always be tailored to the individual athlete, and trial and error during training sessions will yield the most effective strategy to be used during competition (61). Oral intake should be practiced in training since athletes unaccustomed to ingest fluids or foods during exercise experience significantly more GI complaints upon such intake during a competitive run (124). In addition, the athlete’s personal preference for food and fluids should not be neglected since it is a strong determinant for the athlete’s tolerance to nutrition during exercise.

Strategies to improve splanchnic perfusion. Strenuous physical exercise is typically associated with significant splanchnic hypoperfusion, which can be severe enough to impair the structural and functional integrity of the GI tract. In case of significant vascular abnormalities or stenosis due to CACS, revascularization treatment may be required to improve splanchnic perfusion (81). The majority of individuals with exercise-induced splanchnic hypoperfusion will not need revascularization. Numerous less invasive measures are available to improve splanchnic hypoperfusion in the absence of vascular abnormalities. Adequate hydration contributes to splanchnic perfusion maintenance by avoiding systemic hypovolemia. Since there is considerable variability in fluid loss between individuals, customized fluid replacement is recommended to maintain adequate hydration during exercise (114). In addition, specific agents may be used to enhance splanchnic perfusion and improve GI homeostasis during exercise. As stated previously, the splanchnic microvasculature plays a fundamental role in GI homeostasis and provides an additional target for enhancement of splanchnic flow. One of the important endogenous players that significantly contribute to the vasodilator responses within the intestinal microcirculation is nitric oxide (NO) (52). Interventions that increase the intestinal availability of NO may improve splanchnic perfusion.

Normally, intestinal microvessels vasodilate in response to acetylcholine via an NO-dependent mechanism (52, 137). NO synthase (NOS) oxidizes an N atom of L-arginine to produce L-citrulline and NO. To enable this arginine oxidation, NOS requires the cosubstrate NADPH (nicotinamide adenine dinucleotide phosphate-oxidase), O2, and a number of cofactors (78). Stimulation via acetylcholine increases the cytosolic calcium levels and activates endothelial NOS (eNOS), leading to NO production (78). Of the three identified NOS isoforms, eNOS is reported to be responsible for vascular regulation, particularly in the splanchnic area (78). Regulation of eNOS...
occurs via guanylyl cyclases (GC), which are transmembrane receptors with an intracellular domain that becomes enzymatically active upon stimulation. The manner of activation is dependent on the type of GC, and activation via NO is one of the possibilities. NO-mediated vasodilatation occurs when the binding of NO to GC induces structural changes in GC. cGMP production in endothelial cells increases, resulting in intracellular signaling to initiate relaxation of the vascular smooth muscles, promoting local vasodilatation (78).

There are a number of options to upregulate intestinal NO availability that may be of value for athletes experiencing abdominal distress associated with splanchnic hypoperfusion. The two experimental interventions that will be discussed in this review are NOS-dependent (glutamine-arginine-citrulline) and NOS-independent (nitrate-nitrite) supplementation. An overview of these potentially useful strategies is given in Table 2. It is important to bear in mind that, although these interventions may improve splanchnic perfusion, it is possible that this will lead to hypoperfusion of other tissues such as the active muscles, which may deteriorate athletic performance. Additionally, since most of these strategies are still in the experimental phase, it remains to be determined whether the use of the described supplements by athletes is safe. Future studies are warranted to clarify these issues.

Glutamine, arginine, and citrulline supplementation. Glutamine plays an important role in the arginine-NO pathway, since it can be converted in the intestine into citrulline, the precursor of arginine (130). Arginine is the sole natural precursor for the synthesis of NO (55) and can be converted to NO and citrulline in the intestine or metabolized in the liver into urea and ornithine by arginase. Citrulline is synthesized and released into the circulation, from which it is taken up by the kidneys and converted back into arginine for production of NO and other amino acids (84). The supplementation of glutamine in patients resulted in enhanced citrulline uptake and higher arginine levels (56, 72). However, the outcome and positive effects on arginine production depend on the route of administration and the molecular form of the supplemented glutamine (139). Parenteral glutamine supplementation resulted in higher plasma arginine levels compared with enteral supplementation (72). Unfortunately, nutritional enrichment with glutamine is complicated because of the relative aqueous instability (139). A promising alternative is supplementation of the dipeptide form, alanyl-glutamine, a stable alternative in aqueous solutions with the same positive effects on arginine plasma availability (57). Glutamine supplementation showed no adverse events even in high dosage (93), making the latter a promising alternative to enhance the arginine-NO production in the splanchnic vascular bed during abdominal distress associated with splanchnic hypoperfusion.

To improve arginine availability for NO synthesis, oral arginine supplementation was suggested, but controversy exists on the results of arginine supplementation (12). Arginine supplementation has been described to result in elevated NO synthesis in the hepatosplanchnic area in human and animal studies supplementation (12, 19, 106). Blood flow in the porcine portal vein increased (106), whereas systemic cardiovascular variables such as mean arterial pressure and cardiac index did not deteriorate (73, 106). In fact, a single 500-ml drink containing 6 g of arginine significantly reduced the O2 cost of the athletes during moderate-intensity exercise and enhances high-intensity exercise tolerance (3), suggesting improved cardiopulmonary function. On the other hand, inability to increase porcine mesenteric blood flow by enteral supplementation of arginine has also been reported (108). Furthermore, high dosages of arginine have been reported to cause osmotic diarrhea during exercise (46). Therefore, it can be concluded that the effect of arginine supplementation on the splanchnic vascular bed in humans, especially in athletes, remains to be clarified.

Citrulline, derived from glutamine conversion, can also be converted to arginine and used for NO synthesis after entering the systemic circulation. Furthermore, it is not subjected to extensive hepatic metabolization like arginine,
making it a promising exogenous source of NO, possibly enabling local vasodilation and improved splanchnic blood flow. Comparing oral citrulline to oral arginine supplementation, oral citrulline intake is more efficient in increasing body arginine levels (96) and has a higher bioavailability (85). Furthermore, high doses of citrulline do not cause osmotic diarrhea, whereas arginine does (46, 75). Citrulline has been demonstrated to increase arginine availability for NO production (96), but whether the latter will improve splanchnic perfusion and reduce GI distress in athletes remains to be clarified.

**Nitrate and nitrite supplementation.** An alternative, NOS-independent pathway to increase NO availability for vasodilation is to generate NO via nitrate and nitrite, which involves the reduction of ingested nitrate to nitrite and NO, particularly in acidic or hypoxic conditions. Nitrate is normally ingested via food and drinking water and via the ingestion of mainly green leafy vegetables such as lettuce, spinach, as well as beetroot (74, 136). After ingestion, much of the nitrate is reduced to nitrite by commensal bacteria in the saliva of the oral cavity, whereas the remaining nitrate enters the enterosalivary pathway after absorption in the upper GI tract. The nitrite formed by the bacteria is reduced to NO upon entering the acidic environment of the stomach, a process that is enhanced by the presence of vitamin C and polyphenols (75). A small part of the ingested nitrate and nitrite is absorbed in the small intestine and converted to NO in blood and tissue under physiological acidic and hypoxic conditions (75). The potency of NO to produce vasodilation is enhanced under conditions of hypoxia or metabolic stress such as strenuous physical exercise (75, 83). Nitrate and nitrite should preferably be supplemented per os, for example as a vegetable juice, since such a vegetable juice also contains vitamin C necessary for the reduction of nitrite to NO and, maybe even more important, it is the physiological route of nutrient ingestion. Animal studies have demonstrated that both nitrate and nitrite, administered orally and endoluminally, respectively, increased gastric mucosal blood flow (105). Supplementation of nitrate and nitrite was also demonstrated to act cytoprotectively and decrease formation of reactive oxygen species (116). And recently, dietary nitrate supplementation (≈8 to 11 mmol nitrate in beetroot juice as a single dose or for 6 consecutive days) enhanced tolerance to moderate to high-intensity exercise (20, 136) and improved time-trial performance (20). All together, these data suggest that nitrate ingestion during or immediately after exercise can stimulate splanchnic perfusion, which may reduce intestinal injury and prevent loss of intestinal barrier function triggered by hypoperfusion during exercise. As such, intake of dietary nitrate could prevent exercise-related GI problems.

**Avoidance of medication that may compromise the GI system.** It is of utmost importance to increase the awareness of athletes and trainers toward the deleterious effects of drugs that may compromise the GI system. High numbers of athletes have been reported to use analgesics to relieve existing or anticipated pain (45). The use of specific analgesics may paradoxically aggravate GI distress and cause significant small intestinal injury especially during exercise (van Wijck et al., unpublished data). The use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a three- to fivefold increased risk of upper gastrointestinal complications, mucosal bleeding, or perforation compared with no medication (39). Data indicate that these NSAID-induced complications are the result of two detrimental mechanisms: inhibition of cyclooxygenase (COX)-1 reduces blood flow in the upper GI region, whereas inhibition of COX-2 promotes adherence of neutrophils to the vascular endothelium (40). Furthermore, NSAIDs may interfere with NO production and inhibit the formation of nitrate via regulation of the NF-κB pathway (78), thereby further compromising GI homeostasis during exercise-induced hypoperfusion. Last of all, studies have demonstrated that if active (chronic) intestinal inflammation is present, NSAID-induced COX inhibition may result in vasoconstriction (6, 52). We consider that the latter in combination with exercise-induced splanchnic hypoperfusion may account for the exacerbation of intestinal injury in athletes using NSAIDs.

**Future Perspectives**

Although our knowledge on the role of GI function in relation to exercise has greatly improved over the past decades, future studies are warranted. One of the main issues to be clarified is the significance of exercise-induced hypoperfusion and GI integrity loss for digestive and absorptive processes. Consequently, the tools described previously should be further developed to enable easy, noninvasive monitoring of the intestinal response to exercise by athletes.

Future studies are needed to reveal whether it is feasible to obtain individualized information on GI physiology during and upon cessation of exercise and to use this information to improve training and nutritional strategies to match cardiovascular, musculoskeletal and GI capacities, without significantly compromising of any of these systems. Such individualized information may help symptomatic athletes to increase understanding of the nature of their symptoms, and may also assist professional athletes and patients with compromised cardiopulmonary function to improve athletic performance.

Despite the large number of GI symptoms known to occur during exercise, athletes and trainers pay little attention to improving GI function. Future studies may provide clarification on the potential preventative and therapeutic interventions that may be used for this purpose.

**Conclusions**

The extensive plasticity of the gut is generally sufficient to meet the requirements imposed by strenuous physical exercise. However, redistribution of blood away from the splanchnic bed toward active muscle tissue, the cardiopulmonary system, and skin can strongly affect the GI system negatively. Exercise-induced splanchnic hypoperfusion and the subsequent loss of epithelial integrity may lead to the onset of disturbing GI symptoms. However, even in the absence of such symptoms, athletes may want to consider adjusting training and nutritional strategies in terms of the type, amount, and timing, to meet nutritional needs while taking into account existing GI compromise caused by prolonged exercise-induced splanchnic hypoperfusion.


REFERENCES


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