# Effect of running intensity on intestinal permeability

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**Pals, Kay L., Ray-Tai Chang, Alan J. Ryan, and Carl V. Gisolfi.** Effect of running intensity on intestinal permeability. *J. Appl. Physiol.* 82(2): 571–576, 1997.—Enhanced intestinal permeability has been associated with gastrointestinal disorders in long-distance runners. The primary purpose of this study was to evaluate the effect of running intensity on small intestinal permeability by using the lactulose and rhamnose differential urinary excretion test. Secondary purposes included assessing the relationship between small intestinal permeability and gastrointestinal symptoms and evaluating gastric damage by using sucrose as a probe. Six healthy volunteers [5 men, 1 woman; age = 30 ± 2 yr; peak $O_2$ uptake ($\dot{V}O_{2peak}$) = 57.7 ± 2.1 $ml \cdot kg^{-1} \cdot min^{-1}$] rested or performed treadmill exercise at 40, 60, or 80% $\dot{V}O_{2peak}$ for 60 min in a moderate environment (22°C, 50% relative humidity). At 30 min into rest or exercise, the permeability test solution (5 g sucrose, 5 g lactulose, 2 g rhamnose in 50 ml water; ~800 mosM) was ingested. Urinary excretion rates (6 h) of the lactulose-to-rhamnose ratio were used to assess small intestinal permeability, and concentrations of each probe were determined by using high-performance liquid chromatography. Running at 80% $\dot{V}O_{2peak}$ increased ($P < 0.05$) small intestinal permeability compared with rest, 40, and 60% $\dot{V}O_{2peak}$ with mean values expressed as percent recovery of ingested dose of 0.107 ± 0.021 (SE), 0.048 ± 0.009, 0.056 ± 0.005, and 0.064 ± 0.010%, respectively. Increases in small intestinal permeability did not result in a higher prevalence of gastrointestinal symptoms, and urinary recovery of sucrose did not reflect increased gastric permeability. The significance and mechanisms involved in increased small intestinal permeability after high-intensity running merit further investigation.

exercise; lactulose; rhamnose; human

GASTROINTESTINAL SYMPTOMS including cramps, diarrhea, bloating, nausea, and bleeding have been commonly reported among long-distance runners (2, 6, 20). However, the mechanisms responsible for the development of gastrointestinal dysfunction during and after exercise have not been determined. These symptoms have been associated with alterations in small intestinal permeability (17, 20) and reduced blood flow to the gut during exercise (2, 6, 20). In addition to its role in digestion, the small intestinal epithelia also acts as a barrier between the external and internal environments (3, 11, 18, 23, 26, 27). Penetration of antigenic, carcinogenic, or toxic compounds from the intestinal lumen into the interstitial fluid en route to the systemic circulation is deterred by this barrier (3, 11, 18, 23, 26, 27). Compromised barrier function may produce an inflammatory response and initiate a cytokine cascade that could contribute to gastrointestinal distress during and after running (17, 20).

Substances can cross the epithelium by either transcellular or paracellular transport (11). Transcellular transport involves passage of a substance through the apical membrane, cytoplasm, and the basolateral membrane of an enterocyte. Diffusion, active transport, and endocytosis use transcellular transport. Paracellular transport involves movement of larger molecules (molecular mass >180 Da) through tight junctions into the interstitial space (11). From the interstitial fluid between the enterocytes, these molecules can then enter the systemic circulation. The tight junction functions both to maintain cell polarization (9) and to prevent the passage of substances through the intestinal barrier into the interstitial fluid (9, 11). When tight junctions become relaxed because of disease, osmolar stress, exercise (11), alcohol ingestion (18), or thermal injury (1, 10, 18, 26), permeability to larger molecules is increased.

Urinary excretion of orally administrated permeability probes has been used to assess abnormalities of small intestinal permeability in patients with cystic fibrosis (14), celiac disease (8, 28), and Crohn's disease (12) and after high-intensity running (17, 20). In addition, permeability probes have been used in animal studies to assess changes in small intestinal epithelia after acute inflammation and anaphylaxis (22). Suitable probes penetrate healthy epithelia only to a limited extent, are water soluble, are not metabolized or degraded in the small intestine, and are quantitatively excreted in the urine (11). A solution containing a disaccharide and a monosaccharide, such as lactulose and rhamnose, respectively, has been used as an effective orally administrated probe to evaluate small intestinal permeability (4, 8, 12, 14, 27). The underlying assumption in using this probe is that rhamnose will cross the small intestinal epithelia via a transcellular route, whereas the larger lactulose molecule will transverse the epithelia via a paracellular route through tight junctions (4, 15), although some debate exists on this issue (27). Lactulose is degraded in the large intestine and is not an effective probe to assess changes in large intestinal permeability. By expressing the urinary excretion rate of the two sugars as a ratio (lactulose/rhamnose), factors altering urinary excretion, including gastric emptying, intestinal transit time, and renal function, will affect both sugars equally (4). An increase in the lactulose-to-rhamnose ratio expressed as percent recovery of the ingested dose is interpreted as an increase in small intestinal permeability (4).

Another disaccharide probe, sucrose, is suggested to be an indicator of gastric damage (16, 25). Because sucrose is hydrolyzed in the small intestine by sucrase, alterations in its rate of urinary excretion will reflect changes in permeability that occur in the stomach. Urinary excretion of sucrose is also expressed as the percentage of ingested dose recovered.

The primary purpose of this study was to evaluate the effect of running intensity on small intestinal permeability by using the lactulose/rhamnose differen-

 

tial urinary excretion test. Secondary purposes included examining the relationship between small intestinal permeability and gastrointestinal symptoms and the effect of running intensity on urinary recovery of sucrose. We hypothesized that high-intensity running would *1*) increase the lactulose-to-rhamnose urinary ratio and *2*) increase the urinary excretion of sucrose. We further hypothesized that increased intestinal permeability with exercise would correlate with gastrointestinal symptoms.

## METHODS

Six healthy physically active volunteers (5 men, 1 woman; age 30 ± 2 yr) served as subjects for the experiment. None of the subjects had chronic gastrointestinal disorders. Each subject submitted a signed informed consent, and all procedures were approved by the University Human Use Committee. All subjects refrained from alcohol and nonsteroidal anti-inflammatory drugs for ≥48 h before the experiment. Peak $O_2$ uptake ($\dot{V}O_{2peak}$) for each subject was determined on a treadmill ~1 wk before the experiment.

Each subject reported to the laboratory on four separate occasions separated by ≥2 days. Small intestinal permeability was determined for each subject during 60 min of treadmill running (0% grade) at a speed eliciting 40, 60, or 80% $\dot{V}O_{2peak}$ and also during 60 min of rest. Trials were performed in an environmental chamber maintained at 22°C and 50% relative humidity. A balanced experimental design was implemented to determine the order of the four trials.

Experiments were conducted in the morning after an overnight fast. After arrival at the laboratory, each subject provided a urine sample and recorded a rectal temperature and nude body weight. A questionnaire was completed to determine the level of gastrointestinal symptoms experienced by the subject. The questionnaire consisted of a 100-mm horizontal line in which subjects rated their perception of heartburn, nausea, abdominal cramps, urge to have a bowel movement, and the presence of a side ache with a mark on the line. A mark at 0 mm reflected the absence of that symptom, and a mark at 100 mm indicated severe discomfort attributed to that symptom. The presence of diarrhea and vomiting was also noted via a written response.

Subsequent to these preliminary procedures, the subject ingested water (6 ml/kg body wt) before rest or running. A heart rate monitor (Polar Vantage) was attached to the chest at the level of the sternus, and the subject began the 60-min protocol. During exercise, heart rate, rate of perceived exertion (Borg scale 6–20) (5), and thermal sensation (range 1–7) (7) were recorded every 15 min. $O_2$ uptake was recorded for ~5 min during the first 10 min of running to ensure the correct exercise intensity.

After 30 min of rest or exercise, the permeability test solution (5 g sucrose, 5 g lactulose, and 2 g rhamnose in 50 ml water, ~800 mosM) was ingested. We waited 30 min to ensure transit of the test solution when increased intestinal permeability was most likely to occur. Immediately after the 60-min protocol, rectal temperature and nude body weight were recorded. Water was ingested (ml) to equal weight lost (g). A second questionnaire with an identical format to the first was completed to determine the level of gastrointestinal symptoms immediately after running or rest.

Hourly urine samples were obtained for 5 h beginning 30 min after each trial. Urine volume was recorded, and four 1-ml aliquots containing thimerasol were frozen for subsequent analysis. Water (3 ml/kg body wt) was ingested hourly to facilitate urine production. Subjects were allowed to eat 2 h after ingestion of the test solution and were instructed to avoid foods with a high sucrose content. A third questionnaire was submitted after the fifth hour of urine collection.

Urine concentrations of sucrose, lactulose, and rhamnose were determined by high-performance liquid chromatography (model DX-50, Dionex). Urinary excretion rates of the lactulose-to-rhamnose ratio expressed as the percent recovery of ingested dose were used to assess small intestinal permeability. The urinary excretion rate of sucrose, also expressed as percent recovery of ingested dose, was used to assess gastric permeability. Significant differences ($P < 0.05$) were calculated by using a one-way analysis of variance and Fischer's least significant differences test. Values are presented as means ± SE.

## RESULTS

$\dot{V}O_{2peak}$ for the six subjects was 57 ± 2.12 ml·kg$^{-1}$·min$^{-1}$. Percent $\dot{V}O_{2peak}$ values during the three exercise trials were 40.0 ± 0.85, 62.4 ± 1.02, and 78.3 ± 1.13% $\dot{V}O_{2peak}$. The physiological responses to exercise are presented in Table 1. Final heart rate and rectal temperature showed graded increases with running intensity. Rate of perceived exertion averaged 10.7 ± 1.12, 13.0 ± 0.52, and 17.0 ± 0.55 running at 40, 60, and 80% $\dot{V}O_{2peak}$, respectively. Corresponding values for thermal sensation were 5.2 ± 0.49, 5.3 ± 0.49, and 6.6 ± 0.40. Mean sweat rates during the 60-min runs were 0.76 ± 0.04, 1.10 ± 0.31, and 1.60 ± 0.05 l/h and resulted in corresponding weight losses of 0.61 ± 0.04, 1.16 ± 0.06, and 1.87 ± 0.05%, respectively.

There were no significant differences in the volume of urine produced in each trial (Table 1). Percent lactulose recovered after running at 80% $\dot{V}O_{2peak}$ was significantly higher than the percent recovered at rest, with values of 0.28 ± 0.056, 0.445 ± 0.080, 0.381 ± 0.077, and 0.564 ± 0.105%, respectively, for rest and the increasing intensities of running (Fig. 1). There were no differences in percent rhamnose recovered in each of the four trials with values of 6.50 ± 1.379, 8.277 ± 1.391, 7.078 ± 1.795, and 6.723 ± 1.554%, respectively (Fig. 2). Individual results of the lactulose-to-rhamnose ratios are presented in Table 2. The mean urinary excretion ratio of lactulose to rhamnose was significantly elevated at 80% compared with the ratios at rest and 40 and 60% $\dot{V}O_{2peak}$ with values of 0.107 ± 0.021, 0.048 ± 0.009, 0.056 ± 0.005, and 0.064 ± 0.010%, respectively (Fig. 3). There was a significant ($P = 0.0263$) correlation ($r = 0.48$) between rectal temperature and the lactulose-to-rhamnose ratio (Fig. 4). The values for percent sucrose recovered were 0.301 ± 0.159, 0.369 ± 0.139, 0.264 ± 0.155, and 0.803 ±

Table 1. *Physiological responses*

| Percent $\dot{V}O_{2peak}$ | Actual Percent $\dot{V}O_{2peak}$ | Terminal HR, beats/min | Final Temperature, °C | Urine Volume, liters |
|---|---|---|---|---|
| Rest | | 67 ± 2 | 36.9 ± 0.21 | 1.46 ± 0.32 |
| 40 | 40.0 ± 0.85* | 115 ± 5* | 38.0 ± 0.11* | 1.48 ± 0.21 |
| 60 | 62.4 ± 1.02*† | 150 ± 4*† | 38.7 ± 0.11*† | 1.18 ± 0.25 |
| 80 | 78.3 ± 1.13*†‡ | 180 ± 5*†‡ | 39.6 ± 0.15*†‡ | 1.40 ± 0.18 |

Values are means ± SE. $\dot{V}O_{2peak}$, peak $O_2$ uptake; HR, heart rate. Significantly different at $P < 0.05$ compared with values at: *rest; †40% $\dot{V}O_{2peak}$; ‡60% $\dot{V}O_{2peak}$.

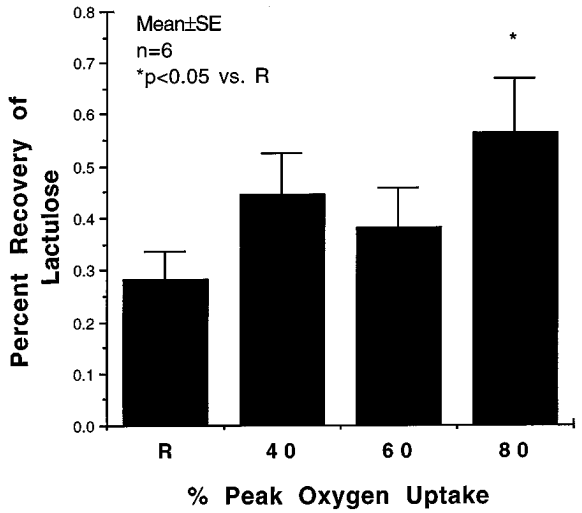


Fig. 1. Urinary excretion (6 h) of lactulose expressed as percent recovery of ingested dose after 60 min of rest (R) and running at 40%, 60, and 80% peak $O_2$ uptake ($\dot{V}O_{2peak}$). *n*, No. of subjects. *Significantly different compared with R, $P < 0.05$.

0.451% (Fig. 5) for rest and running at 40, 60, and 80% $\dot{V}O_{2peak}$, demonstrating no significant differences among trials.

Results from the questionnaire indicated that none of the subjects experienced heartburn, nausea, vomiting, or diarrhea during the four trials. Only one subject reported abdominal cramps (78 mm) and a side ache (82 mm) during exercise at 80% $\dot{V}O_{2peak}$.

## DISCUSSION

This is the first study to show that small intestinal permeability is increased after 60 min of treadmill running at 80% $\dot{V}O_{2peak}$ in a moderate environment while not being elevated after low-intensity running. The urinary excretion ratio of lactulose to rhamnose after running at 80% $\dot{V}O_{2peak}$, expressed as a percentage of the ingested dose recovered, was significantly different from rest and running at 40 and 60% $\dot{V}O_{2peak}$. Exercise intensity (50 vs. 80% $\dot{V}O_{2peak}$) also affects the magnitude of increases in cortisol, catecholamine, and lactate concentrations after exercise (19) as well as the degree of renal and splanchnic vasoconstriction (13). Because the lactulose-to-rhamnose ratio was not elevated at lower intensities of running, there may be a threshold effect of intensity on small intestinal permeability. Our observation of increased small intestinal permeability after high-intensity running should be included in the many physiological responses to exercise that are intensity dependent. The magnitude of this permeability change may be underestimated because the time course of the measurement only evaluated the last 30 min of exercise and the first 5 h of recovery.

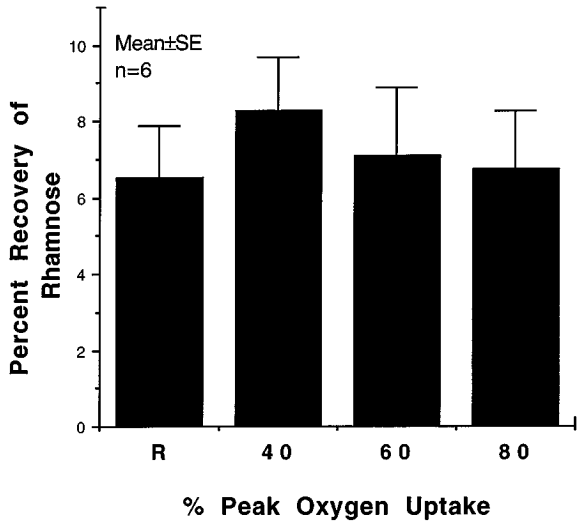


Fig. 2. Urinary excretion (6 h) of rhamnose expressed as percent recovery of ingested dose after 60 min of R and running at 40, 60, and 80% $\dot{V}O_{2peak}$.

Other studies have previously reported an increase in intestinal permeability after high-intensity running but did not examine this relationship at lower intensities. Moses et al. (17) demonstrated an increase in intestinal permeability after 90-min of treadmill running alternating 15 min at 60 and 85% maximal $O_2$ uptake with 30-s sprints. Polyethylene glycol 400 was given as a probe immediately before running. Oktedalen et al. (20) also showed intestinal permeability to be elevated after the completion of a half or full marathon. In their study, chromium-labeled EDTA was ingested immediately after completion of the run. The present study differs from previously published work in that it emphasized the relationship between the relative intensity of running to small intestinal permeability and used the lactulose-to-rhamnose ratio to assess small intestinal permeability.

The lactulose-to-rhamnose ratio has been widely used to assess small intestinal permeability in patients with cystic fibrosis (14), Crohn's disease (12), and celiac disease (8). It has been demonstrated that lactulose excretion correlates with excretion of chromium-labeled EDTA (15), the probe successfully used to show increased intestinal permeability during a running protocol (20). The inclusion of rhamnose allows for greater discriminatory power of the probe, since factors that affect transit time and excretion will affect both sugars equally (27). It is, therefore, appropriate to use the lactulose-to-rhamnose ratio during a running protocol. The use of polyethylene glycol 400 to assess changes in intestinal permeability has encountered some criticism because of its low rate of recovery after intravenous adminstration and its variability in urinary recovery rates (3).

The premise underlying the use of the lactulose-to-rhamnose ratio to assess small intestinal permeability is the different permeation routes of the two sugars, although there is still ongoing debate on the permeation routes (27). Rhamnose, a molecule with a molecular mass of 164 Da and a diameter of 8.3 Å (11), is proposed to transverse intestinal epithelial cells via small electroneutral pores in the apical membrane and subsequently exits the cell through pores in the basolateral membrane (27). Lactulose, a larger molecule with a molecular mass of 342 Da (27) and a diameter of 9.5 Å

Table 2. *Individual results: percent lactulose/rhamnose recovered after 60-min rest and running at 40, 60, and 80% $\dot{V}O_{2peak}$*

| | | Percent $\dot{V}O_{2peak}$ | | |
|---|---|---|---|---|
| Subject No. | Rest | 40 | 60 | 80 |
| *1* | 0.045 | 0.074 | 0.064 | 0.051 |
| *2* | 0.041 | 0.041 | 0.069 | 0.085 |
| *3* | 0.078 | 0.047 | 0.046 | 0.065 |
| *4* | 0.022 | 0.047 | 0.026 | 0.100 |
| *5* | 0.069 | 0.060 | 0.097 | 0.168 |
| *6* | 0.032 | 0.064 | 0.082 | 0.170 |
| Mean ± SE | 0.048 ± 0.009 | 0.056 ± 0.005 | 0.064 ± 0.010 | 0.107 ± 0.021* |

* Significantly different compared with values at 40 and 60% $\dot{V}O_{2peak}$, $P < 0.05$.

(11), is proposed to transverse intestinal epithelia via a paracellular route (27). Increases in the lactulose-to-rhamnose ratio are interpreted as increases in paracellular transport through "leaky" tight junctions, suggesting compromised function of the small intestine as a barrier. In human and animal studies, the barrier function of the gastrointestinal tract is altered after thermal injury, hemorrhage, sepsis, and immunosuppression (18). The leakiness of tight junctions is increased by cytokines, osmotic stress, $O_2$ free radicals (27), and, as shown in the present study, by high-intensity running exercise.

The urinary excretion of the ingested probes were similar to those reported in the literature. Mean lactulose-to-rhamnose ratio at rest (0.048 ± 0.009%) was similar to the control lactulose-to-rhamnose ratio reported by Leclercq-Foucart et al. (0.038 ± 0.003%; Ref. 14), Howden et al. (0.029 ± 0.012%; Ref. 12), and Greco et al. (0.029%; Ref. 8). Our lactulose-to-rhamnose ratio after running at 80% $\dot{V}O_{2peak}$ (0.107 ± 0.021%), indicative of enhanced small intestinal permeability, is comparable to the increases in this ratio reported in celiac disease (0.106%; Ref. 8), Crohn's disease (0.061 ± 0.115%; Ref. 12), and cystic fibrosis (0.16 ± 0.022%; Ref. 14). Therefore, running at high intensity results in a lactulose-to-rhamnose ratio similar to that observed in patients with conditions associated with increased small intestinal permeability and damage.

The urinary recovery of rhamnose did not differ among the four trials. The rhamnose excretion rate observed in the present study (6.50 ± 1.379%) is comparable to results previously published (8, 12, 14) and near the standard ~10% recovery rate in 6 h reported by Travies and Menzies (27) and Hollander (11). One limiting factor in the use of rhamnose as a permeability probe is that only 72–74% is recovered in 24-h urine sampling after intravenous administration (4, 15).

The urinary recovery of lactulose was significantly elevated from rest after exercise at 80% $\dot{V}O_{2peak}$, indicating changes in the barrier function of the small intestinal epithelia to larger molecules. The lactulose recovered at rest in the present study (0.28 ± 0.056%) was similar to results from previous control studies (0.28 ± 0.02%; Ref. 14; and 0.31 ± 0.26%; Ref. 12). After exercise at 80% $\dot{V}O_{2peak}$, the percent lactulose recovery (0.564 ± 0.105%) exceeded the values of lactulose recovered in patients with Crohn's disease (0.45 ± 0.56%; Ref. 12) and celiac disease (0.43%; Ref. 8).

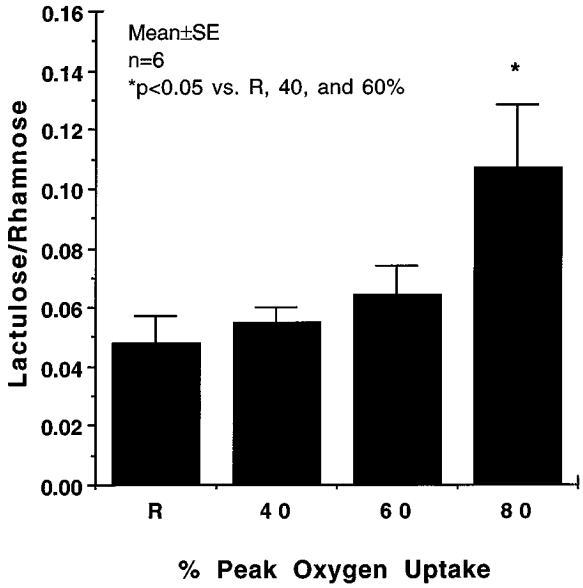


Fig. 3. Urinary lactulose-to-rhamnose ratio after 60 min of R and running at 40, 60, and 80% $\dot{V}O_{2peak}$. * Significantly different compared with R and running at 40 and 60% $\dot{V}O_{2peak}$, $P < 0.05$.

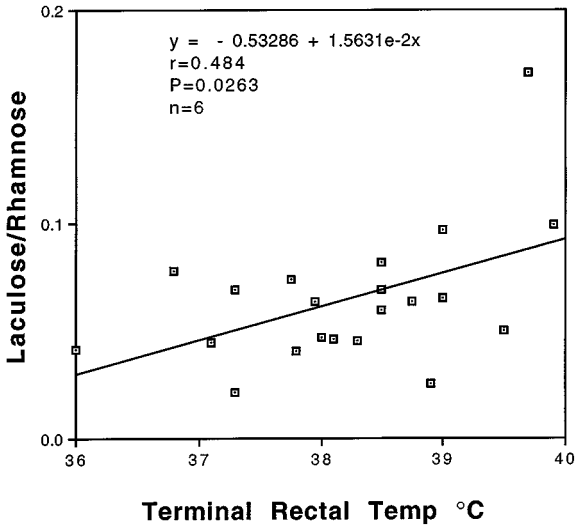


Fig. 4. Correlation between urinary lactulose-to-rhamnose ratio and final rectal temperature.

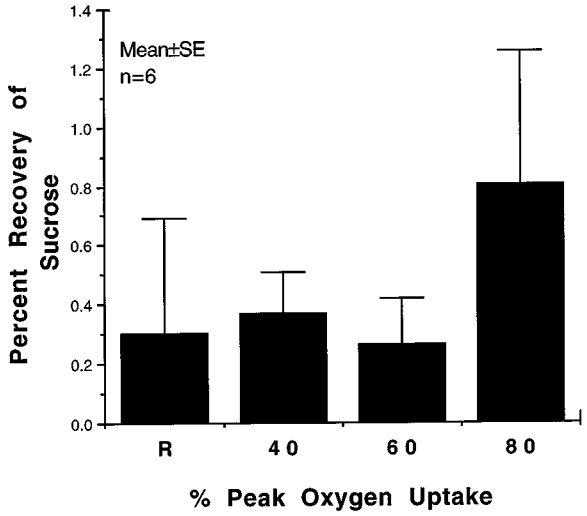


Fig. 5. Urinary excretion (6 h) of sucrose expressed as percent recovery of ingested dose after 60 min of R and running at 40, 60, and 80% $\dot{V}O_{2peak}$.

Urinary excretion of lactulose after intravenous administration results in over 90% recovery in 24 h (15), validating its use as an effective probe.

The mechanisms and significance of increased small intestinal permeability are unclear. It has been proposed that increased leakiness of tight junctions allows macromolecules to cross the intestinal epithelia (3, 22–24). The passage of luminal aggressive agents, including bile, pancreatic secretion, and bacteria from the small intestine, across tight junction may stimulate neutrophil migration to the localized area (3, 22, 24). The activated neutrophils could generate a local immune response involving the generation of $O_2$ free radicals and lysozomal enzymes, resulting in more damage to the small intestinal epithelia (2). This sequence of events could contribute to the potentiation of increased small intestinal permeability and the development of gastrointestinal symptoms.

Several studies have investigated the compromised barrier function of the small intestinal epithelia and its significance after thermal injury (1, 10, 18, 26). It has been suggested that translocation of endotoxin from the gut into the systemic circulation due to breakdown of the intestinal epithelia plays a key role in the development of sepsis (1, 10, 18) and multiorgan failure (1) after severe burns. The pathophysiological effects of endotoxin are mediated by cytokines (10) initiating a response known as systemic inflammatory response syndrome (1). Whether this sequence of events can also occur in humans during exercise, specifically when core temperatures are elevated to dangerous levels, remains to be determined.

Another factor that must be considered when examining the mechanisms and significance of increased small intestinal permeability running at 80% $\dot{V}O_{2peak}$ is splanchnic vasoconstriction. In porcine models of thermal injury, splanchnic ischemia has been linked to bacterial and endotoxin translocation from the gut into the circulation (1, 26). Baron et al. (1) suggest that reduced mesenteric blood flow generates $O_2$ free radicals. Mesenteric hypoperfusion, accumulation of hypoxanthine during ischemia, and the conversion of xanthine dehydrogenase to xanthine oxidase contributes to the response. When blood flow is restored, xanthine oxidase catalyzes the production of reactive $O_2$ species from molecular $O_2$ and hypoxanthine. The result is a local and systemic inflammatory response often observed in burn patients. Consequently, the increase of small intestinal permeability after high-intensity running that markedly reduces splanchnic blood flow (21) has the potential for adverse effects.

As briefly referred to earlier, a possible link between running intensity and increased small intestinal permeability may be the elevation in core body temperature observed during high-intensity running. The rise in rectal temperature in the present study accounted for ~34% of the variance in the lactulose-to-rhamnose ratio. This elevation in core temperature coupled with gut vasoconstriction may be factors that mediate the increase in small intestinal permeability, since these factors are also associated with thermal injury (1).

In the present study, no significant differences were observed in the percent sucrose recovered at each intensity of running. Sucrose has been suggested as a marker for gastroduodenal permeability (16, 25). Previously published studies demonstrate an increase in urinary sucrose excretion after oral administration in patients with severe gastritis and gastric ulcers (25). A fourfold increase in urinary sucrose recovery after gastric damage induced by acetylsalicylic acid and alcohol has also been reported (16). In these studies, 100 g of orally ingested sucrose were used as a probe, whereas in our study only 5 g were ingested. This difference in dose and our low experimental power ($n$ = 6) may have limited our ability to assess gastric damage. However, according to our results, we cannot definitively conclude that gastric damage occurred due to the large variability in this measurement.

The results from the gastrointestinal symptom questionnaire indicated that increases in small intestinal permeability were not related to the severity of gastrointestinal symptoms during or after running. We suggest from these results that increased small intestinal permeability precedes the development of gastrointestinal symptoms or that these two variables are not directly related. The mechanisms responsible for the development of gastrointestinal symptoms require elucidation.

In summary, this was the first study to demonstrate a threshold effect of running intensity on small intestinal permeability. Running at 80% $\dot{V}O_{2peak}$ increased small intestinal permeability compared with rest and running at 40 and 60% $\dot{V}O_{2peak}$. The increase in small intestinal permeability was not accompanied by gastrointestinal symptoms but correlated with the rise in rectal temperature. However, the rise in rectal temperature accounted for only 34% of this response. Permeation of chemoattractants after breakdown of the small intestinal barrier may initiate a local immune response and generate tissue damage to account for the remain-

der of the rise in permeability. No conclusive evidence of enhanced gastric permeability was found.

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