

# Health & Fitness Journal of Canada

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Volume 8

January 30, 2015

Number 1

## ARTICLE

### Occult bleeding, haematochezia and the endurance athlete: What are the risks?

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#### Abstract

*Objective:* To examine the risks of visceral ischaemia associated with participation in endurance sport, including gastro-intestinal bleeding and systemic endotoxaemia. *Methods:* A systematic search of the Ovid/Medline data-base from January 1996 to May 2015, combining the terms ischaemia/visceral ischaemia/gastro-intestinal haemorrhage/bleeding/and endotoxins with exercise/endurance exercise/physical endurance/marathon/ultra-marathon/triathlon, supplemented by a review of reference lists and personal files. *Results:* Around 20% of participants in marathons and other endurance events develop objective manifestations of visceral ischaemia in the first 2 days following a race, usually occult gastro-intestinal bleeding. A small proportion of athletes develop overt bleeding. This generally resolves over a few days, although there are 2 reported cases that required a partial colectomy, and 1 reported death. In some individuals, plasma levels of bacterial endotoxins may also rise. *Conclusions:* Once other more dangerous diagnoses have been excluded, the blood loss associated with exercise-induced visceral ischaemia can usually be treated expectantly. A watch must be kept for anaemia secondary to repeated blood loss, but the risks of bleeding requiring colectomy and bacterial sepsis seem too small either to require other specific treatment or to influence clinical advice on the wisdom of participating in ultra-endurance events. **Health & Fitness Journal of Canada 2015;8(1):22-31.**

*Keywords:* Athletic anaemia; Colonic ischaemia; Endotoxins; Endurance exercise; Gastro-intestinal bleeding; Marathon; Risks of exercise; Triathlon; Ultramarathon; Visceral blood flow

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#### Introduction

In a 6-year study of joggers on Rhode Island, Paul Thompson and his associates (Thompson et al., 1982) encountered 12 exercise-related deaths, an estimated one fatal incident per year for every 7620 joggers. Eleven of these deaths were attributed to coronary arterial disease, but one was classed as acute gastro-intestinal haemorrhage. Unfortunately, details were not provided, and the bleeding could have originated in the upper part of the gastro-intestinal tract (for instance, from an acute gastro-duodenal ulcer or cancer), from a colorectal cancer or adenoma, from haemorrhoids, or from the abuse of non-steroidal anti-inflammatory drugs (NSAIDs). However, the Rhode Island report raises the question as to the risks the recreational exerciser faces from bleeding secondary to an exercise-induced visceral ischaemia. Current information on this question is summarized in the present brief review.

After a brief description of search techniques and a general consideration of the manifestations of visceral ischaemia, we consider the prevalence of occult and overt gastro-intestinal bleeding, its prevention and management, we draw some practical conclusions for health and fitness practitioners.

### Methods

#### Search techniques

The Ovid/Medline database was scanned from January 1996 to May 2015. The terms "Exercise/Endurance exercise/Physical endurance" (112,995 citations), "Marathon" (1386 citations), "Ultra-marathon" (148 citations) and "Triathlon" (436 citations) were combined for a total of 113, 427 hits. The terms "Ischaemia/Visceral ischaemia" (24,012 citations) and "Gastro-intestinal bleeding/Haemorrhage/Endotoxins" (20,025 citations) were also combined, for a total of 43,887 hits. Pairing these two groupings by use of the "AND" function yielded a total of 389 references. A review of the corresponding abstracts revealed 31 articles that were relevant to the present review. These were supplemented with papers drawn from reference lists and the author's personal files.

#### Visceral ischaemia

Visceral blood flow is reduced drastically to meet the needs of the muscles and the cutaneous circulation during vigorous exercise (Rowell, 1986; Rowell et al., 1964). Changes are seen even with a brief bout of vigorous activity, but the redistribution of the cardiac output is much larger if exercise is prolonged, if it is undertaken in a hot environment, if fluid losses are not replenished, and if visceral blood flow is impeded by polycythaemia, hypercoagulability, and an accumulation of vasoactive metabolites.

The decrease of visceral flow tends to follow a dose-response relationship. Studies of hepatic arterial flow, based upon clearance of the dye indocyanine, have shown reductions of ~40% when exercising at 40% of maximal aerobic

power ( $\dot{V}O_2\text{max}$ ) (Busse et al., 2003), of 60-70% when exercising at 60-70% of  $\dot{V}O_2\text{max}$  (Kempe et al., 2000), and of 83% during near-maximal exercise (de Oliveira and Burini, 2011; Schoemaker et al., 1998). Ultrasonographic studies of mesenteric and coeliac blood flow show exercise-related decreases that seem to run parallel with the reduction of hepatic blood flow. Thus, Perko et al. (1998) observed that during sub-maximal cycle ergometry, a 43% reduction of overall splanchnic flow was accompanied by a 50% reduction in coeliac blood flow.

The viscera can accommodate modest reductions of arterial flow by a 2- or 3-fold increase in the capillary extraction of oxygen from the blood perfusing the viscera. One study suggested that mesenteric blood flow could be reduced by as much as 75% for 12 hours without microscopic evidence of tissue damage (Boley et al., 1981). Further, in a large U.S. survey of subjects over the age of 68 years, regular moderate physical activity such as walking was associated with a 50% reduction in the overall risk of serious gastrointestinal bleeding, and a 20% decrease in the risk of visceral ischaemia (Pahor et al., 1994). But as the intensity of exercise is increased, blood flow is progressively restricted, and the point is reached where compensation is no longer possible (Otte et al., 2001). Visceral ischaemia then develops. Acute mesenteric ischaemia is potentially a life-threatening condition. Less severe incidents cause nausea, abdominal cramping, vomiting and occult bleeding (detected by a stool guaiac test or fecal immunochemical testing), and sometimes tarry or red blood is seen in the stools (melaena and haematochezia, respectively). Visceral ischaemia can also cause a loss of integrity of the normal

gastro-intestinal barrier, allowing systemic absorption of endotoxins (Derikx et al., 2007; Marshall, 1998) and a resulting immune response (Zuhl et al., 2014).

Most investigations of visceral ischaemia have focused upon colonic lesions, but one report found endoscopic evidence of mucosal damage in the stomach in 5 of 9 runners after completion of a marathon (Øktedalen et al., 1992). In terms of the integrity of the intestinal membrane, an hour of cycling at 70% of  $\dot{V}O_2\text{max}$  provided evidence of mucosal damage in the form of increased concentrations of intestinal fatty acid binding protein (I-FABP), markers of inflammation (myeloperoxidase and calprotectin), and an increased intestinal permeability to carbohydrates, but in this study there was no evidence of an increased production of antibodies to bacterial endotoxins (van Wijck et al., 2011). Moore et al. (1995) confirmed that an endotoxaemia was not responsible for the symptoms seen in endurance cyclists following a 100-mile ride; in contrast Brock-Utne et al. 1988 found elevated plasma endotoxin concentrations in contestants after an 83 km run, as did Bosenberg and colleagues (1988) following an ultra-distance triathlon.

Kehl et al., (1986) estimated mesenteric blood flow by duplex scanning immediately post-race. In one subject with no symptoms, flow was essentially normal, but in a second individual, flow was 20% of normal at 30 minutes, and 40% of normal at 90 minutes post-race. Recovery of blood flow is often quite rapid, even following a heavy bout of exercise (Qamar and Read, 1987; van Wijck et al., 2011). Indeed, perhaps because of inflammation developing in the ischaemic area, ultrasound studies of

human hepatic portal blood flow suggest a greater than normal flow for a few hours following vigorous physical activity (Hurren et al., 2011).

### **Prevalence of occult and overt bleeding in endurance athletes**

Many runners have learned to dissociate pain while competing. Thus, some of those who develop ischaemic colitis ignore their symptoms for as long as 24 hours after a race, and others may fail to report their symptoms (Sullivan and Wong, 1992). There are also substantial inter-observer differences in the sensitivity and specificity of the tests used to detect fecal occult blood. These factors make it difficult to be certain of the prevalence of gastro-intestinal bleeding following a bout of prolonged exercise. Reported values for occult bleeding range from 1.3% to 85% of distance runners (Table 1), with the highest figures seen after a 100-mile ultra-marathon (Baska et al., 1990), and the lowest seen in a survey where subjects were asked to report stool abnormalities without objective monitoring (Porter, 1983). Often, the bleeding was seen on only one occasion, although in some individuals it recurred on as many as four occasions (Sullivan and Wong, 1992).

Although the likelihood of detecting occult bleeding is greatest 24-48 hr following a race (Moses et al., 1991; Stewart et al., 1984), the ischaemic colitis may have built up over the previous weeks of increasing training (Heer et al., 1987; Lucas and Schroy, 1998). The immediate precipitating factor is typically a distance or ultra-distance run, sometimes exacerbated by a hot day, but one reported case seems to have been initiated by a series of anaerobic dashes (Cantwell, 1981), and another by

compulsive running on the spot in a patient with anorexia nervosa (Ferron, 1999). Robertson et al. (1987) further noted a dependency on the intensity of effort; whereas a marathon run increased fecal haemoglobin loss, walking 37 km on each of four consecutive days did not have such effect.

Ischaemic colitis can be diagnosed by computed tomography (Wiesner et al., 2003), endoscopy (Choi et al., 2001; Moses et al., 1988; Schaub et al., 1985; Schwartz et al., 1990), or (in the case of ileal lesions) by capsule endoscopy (Ginard et al., 1999; Valle et al., 2004). Computed tomographic (CT) findings include thickening of the bowel wall, fat stranding, mesenteric fluid, ascites, air in mesenteric or portal veins, and extraluminal air (Kyriakos et al., 2006). If a colonoscopy or a CT scan can be performed immediately after an event, there is often evidence of ischaemic colitis. However, recovery from a minor bleeding episode is rapid, and no abnormal findings may be seen if laboratory examination is delayed (Schwartz et al., 1990).

What are the risks of more serious haemorrhage? One report suggested that 16% of marathoners presented with bloody stools on at least one occasion (Sullivan and Wong, 1992). Most observers regard frank bleeding (haematochezia) as a much rarer occurrence, although case reports have described a number of incidents (Table 1). The most dramatic incident was the death of a Rhode Island jogger, as reported by (Thompson et al., 1982), but the details describing this case are so sparse that we cannot be sure that visceral ischaemia was the cause. Two other cases required a partial colectomy (Beaumont and Teare, 1991; Cohen et al., 2009). There has also been a case of

exercise-induced mesenteric infarction requiring surgery (Kam et al. 1994), as well as episodes of omental infarction and acute pancreatitis (Scobie, 1998; Stewart and Waxman, 2004). However, most patients were subsequently able to return to competitive running without specific treatment following an acute episode of overt gastro-intestinal bleeding.

### **Prevention of visceral ischaemia**

The data presented in Table 1 provide few clues as to potential preventive measures. Diversion of blood flow from the intestines during a bout of endurance exercise is likely to be greatest if the competitor becomes dehydrated; temperature limits should thus be placed upon competitions, and care taken to maintain fluid balance. Studies to date have shown little relationship to the use of non-steroidal anti-inflammatory medication (NSAIDs), but in view of the propensity of such drugs to cause gastrointestinal haemorrhage, their usage should be held to a minimum. Optimization of training will certainly increase the overall cardiac output, but any advantage of visceral blood flow due to this response is likely to be dissipated in competitive events, because a fitter runner will simply run faster. There may possibly be value in taking a history of previous episodes of gastro-intestinal bleeding, although for many competitors one episode of haemorrhage does not necessarily predict a problem during subsequent incidents.

## Visceral Ischaemia and the Endurance Athlete: What are the Risks?

**Table 1: Reports of bleeding during or immediately following exercise.**

Authors	Participants	Exercise	Prevalence of blood loss	Comments
<b>Surveys of runners</b>				
Baska et al., 1990a	25 participants	100-mile ultra-marathon	14/16 controls, 1/9 experimental group became haemoccult positive	Observational trial shows apparent protection from cimetidine (800 mg x 2)
Baska et al., 1990b	34 M, 1 F participants	100-mile ultra-marathon	29/34 became haemoccult positive over event (85%)	No relation to age, training. Greater use of NSAIDS by negative group
Buchman et al., 1999	24 M, 2 F	Marathon	4/26 became heme positive (15%)	No benefit from Vit. E supplements in controlled trial
Halvorsen, Lyng and Ritland 1999	56 M, 7 F/63	Drammen marathon	8/63 had positive occult blood test after event (13%)	No GI disease, no effect of age or training
Kehl et al., 1986	41 skiers	Engadin ski marathon	3/41 had occult blood after event (7%)	One runner showed little change of mesenteric blood flow post-race; second subject, flow 20% and 40% at 30 & 90 min post-race
McCabe et al., 1986	68 M, 57 F	Marine corps marathon	28/125 converted from negative to positive occult blood test over event (22%)	No relation to age, sex, running ability, NSAIDS or steak ingestion
McMahon et al., 1984	34 runners, sex not specified	Boston marathon	7/34 became guaiac positive (21%)	Affected younger & faster runners. No effect of NSAIDS
Moses et al., 1991	30 runners (15 M, 15 F)	Marathon	7/27 hemo-occult positive after run	No benefit from cimetidine in blind placebo-controlled trial
Øktedalen et al., 1992	9 M	Marathon	5/9 show bleeding (56%)	Endoscopy shows source of bleeding in stomach
Porter, 1983	287 M, 12 F	Guilford marathon	4/299 demonstrated melaena after race (1.3%)	None of 4 had haemorrhoids
Robertson et al., 1987	6 M	37 km walk on 4 consecutive days	No increase of fecal haemoglobin	
Robertson et al., 1987	43 M, 3 F (5 eliminated because high pre-race values)	Aberdeen marathon	Increase of fecal haemoglobin, averaging 0.42 mg·g <sup>-1</sup>	Increase of haemoglobin rose to 0.87 mg·g <sup>-1</sup> in athletes taking drugs before race. Bleeding not related to age or training status

### **Are there any helpful medications?**

Cooper et al. (1987) found that the administration of H<sub>2</sub> receptor antagonists checked bleeding in a 33-year-old female runner who was becoming anaemic as a result of exercise-induced bleeding. In an observational trial, (Baska et al., 1990) examined the effects of taking 800 mg of the histamine H<sub>2</sub> receptor antagonist cimetidine 1 hour before and at the 50-mile mark of a 100-mile ultra-marathon. Fourteen of 16 controls were haemo-occult positive following the race, as compared with only 1 of 9 experimental subjects. Those taking cimetidine also experienced less nausea and vomiting, but their physical performance did not differ from that of the controls. These results encouraged a blinded, placebo-controlled trial in 30 marathon runners during the following year; 14 athletes took 800mg of cimetidine 2 hours before running, and 16 controls ingested a placebo (Moses et al., 1991). In the second study, Haemo-occult and Haemoquant tests showed no differences of occult bleeding between experimental and control subjects. Another uncontrolled trial administered the related drug ranitidine (150 mg orally, twice a day for 14 days) to long-distance runners (Choi et al., 2001); subsequent endoscopy suggested improvement in 11/14 cases of erosive gastritis, and 4/5 cases of oesophagitis. In a randomized, double-blinded trial, Thalmann et al. (2006) administered the proton pump inhibitor pantoprazole (20 mg for 3 days) to participants in an ultra-marathon race; this seemed relatively effective, reducing occult bleeding to 10% in the experimental subjects, as compared with 71% in a control group. However, the need for histamine receptor antagonists or proton pump inhibitors remains debatable unless a long distance athlete

has severe bleeding; caution must be shown in using cimetidine and related drugs, since they can cause cardiac conduction defects and alterations in mental status.

Some investigators have ascribed bleeding following visceral ischaemia to a re-perfusion injury, and in animal models benefit has been seen from the administration of anti-oxidants such as Vitamin E supplements to prevent free radical damage. However, a placebo controlled trial in humans found that a course of 1000 IU per day of alpha-Tocopherol for 14 days prior to a marathon race did not reduce the prevalence of occult bleeding (Buchman et al., 1999).

There has also been a recent surge of interest in dietary supplements that can protect intestinal junction proteins and thus reduce the passage of endotoxins into the blood stream following visceral ischaemia. Many of these substances apparently act by up-regulating heat-shock proteins. Benefit has been ascribed to bovine colostrum (Marchbank et al., 2011), the zinc-containing anti-ulcer drug Polaprezinc (Ohkawara et al., 2006), oral glutamine supplements (Singleton and Wischmeyer, 2006) and probiotics, although there has as yet been little study of their effectiveness in reducing gastrointestinal symptoms and enhancing the performance of athletes (Ohland and Macnaughton, 2010).

### **Management of visceral ischaemia**

If an athlete presents with either occult or overt gastro-intestinal bleeding, it is first important to exclude other more serious pathologies, such as a gastric ulcer or carcinoma, and a colonic adenoma or carcinoma. The hasty cleansing of diarrhoea may also have provoked bleeding from haemorrhoids,

and many distance runners provoke gastro-intestinal bleeding by an excessive intake of NSAIDS (Shoor, 2002). If the diagnosis of ischaemic colitis is confirmed, as discussed above, it usually responds quite rapidly to a tapering of training and supportive therapy (Heer et al., 1987; Lucas and Schroy, 1998; Sanchez et al., 2006). McMahon et al. (1984) found that in 5 of 7 runners, bleeding ceased within 72 hours, although the occasional case can persist for several weeks (Dodds, 1992).

The main risk from repeated incidents is a progressive anaemia (Cooper et al., 1987; Mechrefe et al., 1997; Nielsen and Nachtigall, 1998; Rudzki et al., 1995; Treff et al., 2014), with a resulting deterioration in performance. Haemoglobin levels should be monitored on a regular basis, taking due account of the haemodilution associated with an expansion of blood volume in a well-trained athlete (Chataerd et al., 1999). More serious long-term effects are very rare. The penetration of endotoxins may contribute to symptoms of collapse following an exhausting race, but there do not seem any reports of cases progressing to sepsis. There are two published reports of patients requiring a partial colectomy following visceral ischaemia during a period of 18 years (Beaumont and Teare, 1991; Cohen et al., 2009), but given the number of marathons performed annually, the average endurance runner must consider this as a very remote contingency.

### Conclusions and practical implications for health practitioners

Many of the health benefits associated with regular physical activity can be achieved with a relatively modest component of exercise (including 30-60 minutes of daily activity in the aerobic

training zone). However, a growing proportion of the active sector of the world's population finds a personal challenge and motivation to exercise as they prepare themselves for marathon, ultra-marathon and triathlon events. It remains unclear how far such efforts add to the health benefits of more modest levels of physical activity, and there are certainly some negative consequences of very demanding events. Visceral ischaemia and associated gastro-intestinal bleeding is one such issue. About 1 in 5 participants in very prolonged endurance races will suffer some occult gastro-intestinal blood loss, and if this is repeated it may predispose to an athlete's anaemia. However, persistent bleeding sufficient to require a partial colectomy and the loss of intestinal barrier function with absorption of bacterial endotoxins are sufficiently rare contingencies that they should not influence decisions regarding participation in ultra-endurance events.

### Author's Qualifications

The author's qualifications are Roy J. Shephard, C.M., M.B.B.S., M.D.[Lond.], Ph.D., D.P.E., LL.D., D.Sc.

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