Exercise induces gastric ischemia in healthy volunteers: a tonometry study

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Exercise induces gastric ischemia in healthy volunteers: a tonometry study. J Appl Physiol 91: 866–871, 2001.—Heavy physical exercise may cause gastrointestinal signs and symptoms, and, although splanchnic blood flow may decrease through redistribution by more than 50%, it is unclear whether these signs and symptoms relate to gastrointestinal ischemia. In 10 healthy volunteers, we studied the effect of exercise on gastric mucosal perfusion adequacy using air tonometry. Two relatively short (10 min) exercise stages were conducted on a cycle ergometer, aiming for 80 and 100% of maximum heart rate, respectively. The intragastric-arterial PCO2 gradient (ΔPCO2) was elevated by 1.1 ± 1.0 kPa over baseline values (−0.1 ± 0.3 kPa) only after maximal exercise (P < 0.001). ΔPCO2 positively correlated with the arterial lactate level taken as an index of exercise intensity (Spearman’s rank test: r = 0.76, P < 0.0001). By bilinear regression analysis, a lactate level of 12 mmol/l, above which a sharp rise in the ΔPCO2 occurred, was calculated. We conclude that, in healthy volunteers with normal splanchnic vasculature, gastric ischemia may develop during maximal exercise as judged from intragastric PCO2 tonometry.

DURING HEAVY PHYSICAL EXERCISE, up to 80% of the increase in cardiac output may be directed to the working muscles to match the increased metabolic demands, thereby curtailing blood flow to splanchnic organs (43). With the use of Doppler ultrasonography, a decrease in splanchnic blood flow of up to 50% has been observed after physical exercise (32, 34). The consequences of such a decrease in blood flow are unclear but may lead to gut mucosal ischemia as observed in animal models of shock (16).

It is well established that strenuous exercise may lead to gastrointestinal abnormalities and cause symptoms such as abdominal pain or discomfort, nausea, vomiting, and diarrhea. Numerous studies have focused on gastrointestinal disorders during exercise (2, 21, 24, 25, 28, 29, 33, 35, 41). The majority of these studies addressed the subject of gastrointestinal motility, but few have investigated the possible role of ischemia as the underlying cause (3, 9, 13, 22, 36, 38, 42). This may be partly explained by the lack of an accurate test to assess actual ischemia independent of metabolic rate and absolute perfusion.

Changes in perfusion per se do not necessarily indicate changes in oxygen supply-to-demand balance, when demand decreases as a consequence of fasting, for instance. The luminal intragastric Pco2 (PgCO2) as measured by tonometry, however, is considered to reflect the mucosal oxygen supply-to-demand balance (18) so that hypoperfusion increases the intragastric-arterial PCO2 gradient (ΔPCO2) following a decreased washout and an increased production of CO2 in ischemic tissue by liberation of CO2 from HCO3 buffering of anaerobically produced metabolic acids (11). In fact, heavy exercise may result in an increase of ΔPCO2 (31). The latter study, however, does not give insight into the level of exercise inducing gastric mucosal ischemia. This is of importance because exercise tonometry has been suggested in a previous paper (17) to be a noninvasive diagnostic tool for stenotic splanchnic vascular disease, but the specificity of abnormal exercise tonometry for vascular disease should be confirmed by normal tonometric values at a similar level of exercise in healthy volunteers with normal splanchnic blood vessels. The cited study was done with the help of the slow manual saline tonometry system; however, the introduction of air tonometry thereafter has allowed for more rapid and accurate PgCO2 tonometry (20).

In consideration of the above data, we hypothesised that maximal rather than submaximal exercise in healthy volunteers with normal splanchnic blood vessels causes gastric mucosal ischemia as judged from intragastric air PCO2 tonometry.

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MATERIALS AND METHODS

Subjects
Ten healthy untrained and nonsmoking volunteers (5 men and 5 women, mean age 25.4, range 23–28 yr), taking no medication other than oral contraceptives, were included in the study. All subjects were informed about the nature, purpose, and possible risks involved in the study before giving their consent. The study was performed according to the ethical guidelines of our institution after approval from the Institutional Ethics Committee.

Duplex Sonography
To exclude splanchnic arterial abnormalities, all subjects underwent duplex ultrasonography of the splanchnic vessels. In the week before the exercise studies and after an overnight fast, duplex sonography was performed by an experienced investigator (R. H. Geelkerken) using a Diasonics VST-master ultrasonography device. After we identified the vessels and confirmed the patency and antegrade flow, the peak-systolic and end-diastolic flow velocities during inspiration and expiration were measured in the celiac artery (CA), superior mesenteric artery (SMA), and aorta. Peak-systolic flow velocities below 200 and 275 cm/s and end-diastolic flow velocities below 55 and 45 cm/s were regarded as normal for the CA and SMA, respectively (26, 30).

Tonometry
Subjects were studied in the afternoon after a fasting episode of at least 4 h following a light breakfast. One week before tonometry exercise testing, the maximum workload and heart rate (HRmax) were determined utilizing an incremental exercise protocol (cycle ergometry, incrementation rate = 25 W/min) until exhaustion (12). A standard balloon-tipped tonometry catheter (Trip sigmoid catheter, Tonometrics, Helsinki, Finland) was inserted nasogastrically and placed 55 cm from the tip of the nose. The catheter was attached to an automated air tonometry device (Tonocap, Datex-Engstrom, Helsinki, Finland), which uses a pump to measure PgCO2 every 10 min. To prevent CO2 production by buffering of gastric acid, 100 mg of ranitidine were administered intravenously 1 h before the baseline tonometry measurements (time (t) = −60 min) and again immediately after the first exercise episode (t = 30 min). This dose of ranitidine sufficiently suppresses acid production within 1 h (19, 39).

A radial artery catheter was inserted in the nondominant arm to allow blood sampling.

Exercise Testing
We applied two exercise periods, 10 min of duration each, with 60 min of rest between the two periods. The two exercise periods were aimed to result in steady-state exercise at a submaximal (80% of HRmax) and maximal work rate level (100% of HRmax). To achieve this, the workload was gradually increased during the first 5 min of exercise period 1 and 7–8 min of exercise period 2 and remained constant thereafter. Exercise was performed on an electromagnetically braked bicycle ergometer (Lode, Groningen, The Netherlands). During the exercise stages, a 12-lead electrocardiogram was recorded (Case 12, Marquette Electronics, Milwaukee, WI), and, in all but one subject, breath-by-breath oxygen uptake (Vo2) and respiratory gas exchange ratio (RER) were measured by a respiratory gas analyzer system (Oxycon-alpha Jaeger, Bunnik, The Netherlands).

Protocol
In Fig. 1, the time frame of the study protocol is schematically displayed. Baseline measurements of blood and tonometric variables were done at t = 10 and 20 min. The submaximal exercise period (EX1) was from t = 20 to 30 min, with measurements at t = 30 min. Recovery measurements were done at t = 40 min. After a washout period, the second baseline period measurements were done at t = 70 and 80 min, which was followed by a maximal exercise period (EX2) from t = 80–90 min, with measurements at t = 90 min. A second recovery measurement (RC2) was done at t = 100 min. During exercise, the heart rate (HR) was recorded and the percentage of HRmax was calculated every 30 s. Vo2 and RER were averaged and stored every 30 s during the exercise periods. Vo2 is expressed as a percentage of predicted maximum Vo2 (Vo2max). Predicted Vo2max was calculated using equations by Wasserman et al. (44). At t = 10, 20, 30, 40, 70, 80, 90, and 100 min, arterial blood samples were drawn for determination of arterial PCO2 (PaCO2), base excess, bicarbonate (blood-gas analyzer; Radiometer ABL520, Copenhagen, Denmark), and lactate (enzymatic assay; Cobas Faro, Roche Diagnostics, Branchburg, NJ). Every 10 min, the Tonocap measured PgcO2, ΔPCO2, which is equal to PgCO2 − PaCO2, was calculated.

Statistics
Values are given as means ± SD unless otherwise stated. For all baseline values, the mean of the two consecutive measurements was taken. Differences between study periods for any given parameter were tested by one-way ANOVA for repeated measurements, followed by a Tukey-Kramer multiple-comparison test. For the pooled results of both exercise periods, the relation between maximal lactate levels and ΔPCO2 was calculated using Spearman’s rank correlation coefficient. Bilinear regression analysis was done to evaluate the lactate level threshold for PgcO2 rises (8). A P value < 0.05 was considered statistically significant.

RESULTS

Duplex Sonography
All subjects had normal patent CA and SMA, with antegrade flow in both vessels. Due to intestinal gas,
Table 1. Study parameters at different baseline, exercise, and recovery periods

<table>
<thead>
<tr>
<th></th>
<th>BL1</th>
<th>EX1</th>
<th>RC1</th>
<th>BL2</th>
<th>EX2</th>
<th>RC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>78 ± 14</td>
<td>162 ± 6†</td>
<td>83 ± 12</td>
<td>189 ± 8†</td>
<td>97 ± 4§</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Percentage of HRmax</td>
<td>83 ± 3</td>
<td>2.12 ± 0.64†</td>
<td>0.43 ± 0.18</td>
<td>0.43 ± 0.06</td>
<td>3.04 ± 0.75†</td>
<td>3.04 ± 0.75†</td>
</tr>
<tr>
<td>Vo2, l/min</td>
<td>0.43 ± 0.17</td>
<td>0.99 ± 0.07†</td>
<td>0.72 ± 0.06</td>
<td>1.11 ± 0.087§</td>
<td>4.04 ± 0.06</td>
<td>4.04 ± 0.06</td>
</tr>
<tr>
<td>RER</td>
<td>0.72 ± 0.04</td>
<td>0.99 ± 0.07†</td>
<td>0.72 ± 0.06</td>
<td>1.11 ± 0.087§</td>
<td>4.04 ± 0.06</td>
<td>4.04 ± 0.06</td>
</tr>
<tr>
<td>PacO2, kPa</td>
<td>5.1 ± 0.7</td>
<td>5.0 ± 0.5</td>
<td>4.9 ± 0.4</td>
<td>5.0 ± 0.6†</td>
<td>4.4 ± 0.71‡</td>
<td>4.3 ± 0.5†</td>
</tr>
<tr>
<td>HCO3, mmol/l</td>
<td>23.9 ± 2.2</td>
<td>19.1 ± 1.6†</td>
<td>20.4 ± 1.3†</td>
<td>23.7 ± 1.9</td>
<td>14.2 ± 2.5†</td>
<td>14.9 ± 2.9‡</td>
</tr>
<tr>
<td>BE, mmol/l</td>
<td>-0.3 ± 1.6</td>
<td>-6.0 ± 1.8†</td>
<td>-3.8 ± 1.6†</td>
<td>-0.1 ± 1.5</td>
<td>-11.8 ± 3.0†‡</td>
<td>-10.5 ± 3.9†‡</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.5 ± 0.1</td>
<td>6.5 ± 2.4†</td>
<td>3.3 ± 1.6†</td>
<td>0.7 ± 0.2</td>
<td>12.8 ± 3.2†‡</td>
<td>8.7 ± 3.2†‡</td>
</tr>
<tr>
<td>PgCO2, kPa</td>
<td>4.9 ± 0.6</td>
<td>5.3 ± 0.6*</td>
<td>4.9 ± 0.5</td>
<td>4.9 ± 0.6</td>
<td>5.5 ± 0.6†</td>
<td>5.0 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; Vo2, oxygen consumption; RER, respiratory gas exchange ratio; PacO2, arterial PCO2; PgCO2, intragastric PCO2; BL1, baseline measurement at time (t) = 10 and 20 min; EX1, submaximal exercise period; RC1, recovery measurement done at t = 40 min; BL2, baseline measurements at t = 70 and 80 min; EX2, maximal exercise period; RC2, recovery measurement at t = 100 min; BE, base excess. †P < 0.05 for value vs. baseline value; ‡P < 0.001 for value vs. baseline value; §P < 0.0005 for value comparing EX1 vs. EX2.

Exercise Tonometry

Cardiopulmonary measurements. There were no differences in HR, Vo2, and RER between the two baseline episodes (Table 1). At the end of both exercise stages, all cardiopulmonary parameters differed from baseline. HR increased from 78 ± 14 at baseline to 162 ± 6 beats/min (83 ± 3% of HRmax) after EX1 (P < 0.0001) and 189 ± 8 beats/min (97 ± 4% of HRmax) after EX2 (P < 0.0001). The Vo2 rose to 91 ± 23% of predicted Vo2max at the end of EX1 and to 130 ± 20% of predicted Vo2max at the end of EX2 (P < 0.0001 for both vs. baseline).

Blood parameters. There were no differences between the two baseline episodes. PacO2 did not change after EX1 but decreased after EX2 and remained below baseline in RC2. The lactate increased and the bicarbonate and base excess levels decreased during both exercise periods but more during EX2 than during EX1.

Tonometry. The baseline PgCO2 did not differ between both baseline periods. During EX1, PgCO2 increased, whereas the ΔPCO2 did not change significantly (Fig. 2). During EX2, PgCO2 and ΔPCO2 increased. During RC2, PgCO2 returned to baseline but ΔPCO2 remained elevated over baseline. The mean PgCO2 in both baseline periods was 4.9 ± 0.2 kPa, and the coefficient of variation was 4.3%. The ΔPCO2 during both baseline periods was −0.2 ± 0.4 kPa, with an upper limit of normal (mean ± 2SD) of 0.6 kPa.

Tonometry variables vs. exercise level. A positive correlation was observed between both PgCO2 and ΔPCO2 with exercise level as indicated by serum lactate at the end of the exercise stage (r = 0.50, P < 0.05 and r = 0.76, P < 0.0001, respectively). No increase in ΔPCO2 over the normal upper threshold of 0.8 kPa (19) was seen during exercise with lactate levels below 8 mmol/l, whereas in five of six tests, where resulting lactate levels were above 14 mmol/l, the ΔPCO2 exceeded this threshold. In Fig. 3, the relationship between serum lactate level at the end of the exercise stage and ΔPCO2 is shown. With the use of bilinear regression analysis, a lactate threshold value of 12 mmol/l was calculated, above which ΔPCO2 started to rise (r² = 0.73).

DISCUSSION

The results of the present study show that, in subjects with normal splanchnic vasculature, gastric ische-
mia can develop after only 10 min of maximum physical exercise. The development of gastric ischemia strongly depended on exercise intensity. Furthermore, our study demonstrates that air tonometry can be used for assessment of the adequacy of gastric mucosal perfusion during physical exercise.

The bilinear pattern of the gastric-blood \( \text{PCO}_2 \) gradient during exercise, with a marked increase above a threshold exercise intensity, is in agreement with studies indicating that tonometric measurement of gastric intramucosal \( \text{PCO}_2 \) is a reliable index of the adequacy of splanchnic mucosal perfusion (7, 18). If tonometry results depend on blood flow only, a linear pattern between the \( \text{PCO}_2 \) gradient and lactate should have been observed (14). In contrast, it was previously shown in animal models that a small reduction in gastrointestinal blood flow did not influence \( \text{PCO}_2 \), but, when the blood flow fell to <50% of baseline, hypoperfusion caused an increased \( \text{PCO}_2 \) in parallel with a fall in tissue \( \text{O}_2 \) tension and consumption (16, 40). Indeed, the gastric-blood \( \text{PCO}_2 \) gradient may be the most sensitive and specific tonometric parameter of gastrointestinal perfusion, independent of systemic metabolic and respiratory changes (18).

The increase in \( \Delta \text{PCO}_2 \) during maximal exercise is partly caused by a decrease in \( \text{PaCO}_2 \). The latter is the result of increased alveolar ventilation in response to metabolic acidosis due to anaerobic muscular metabolism (12). However, in mechanically ventilated patients, it has been shown that changes in \( \text{PaCO}_2 \) are closely and swiftly followed by changes in \( \text{PGCO}_2 \), thereby not influencing \( \Delta \text{PCO}_2 \) (23). However, even if the decrease in \( \text{PaCO}_2 \) is neglected, the relationship between the increase in \( \text{PGCO}_2 \) during exercise and arterial lactate level shows a similar bilinear pattern as \( \Delta \text{PCO}_2 \) vs. lactate level [i.e., no increase of \( \text{PGCO}_2 \) up to a threshold lactate level of 12 mmol/l and an increase above this lactate threshold \( r^2 = 0.36 \)].

Our present study confirms the findings of the study of Nielsen et al. (31), which showed that gastric ischemia occurred during heavy exercise in trained rowers at exercise levels close to their maximum aerobic capacity. Using fluid tonometry, they observed, similar to our present study, a gradual increase in \( \text{PGCO}_2 \) during exercise with a concomitant decrease in \( \text{PaCO}_2 \). A direct comparison of both studies is difficult because the Nielsen study reported on the previously advocated but now largely abandoned intracellular \( \text{pH} \) (\( \text{pHi} \)), a calculated value incorporating arterial bicarbonate levels as well. With profound metabolic acidosis, \( \text{pHi} \) might be a poorer predictor of mucosal ischemia than \( \Delta \text{PCO}_2 \). Another potentially confounding factor might have been insufficient acid suppression, since one of their baseline \( \text{PGCO}_2 \) already measured up to 8.5 kPa. Similar to previous studies by our group (19), we used high-dose intravenous ranitidine to ensure adequate acid suppression in our subjects.

Automated air tonometry offers several advantages over manual fluid tonometry, including superior accuracy, speed, and reproducibility (18). It is less laborious and involves less error-prone steps, and the faster diffusion of \( \text{CO}_2 \) in air results in shorter equilibration times. In our study, air tonometry may have slightly underestimated \( \text{PGCO}_2 \) values leading to negative \( \Delta \text{PCO}_2 \) baseline values in the majority of measurements (28 of 40 baseline measurements). In one subject in our study, all \( \text{PGCO}_2 \) values were lower than \( \text{PaCO}_2 \) values resulting in negative gradients, even at maximal exercise. The most likely explanation is the occurrence of air swallowing causing dilution of intragastric gas.

The \( \Delta \text{PCO}_2 \) threshold for anaerobic metabolism is still unclear (18). The range of normal \( \text{PGCO}_2 \) and \( \Delta \text{PCO}_2 \) in our study is in close agreement with the study by Creteur et al. (4) on air tonometry showing a normal upper limit of 0.8 kPa for the gradient. Schlichtig and Bowles (40) demonstrated that a fall in tissue \( \text{O}_2 \) tension and consumption, development of anaerobic metabolism, and production of lactic acid occurred at a \( \Delta \text{PCO}_2 \) of 3.5 kPa or greater, a value that can be regarded as the critical gradient. Thus it may be questioned whether increased \( \Delta \text{PCO}_2 \), as shown in this study, indeed indicates ischemia rather than hypoperfusion of the gastric mucosa. Nevertheless, we cannot exclude ischemia and anaerobic metabolism in the gastric mucosa even at gradients lower than the critical values reported by Schlichtig and Bowles. The 10-min measurement interval of air tonometry may have resulted in an underestimation of the actual peak \( \text{PGCO}_2 \) during exercise periods of 10 min. Indeed, the first minutes of the exercise periods were used to gradually increase the workload. Therefore, anaerobic \( \text{CO}_2 \) production could have occurred only in the last minutes of the exercise episode and not have lasted long enough for full \( \text{PCO}_2 \) equilibration, resulting in a measured \( \text{PGCO}_2 \) that underestimates the actual intraluminal \( \text{PCO}_2 \) at the end of the exercise. Moreover, exercise-induced hypoperfusion might result in patchy ischemia with anaerobic areas surrounded by still well-perfused areas similar to the ischemic pattern demonstrated in hypovolemic shock (6, 27).

An alternative explanation for increasing \( \Delta \text{PCO}_2 \) after strenuous exercise, other than splanchnic vasoconstriction and ischemia, could be an increase in intra-abdominal pressure, which leads to increased wall tension in the digestive tract, reduced mucosal flow and ischemia. Indeed, in pigs it was demonstrated that a prolonged increase in intra-abdominal pressure of 1.5–3 kPa may decrease mucosal blood flow by 30–40% (5). Similar intra-abdominal pressures have been measured during exercise (15). However, during exercise, the intra-abdominal pressure is not continuously elevated but is changing during each respiratory cycle between ~0 and 3 kPa; it is unlikely that these short (1–2 s) periods of intra-abdominal peak pressure will lead to mucosal ischemia. Moreover, if gastric mucosal ischemia would have been caused by an increase in abdominal pressure during exercise, a rapid normalization in the recovery phase would be expected. In the recovery phase of the present study, however, \( \Delta \text{PCO}_2 \) remained elevated in four subjects and increased even further in one subject. This result is in agreement with the finding that, during recovery after exercise, the
An interindividual difference in the response of ΔPCO2 to the two exercise intensities was noted. In three subjects, the ΔPCO2 after maximal exercise (with lactate levels increasing to 14.3 mmol/l) was not, or only slightly, higher than after submaximal exercise and still well below the normal threshold of 0.8 kPa. In contrast, in one subject, ΔPCO2 was already elevated after submaximal exercise (lactate 8.4 mmol/l) and increased greatly after maximal exercise (lactate 15.2 mmol/l) resulting in the highest ΔPCO2 of all subjects. Although splanchic arterial abnormalities were excluded by duplex sonography, differences in microvascular anatomy and physiology might very well explain this interindividual susceptibility to gastric mucosal ischemia. This might result from differences in training status as all subjects were recreationally active to a different degree, although none was a competitive athlete (10).

Our results demonstrate a threshold in exercise intensity, as judged from the arterial lactate level, above which a marked increase in ΔPCO2 was seen as a reflection of gastric mucosal ischemia. This finding of a lactate threshold in individuals with normal splanchic vasculature, beyond which gastric ischemia may develop, has important implications when exercise gastric tonometry is used as a diagnostic tool in patients suspected of having splanchic arterial disease. In these patients, in contrast to control patients, exercise of even moderate intensity has been shown to lead to gastric ischemia as judged from a rise in the tonometric PgCO2 (17). Our current results in healthy volunteers suggest that, for optimal performance of the test in patients and to prevent false positive results, it is mandatory to continuously monitor and, if necessary, adjust the exercise intensity to keep the lactate level below 8 mmol/l.

In many studies, exercise led to a variety of gastrointestinal abnormalities. The etiology of these abnormalities is still unclear, however. Exercise has been shown to lead to delayed liquid gastric emptying (21, 25, 35), with the magnitude of the delay depending on the exercise intensity (29). With the use of ultrasonography, it has been shown that impaired motility may be explained by exercise-induced closure of the pylorus and a decreased gastric antral area (2). Exercise also has been shown to affect intestinal postprandial motor activity (41). The intestinal epithelial barrier function may be impaired because heavy exercise may result in increased intestinal permeability and impaired water absorption (24). Apart from these functional alterations, heavy exercise, especially marathon running, is also known to cause gastrointestinal blood loss, gastritis, and colitis, which are at least partially ascribed to gastrointestinal ischemia (3, 9, 13, 22, 36, 38, 42). Although often suggested as playing a key role in the development of exercise-induced gastrointestinal abnormalities, gastrointestinal hypoperfusion has not yet been proven to be the cause of these exercise-induced abnormalities. Several investigations (1, 32, 34, 37, 43) that used Doppler ultrasound and thermodilution techniques have shown an exercise-induced decrease of splanchic blood flow but failed to address the issue of metabolic demand. Our present study using air tonometry shows that, in subjects with normal splanchic vasculature, gastric ischemia may indeed develop early during maximum physical exercise and that the development of gastric mucosal ischemia is strongly dependent on the exercise intensity.

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