CHEST

Original Research

COPD

Disturbed Intestinal Integrity in Patients With COPD

Effects of Activities of Daily Living

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Background: **COPD is accepted to be a multicomponent disease with various comorbidities. To our knowledge, the contribution of the GI tract to the systemic manifestation of COPD has never been investigated. This metabolically active organ may experience recurring local oxygen deficits during daily life, leading to disturbed intestinal integrity in patients with COPD.**

Methods: **Eighteen patients with moderate COPD (mean FEV_1, 55 ± 3% predicted) and 14 matched healthy control subjects were tested on two occasions: a baseline measurement at rest and, on another day, during the performance of activities of daily living (ADLs). To assess enterocyte damage, plasma intestinal fatty acid binding protein (IFABP) levels were determined, whereas urinary excretion of orally ingested sugar probes was measured using liquid chromatography and mass spectrometry to assess GI permeability.**

Results: **Plasma IFABP concentrations were not different between patients with COPD and healthy control subjects at rest. In contrast, 0- to 3-h urinary lactulose to rhamnose and sucralose to erythritol ratios and 5- to 24-h urinary sucralose to erythritol ratios were significantly higher in patients with COPD compared with control subjects, indicating increased permeability of the small intestine and colon. Furthermore, the performance of ADLs led to significantly increased plasma IFABP concentrations in patients with COPD but not in control subjects. Similarly, the intestinal permeability difference between patients and control subjects was intensified.**

Conclusions: **Besides an altered intestinal permeability in patients with COPD when at rest, performing ADLs led to enterocyte damage in addition to intestinal hyperpermeability in patients with COPD but not in control subjects, indicating functional alteration in the GI tract. Hence, intestinal compromise should be considered as a new component of the multisystem disorder COPD.**

Trial registry: **ISRCTN Register; No.: ISRCTN33686980; URL: www.controlled-trials.com**

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Abbreviations: ADLs = activities of daily living; AUC = area under the curve; CRP = C-reactive protein; DLCO = diffusion capacity of lung for carbon monoxide; FFMI = fat-free mass index; IFABP = intestinal fatty acid binding protein; L/R = lactulose to rhamnose; S/E = sucralose to erythritol; $\dot{V}O_2$ = oxygen consumption

COPD is a major health problem. COPD is characterized as a multicomponent disease that not only affects the lungs, but also the musculoskeletal, cardiovascular, renal, and immune systems.[1,2] This is reflected by the fact that lung function measurement alone is not sufficient to evaluate a patient's clinical situation.[3] To our knowledge, the contribution of the GI tract as part of the systemic complexity has not been investigated yet.

The primary functions of the small intestine are digestion and absorption of nutrients. In addition, the intestine forms a crucial barrier against the intestinal microbiota present in the lumen. This barrier defense is ultimately dependent on the integrity of the mucosa: Impairment of the structure of the mucosa can lead to increased permeability. The intestinal epithelium is dependent on sufficient oxygen and energy supply for both its absorptive and barrier functions. Therefore, the intestine has a highly vascularized luminal

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surface area. Under physiologic conditions, the intestinal mucosa experiences profound fluctuations in blood flow. For instance, intestinal perfusion is enhanced following meal ingestion (up to a sixfold increase in intestinal blood volume), and perfusion is considerably diminished during physical exercise.[4,5]

Reduced splanchnic perfusion will lead to tissue hypoxia, which damages the small intestinal villus epithelial cells.[5] Intestinal damage occurs in healthy volunteers performing exhaustive endurance exercise.[5] In patients suffering from chronic heart failure, splanchnic hypoperfusion develops during low-level exercise, whereas this is not the case in healthy control subjects.[6] Similarly, increased resting intestinal permeability is shown in these patients.[7] An important pathophysiologic feature of COPD is impaired gas exchange that worsens during exercise due to ventilation-perfusion mismatching, and profound oxygen desaturation may develop.[8] It has become clear that tissue hypoxia is a key player in the extrapulmonary comorbidities that characterize COPD.[9] Moreover, blood flow through the intestinal tract reduces during exercise in favor of increased flow through skeletal muscle, skin, and brain,[10] suggesting that tissue hypoxia in the splanchnic area even occurs in the absence of hypoxemia.

Based on these findings, we consider intestinal compromise as a factor in the pathogenesis of COPD. We hypothesized that patients with COPD would show functional alterations of the GI tract, which would deteriorate during household activity. To test the hypothesis, intestinal integrity was assessed at rest and during activities of daily living (ADLs) in patients with COPD and in sex-, age-, and BMI-matched control subjects. In patients with COPD, performing ADLs induces a high metabolic load when compared with incremental cycle ergometry.[11] Markers of intestinal integrity were plasma concentration of intestinal fatty acid binding protein (IFABP) to detect enterocyte damage, and the urinary excretion of inert sugars to assess intestinal hyperpermeability.[12]

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Materials and Methods

Subject Inclusion

This study was approved by the institutional review board of Maastricht University Medical Centre (MUMC, MEC09-3-062) and conducted in the Centre of expertise for chronic organ failure (the portions of the study involving patients) and at Maastricht University Medical Centre (laboratory work), according to the Declaration of Helsinki (revised version, October 2008) and Good Clinical Practice guidelines.

To minimize the effect of the rehabilitation on the study results, only patients who had finished a pulmonary rehabilitation program at the Centre of expertise for chronic organ failure[13] at least 1 month before entering the study were included. Control subjects were selected from an existing database created from previous studies. Written informed consent was obtained from patients and control subjects. Exclusion criteria for the patients with COPD were use of external oxygen supplementation (we also measured ventilation during the household activity) and the presence of an exacerbation < 4 weeks prior to the study entrance. Exclusion criteria for all subjects were the presence of GI or renal disease; chronic heart failure; use of nonsteroidal antiinflammatory drugs, because this is also known to damage the intestine[14,15]; and inability to perform a maximal ergometer test.

Study Design

During the assessment day, all participants underwent postbronchodilator spirometry (Masterlab; Jaeger AG) to measure FEV_1. Diffusion capacity of lung for carbon monoxide (Dlco) was assessed using the single-breath method (Masterlab). All values were expressed as percentages of the predicted value.[16] In addition, to determine each subject's peak workload, all subjects performed a symptom-limited incremental cycle ergometer test under supervision of a physician. After 1 min of unloaded cycling power, power was increased by 10 W every minute for patients with COPD. For control subjects, the load was increased by 15 to 25 W every minute to equate test duration between patients and control subjects. Total body weight and height were measured to calculate BMI. Fat-free mass (lean mass plus bone mass) was measured using dual x-ray absorptiometry scan (Lunar Prodigy system; General Electric Co). Fat-free mass index (FFMI) was calculated as fat-free mass divided by height^2. Low muscle mass was defined as FFMI < 17 kg/m^2 for men and FFMI < 15 kg/m^2 for women.[17] The number of pack-years smoked was recorded for each subject.

The subjects were tested on two occasions on separate days, with an interval of at least 2 days. On the first test day (resting condition), subjects came to the center in a fasted state. After collecting blood and urine samples, a sugar solution was administered to assess GI permeability. A second blood sample was collected after subjects rested for 1 h, while urine was collected over a 3-h period. Thereafter, subjects consumed a standard breakfast: two slices of bread (with margarine), one with cheese and one with jam; one cup of whole milk (250 mL); and one cup of coffee with sugar and milk (175 mL), after which urine was collected for another 2 h. Additionally, urine was collected until 24 h after consuming the sugar solution while subjects were allowed to perform normal activities at home. The second test day started in the fasted state with collecting blood and urine samples. A 20-gauge catheter (B. Braun Melsungen AG) was placed in the participant's forearm vein to sample blood regularly. Thereafter, the sugar solution was administered, and subjects started the performance of the following five ADLs with a 4-min rest period between while the subject sat on a chair[11]: ADL1: put on shoes, socks, and a coat; ADL2: fold up 16 towels and place them in the laundry basket; ADL3: place 12 cans (400 g) in a shopping basket; ADL4:

wash eight plates, eight cups, and eight saucers and place them in a plate rack; ADL5: sweep plastic blocks with a broom for 4 min. Blood sampling occurred every 10 min until 1 h after finishing the ADLs; urine collection was done from 0 to 3 h and from 3 to 5 h. Oxygen consumption ($\dot{V}O_2$) was measured using an Oxycon mobile device (CareFusion Corp) throughout the test, and plasma lactic acid concentration was assessed before and immediately after the test.

Assessment of Small Intestine Injury

To evaluate the presence and the extent of small intestine injury, plasma concentrations of IFABP were determined by an enzyme-linked immunosorbent assay developed in-house as previously described.[15] IFABP is a 15-kDa, cytosolic, water-soluble protein exclusively present in the gut, especially in the mature enterocytes of the small intestine and to a lesser extent in the colon.[18] IFABP rapidly diffuses through the interstitial space into the circulation upon enterocyte membrane integrity loss, making it an early and sensitive marker of small intestine injury.

Assessment of GI Permeability

The differential sugar absorption test is based on the oral administration of inert sugars that differentially cross the intestinal barrier to the circulation, with increasing leakage to the circulation upon barrier integrity loss, after which they are rapidly cleared in the urine.[19] The sugar solution contained 1 g lactulose (Centrafarm BV), 1 g sucralose (Brenntag AG), 1 g erythritol (Danisco A/S), and 0.5 g L-rhamnose (Danisco A/S). The sugars were dissolved in 100 mL tap water just before administration. Subjects were allowed to drink another 200 mL water after ingesting the solution. Urinary sugar concentrations were measured by high-pressure liquid mass spectrometry.[20]

The ratio of oligosaccharides (lactulose, sucralose) and monosaccharides (rhamnose, erythritol) in urine collected over 3 h after oral intake was considered to reflect small intestine barrier function loss (lactulose to rhamnose [L/R] and sucralose to erythritol [S/E]). Bacteria, which are more abundantly present in the distal GI tract, are able to metabolize sugars such as lactulose and rhamnose. Sucralose and erythritol remain unaffected, and, therefore, the S/E ratio measured in 3- to 5-h urine collection reflects the permeability of the distal small intestine and proximal colon.[21,22] Colon permeability is reflected by S/E ratio in 5- to 24-h urine collections.

Plasma IL-6, C-Reactive Protein, and Lactic Acid

Plasma IL-6 levels (at baseline and the end of the ALD) were measured using a solid-phase, enzyme-labeled, chemiluminescence sequential immunometric assay on the Immulite 1000 (Siemens AG). Plasma high-sensitivity C-reactive protein (CRP) concentration at baseline during the resting condition was measured by BN ProSpec (Siemens AG), while plasma lactic acid levels (at baseline and the end of the ALD) were analyzed by Pentra 400 (Horiba ABX SAS).

Statistical Analysis

Based on the difference in intestinal permeability index between patients with chronic heart failure and control subjects,[7] a sample size of 14 individuals per group was expected to provide 80% power (two-sided, $\alpha = 0.05$) for detecting a statistically significant difference. If data were distributed normally, the unpaired Student *t* test was used to compare means of patients with COPD and control subject data. Otherwise, the Mann-Whitney test was used. The area under the curve (AUC) of IFABP concentration during ADLs was calculated. Group and time effects were tested with the repeated measurement analysis of variance test. The Pearson correlation coefficient was calculated to check for correlations between the (log-transformed) sugar data and metabolic markers. $P < .05$ was considered significant.

Results

Subjects' Baseline and ADLs-Related Parameters

In total, 18 patients and 14 control subjects were included in the study (Fig 1). Control subjects were matched with patients with COPD for age, BMI, and sex (Table 1). Twenty-eight percent of the patients showed low muscle mass, whereas this did not occur in control subjects. The number of pack-years smoked was higher in the patients, as was the number of current smokers (Table 1). As with patient selection, the lung function parameters and the maximal load cycled were lower when compared with the control subjects. Only two patients had a $D_{LCO} < 50\%$ predicted, indicative for the presence of emphysema. Performance and plasma parameters during ADLs are shown in Table 2. The duration of ADLs, about 30 min, was comparable between the patients with COPD and control groups. However, $\%\dot{V}O_2$ consumed during ADLs relative to the maximal ergometry test was higher in patients compared with control subjects, implying that performing ADLs is an exertion with a relatively high metabolic load for patients with COPD. Since invasive PaO_2 measurements were not performed during ADLs, plasma lactic acid levels were assessed as indicators of an anaerobic metabolism. Baseline plasma lactic acid concentration was significantly higher in patients, but plasma lactic acid level increased in both groups during ADLs. Assessment of the inflammatory status revealed low baseline CRP and IL-6 levels, which were not significantly different between patients and control subjects. Performing ADLs resulted in minimal, though significant, increases in IL-6 levels in both groups.

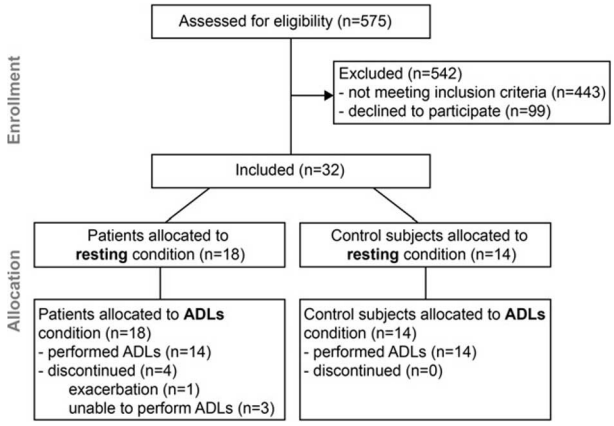

Figure 1. Consort diagram of the subject selection. ADLs = activities of daily living.

Table 1—*Basic Characteristics of the Study Population*

Characteristics	Patients (n = 18)	Control Subjects (n = 14)
Sex, No. (%), male	11 (61)	7 (50)
Age, y	63.6 ± 1.3	62.7 ± 1.7
Pack-y smoked, No.	34.7 ± 4.2	6.8 ± 4.5[a]
Smoking state, No.		
Current smoker	5	0
Ex-smoker	13	6
Never smoker	0	8
Body composition		
BMI, kg/m²	26.0 ± 1.1	28.7 ± 1.2
FFMI, kg/m²	17.7 ± 0.6	18.8 ± 0.9
Low muscle mass, No. (%)	5 (27.8)	0
Lung function, exercise capacity, and level of systemic markers		
FEV_1, L	1.53 ± 0.10	3.21 ± 0.22[a]
FEV_1 % predicted	54.9 ± 2.7	117.2 ± 3.7[a]
FEV_1/FVC	43.9 ± 2.4	77.5 ± 1.5[a]
DLCO, % predicted[b]	63.6 ± 4.6	…
PaO_2, kPa[b]	9.5 ± 0.3	…
Hb, g/dL[b]	14.1 ± 0.3	…
Maximal load, W	88.3 ± 6.5	191.1 ± 12.3[a]
Maximal $\dot{V}O_2$, mL/min	1334.5 ± 79.5	2232.7 ± 168.6[a]
CRP, mg/L	1.9 ± 1.8	1.2 ± 1.2

Data are given as mean ± SEM unless otherwise indicated. CRP = C-reactive protein; DLCO = diffusion capacity of lung for carbon monoxide; FEV_1/FVC = Tiffeneau index; FFMI = fat-free mass index; $\dot{V}O_2$ = oxygen consumption.
[a]$P < .01$ vs patients.
[b]Patients only.

Enterocyte Damage Occurs in Patients With COPD During ADLs

Plasma IFABP levels in resting conditions did not differ between the control subjects and patients with COPD (Fig 2A). To assess the acute changes in plasma IFABP during ADLs, plasma IFABP was measured every 10 min and calculated as a percentage from baseline (0 min) (Figs 2B-D). From Figure 2B, it appears

Table 2—*Data Related to the Performance of ADLs*

Variables	Patients (n = 14)	Control Subjects (n = 14)
Duration, min	36.5 ± 0.4	35.2 ± 0.6
Peak $\dot{V}O_2$, mL/min	920.5 ± 48.1	964.5 ± 55.7
%peak $\dot{V}O_2$ from maximal ergometry	69.6 ± 4.1	45.1 ± 3.1[a]
Plasma lactic acid, mmol/L		
Baseline	1.4 ± 0.1	0.9 ± 0.1[a]
End	1.6 ± 0.2[b]	1.1 ± 0.2[b]
Plasma IL-6, pg/mL		
Baseline	2.1 ± 0.6	1.1 ± 0.1
End	2.7 ± 0.6[b]	1.8 ± 0.2[b]

Data are given as mean ± SEM. ADLs = activities of daily living; $\dot{V}O_2$ = oxygen consumption.
[a]$P < .05$ vs patients.
[b]$P < .05$ vs baseline.

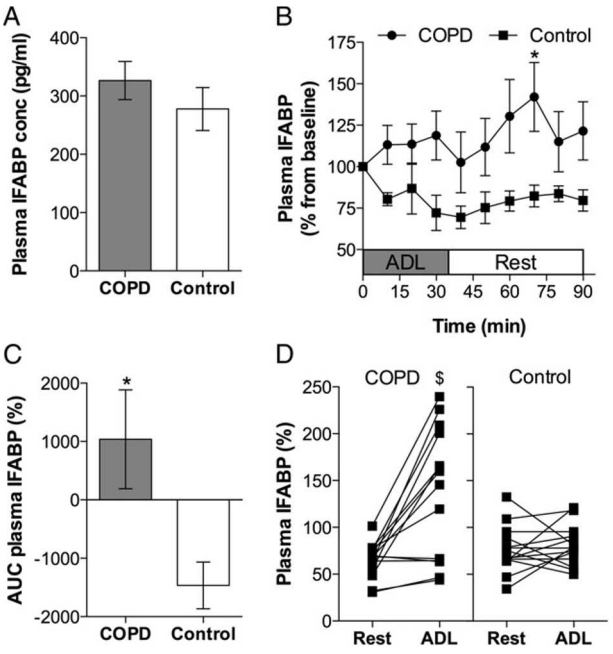

FIGURE 2. Enterocyte damage. A, Plasma IFABP levels in patients with COPD (n = 17) and control subjects (n = 14) in resting condition. The IFABP concentration at baseline of one patient with COPD was excluded because it was extremely high (12,507 pg/mL), whereas the average IFABP level was 327 pg/mL and 278 pg/mL for patients and control subjects, respectively. B, Percentage change in plasma IFABP from baseline in patients with COPD (n = 14) and control subjects (n = 14) during and after performing ADLs. C, Area under the curve of percentage IFABP change until 70 min after start of ADLs in patients and control subjects. D, Percentage plasma IFABP change from baseline to 70 min after start of ADLs or to 60 min in resting condition in patients and control subjects. Data are depicted as mean ± SEM. *$P < .05$ vs control subjects. $$P < .001$ vs rest. AUC = area under the curve; conc = concentration; IFABP = intestinal fatty acid binding protein. See Figure 1 legend for expansion of other abbreviation.

that IFABP levels were significantly higher in patients with COPD compared with control subjects during ADLs (significant group effect until 70 min, $P = .02$). Similarly, the AUC of plasma IFABP calculated until 70 min after starting the ADLs was significantly higher in the patients compared with control subjects (Fig 2C). In addition, most patients showed higher plasma IFABP levels (as percentage from baseline) at 70 min after starting the ADLs, when compared with levels measured after 60 min rest (paired t test, $P < .001$), whereas this was not the case in control subjects (Fig 2D). These data reflect the occurrence of enterocyte damage in patients with COPD while they were performing ADLs, which continued after completion of the activities.

GI Permeability Is Elevated in Patients With COPD Compared With Control Subjects

During resting conditions, there was a tendency observed for a higher L/R ratio in the 0- to 3-h urine collection (Fig 3A), whereas the S/E ratio was significantly

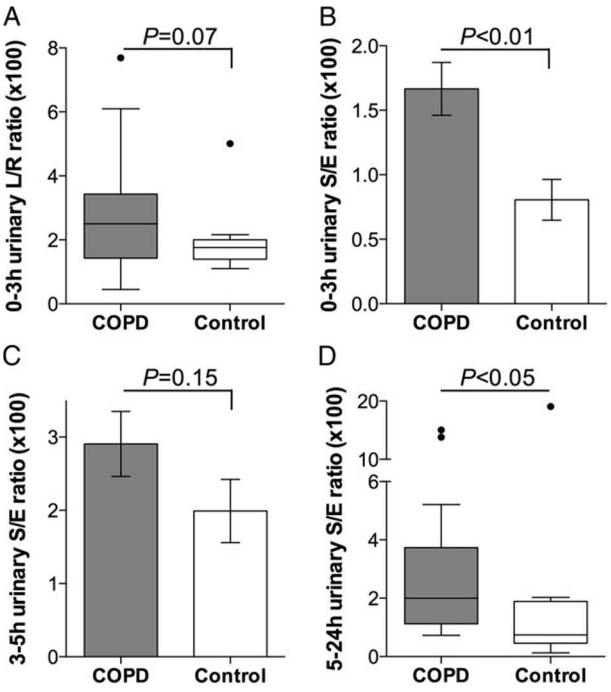

FIGURE 3. GI permeability at rest. A, L/R ratio of urinary excretion over a 3-h period after drinking sugar solution, reflecting small intestine permeability. B, S/E ratio of urinary excretion over 3 h after drinking sugar solution, reflecting small intestine permeability. C, S/E ratio of sugars excreted in urine collected in a 3- to 5-h period after drinking sugar solution, reflecting permeability of the distal small intestine and proximal colon. S/E ratio was 1.46-fold higher in patients vs control subjects, but was not statistically significant ($P = .15$). D, S/E ratio of sugars excreted in urine collected in a 5- to 24-h period after drinking sugar solution, reflecting colon permeability. Data are depicted as mean ± SEM if normally distributed and as Tukey boxplots if not. L/R = lactulose to rhamnose; S/E = sucralose to erythritol.

higher in the patients compared with healthy control subjects (Fig 3B). These data reveal that small intestine permeability is increased in patients with COPD. In 5- to 24-h urine collections, the S/E ratio was significantly higher in patients compared with control

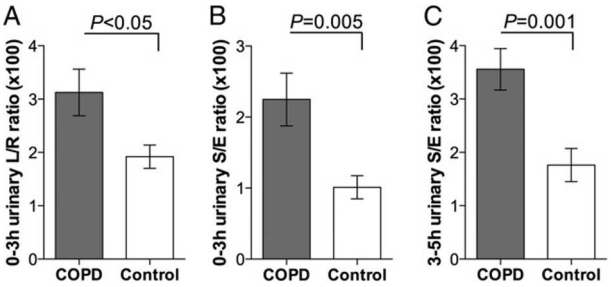

FIGURE 4. GI permeability after executing ADLs. A, L/R ratio of urinary excretion over a 3-h period after drinking sugar solution, reflecting small intestine permeability. B, S/E ratio of urinary excretion over a 3-h period after drinking sugar solution, reflecting small intestine permeability. C, S/E ratio of sugars excreted in urine collected in a 3- to 5-h period after drinking sugar solution, reflecting permeability of the distal small intestine and proximal colon. Data are depicted as mean ± SEM. See Figure 1 and 3 legends for expansion of abbreviations.

subjects. Significance remained after excluding the outliers ($P = .01$) (Fig 3D).

After performing ADLs, both the L/R ratio (Fig 4A) and the S/E ratio (Fig 4B) were significantly higher in the 0- to 3-h urine collection in patients compared with healthy subjects. In addition, the S/E ratio in the 3- to 5-h urine collection was significantly higher in patients vs control subjects. Overall, the differences in intestinal permeability between patients and control subjects were more pronounced during performing ADLs than in resting conditions. Interestingly, in patients, but not in control subjects, both the L/R and S/E ratios in 0- to 3-h urine collection correlated significantly with plasma lactic acid concentration as well as change in lactic acid concentration (δ lactic acid) immediately after execution of the ADLs (Fig 5).

Discussion

To our knowledge, this is the first study to report functional alterations in the GI tract of clinically stable

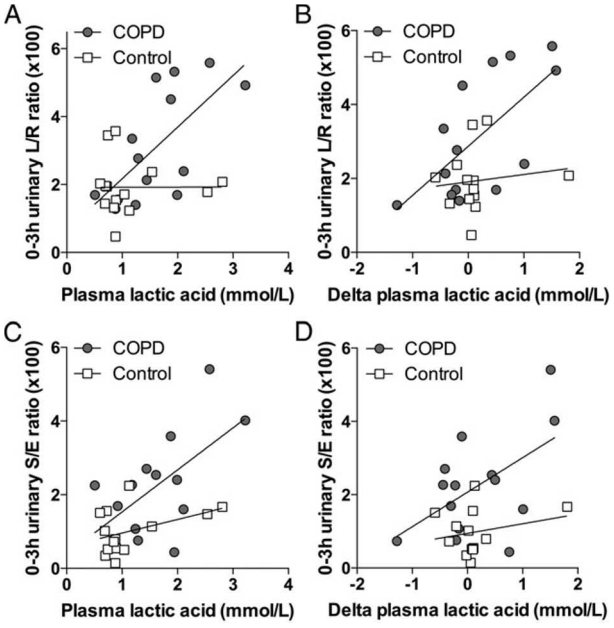

FIGURE 5. Correlation between plasma lactic acid concentration and small intestine permeability after performing ADLs. A, L/R ratio of urinary excretion over a 3-h period after drinking sugar solution. Plasma lactic acid concentration: Pearson correlation coefficient in patients with COPD, $r = 0.67$, $P < .01$; in control subjects, $r = 0.002$, $P = .99$. B, L/R ratio of urinary excretion over a 3-h period after drinking sugar solution. Change in plasma lactic acid concentration: Pearson correlation coefficient in patients with COPD, $r = 0.66$, $P = .01$; in control subjects, $r = 0.13$, $P = .67$. C, S/E ratio of urinary excretion over a 3-h period after drinking sugar solution. Plasma lactic acid concentration: Pearson correlation coefficient in patients with COPD, $r = 0.59$, $P = .03$; in control subjects, $r = 0.42$, $P = .13$. D, S/E of urinary excretion over a 3-h period after drinking sugar solution. Change in plasma lactic acid concentration: Pearson correlation coefficient in patients with COPD, $r = 0.55$, $P = .04$; in control subjects, $r = 0.24$, $P = .43$. See Figure 1 and 3 legends for expansion of abbreviations.

patients with moderate COPD. We provided clear evidence for the occurrence of enterocyte damage in these patients during ADLs. In resting conditions, permeability of both the small and large intestine is higher in patients with COPD compared with control subjects of similar age, BMI, and sex. The differences in intestinal permeability between patients and control subjects are intensified during standardized household activities. Hence, intestinal compromise should be considered as a new component in the systemic manifestation of COPD.

The present findings are in-line with those reported earlier in patients with chronic heart failure. Increased intestinal permeability, in addition to an altered colonic bacterial biofilm, has been shown in these patients.[7] Since moderate exercise led to increased intragastric CO_2 pressure, indicative of splanchnic hypoperfusion, it was suggested that compromised intestinal integrity contributes to the systemic manifestation seen in patients with chronic heart failure as a consequence of local oxygen shortage.[6] Although the etiology of chronic heart failure is different than that of COPD, these patients experience similar periods of oxygen desaturation due to a ventilation-perfusion mismatch during activity, which may evoke splanchnic hypoxia. We propose blood flow redistribution from the splanchnic bed to the active skeletal muscle tissue as the mechanism responsible for enterocyte damage observed in patients with COPD. Remarkably, the plasma levels of enterocyte-damage marker IFABP peaked after completion of ADLs, which suggests splanchnic blood flow normalization and concomitant intestinal reperfusion injury and, hence, prolonged intestinal compromise in this patient population.

Besides reperfusion injury, inadequate mucosal perfusion is known to increase intestinal permeability, as is shown in healthy trained volunteers when performing exhaustive physical exercise.[5] We detected higher permeability of both the small intestine and colon in patients with COPD compared with control subjects under resting conditions. Interestingly, executing ADLs resulted in an augmentation of this intestinal permeability difference between patients and control subjects. A previous study already showed that the performance of ADLs induces a higher metabolic load in patients with COPD compared with healthy elderly subjects,[11] which was confirmed in the present study. In addition, plasma lactic acid concentration and production during ADLs was positively correlated with intestinal permeability in patients with COPD but not in the control subjects, suggesting a generalized oxygen deficit in the former, affecting both muscle and intestinal tissue. Notably, the intestinal mucosal surface has a relatively low baseline oxygen tension and high energy demands, and intestinal epithelial cells have evolved molecular mechanisms to cope with this challenging condition, making them relatively resistant to hypoxia.[23] Nevertheless, these protective mechanisms seem overstretched in patients with COPD, based on our findings on ADLs-induced, likely ischemia-related, intestinal damage.

The mucosal barrier is made up of epithelial apical junction complexes, consisting of tight junctions and adherence junctions. These junctions are sensitive to hypoxia, but also to other COPD-related factors such as circulating proinflammatory cytokines.[24] In addition, translocation of bacteria or their products due to increased intestinal permeability may induce systemic inflammation, suggesting that the latter can also be a consequence rather than a cause of intestinal disturbances. COPD is recognized as a chronic, systemic, low-grade inflammatory disease; however, the occurrence of systemic inflammation is highly heterogeneous, ranging from no evidence of systemic inflammation to persistent systemic inflammation.[25] Although an important component associated with poor clinical outcome,[25] systemic inflammation, based on CRP and IL-6 levels, was not overt in the patients recruited in the current study, and did not differ from control subjects, indicating that this factor did not play a major role in the intestinal compromise observed here. Another important factor in COPD-related pathology is smoking. Smoking is known to influence the risk of inflammatory bowel diseases,[26] suggesting an effect of smoking on intestinal homeostasis. Interestingly, several reports showed, however, no difference in intestinal permeability between healthy smokers and nonsmokers.[27,28] In addition, in patients with heart failure, smokers and nonsmokers showed similar permeability indexes.[7] Since smoking has a significant effect on vascular function, we cannot exclude that smoking impaired splanchnic perfusion further during ADLs. The small study population does not allow drawing conclusions on the effect of smoking on the study outcomes.

In view of the results of this study, we expect patients with moderate COPD to experience recurrent episodes of enterocyte damage throughout the day, when walking, dressing, doing the laundry, shopping, cleaning, or performing other activities. They exhibit clearly a lower threshold for developing intestinal compromise during standardized household activities compared with healthy matched control subjects, making this potentially a part of their clinical picture. The functional alterations in the intestines of these patients may result in decreased host defense against bacteria, and increased systemic inflammation as we have discussed. Next, disturbed membrane integrity of mature absorptive enterocytes at the villus tips, as evidenced by IFABP release into the circulation, may reduce the digestive and absorptive capacity of the intestinal tract. Furthermore, the repeated

intestinal stress might induce a cellular repair program to restore the damage at the expense of supporting enterocyte absorptive function, possibly leading to temporarily diminished nutrient absorption and metabolic compromise in patients with COPD. In patients with chronic heart failure, a decrease in active and passive carrier-mediated transport for, respectively, 3-O-methyl-D-glucose and D-xylose was shown, indicating dysfunction of transport proteins and diminished intestinal absorptive function, which might be involved in nutritional perturbations that promote cachexia.[7,29] We recently reported a negative correlation between IFABP levels and in vivo rates of protein digestion and absorption following an exercise bout in young, healthy subjects, indicating reduced gut absorptive capacity in this situation.[30] In addition, evidence was provided for reduced splanchnic extraction of amino acids in patients with COPD,[31] potentially implying compromised intestinal function. Future studies including functional tests with, for example, D-xylose or fat absorption tests should be carried out to find a direct link between intestinal compromise and nutrient absorption in COPD. Another consequence of altered intestinal function could be impaired micronutrient absorption, as patients with COPD often exhibit deficits of vitamins such as vitamin D.[32] Clinical studies should be performed to assess the effect of intestinal compromise on macronutrient and micronutrient uptake in patients with COPD. Further, practicing food and fluid intake may decrease GI stress during exercise,[33] possibly also in patients with COPD in whom it is important to meet energy requirements. In addition, nutritional compounds like the amino acids arginine, glutamine, and citrulline, or lipids may enhance splanchnic perfusion and reduce intestinal damage during physical activity[34] or stress situations,[35] but effectiveness of these agents in patients with chronic diseases remains to be investigated.

To our knowledge, the present study is the first to provide compelling evidence that patients with COPD show intestinal compromise, which is potentially a new important aspect of their disease. A limitation of the present work is, however, that the study population was relatively small, making within-group associations hard to investigate. However, the fact that clear differences are detected between patients with COPD and healthy elderly subjects with this sample size strengthens our hypothesis. Interestingly, the pulmonary-intestinal crosstalk has been proposed previously,[36] and decreased pulmonary function has been shown in patients with inflammatory bowel disease.[37] These data emphasize the complex systemic interplay of organs in patients with chronic diseases.

In conclusion, intestinal integrity is disturbed in patients with COPD. Intestinal hyperpermeability is observed at rest and intensifies after performing standardized household activities, with concomitant enhanced enterocyte loss. These intestinal alterations should not be overlooked in both basic and clinical research. Clinical studies should also consider the GI tract as a therapeutic target in patients with COPD with respect to exercise and nutrition.

Acknowledgments

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Dr Rutten: contributed to writing the study protocol, patient inclusion, data analysis, and writing the manuscript.
Dr Lenaerts: contributed to writing the study protocol, sample and data analysis, and writing the manuscript.
Dr Buurman: contributed to writing the protocol and reviewing the manuscript.
Dr Wouters: contributed to writing the protocol and reviewing the manuscript.
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