Changes in Pulmonary Hyperinflation and Bronchial Hyperresponsiveness Following Treatment With Lansoprazole in Children With Cystic Fibrosis

J.J.E. Hendriks, MD,[1]* A.D.M. Kester, PhD,[2] R. Donckerwolcke, MD, PhD,[1] P.P. Forget, MD, PhD,[1] and E.F.M. Wouters, MD, PhD[3]

Summary. In this prospective open study of 14 children with cystic fibrosis (CF), we evaluated the effect of 1 year adjuvant therapy with lansoprazole, a proton pump inhibitor (PPI), on growth, fecal fat loss, body composition and lung function. Only stable patients with pancreatic insufficiency were included, and their data were compared to those of a large Dutch pediatric normal reference population.

During the use of the PPI, mean weight and height did not change significantly, while body mass index improved ($P < 0.05$). An immediate significant and persistent reduction of fecal acid steatocrit ($P < 0.05$) was demonstrated. Compared to normal Dutch children, the CF patients showed significantly decreased standard deviation scores (SDS) for total body fat (TBF, −0.966) and fat-free mass (FFM, −1.826). Under lansoprazole, TBF improved significantly ($P < 0.05$), while mean FFM remained unchanged. A significant improvement in total lung capacity ($P < 0.05$), residual volume ($P = 0.055$), and maximal inspiratory mouth pressure ($P = 0.002$) was also demonstrated. Hyperinflation tended to decrease during the use of a PPI. Daily recordings of peak expiratory flow (PEF) showed a maximal diurnal variability of 28% of recent best PEF and minimal morning PEF of 72% of recent best PEF, confirming that bronchial hyperresponsiveness is increased in CF.

We conclude that adjuvant therapy with lansoprazole in young CF patients with persistent fat malabsorption, decreased fat losses and improved total body fat. Lung hyperinflation decreased, which may partly explain the improvement in inspiratory muscle performance. The simultaneous improvements in body composition and lung hyperinflation suggest a relationship between these two parameters. Further research is necessary to confirm such a relationship and to elucidate the mechanisms involved. **Pediatr Pulmonol. 2001; 31:59–66.** © 2001 Wiley-Liss, Inc.

Key words: **cystic fibrosis; children; fat malabsorption; proton pump inhibitor; body composition; lung hyperinflation; respiratory muscles force; bronchial hyperresponsiveness; lansoprazole.**

INTRODUCTION

Cystic fibrosis (CF) is the most common lethal hereditary disease among Caucasians. The CF gene is located on chromosome 7, and so far more than 900 mutations have been reported. The basic defect is a dysregulation of the chloride channels resulting in dehydration of the luminal surface of exocrine cells. In the lungs this leads to an increase of mucus viscosity, altering normal ciliary clearance. Bacterial colonization, infection, and chronic pulmonary inflammation develop subsequently. Pulmonary complications account for most of the morbidity and mortality in CF patients.

Besides the respiratory complications, gastroenterological abnormalities give rise to significant morbidity. In children with CF, fat malabsorption leads to malnutrition and growth failure, often associated with increased catabolism. Administration of pancreatic enzymes improves, but does not reverse fat malabsorption completely. It has been hypothesized that the use of a proton pump inhibitor (PPI) could improve the effectiveness of the administered pancreatic enzymes. The aim of adding a PPI is to decrease gastric acid production. This is necessary in CF because of a decreased buffering capacity of

[1]Department of Paediatrics, University Hospital and University of Maastricht, The Netherlands.

[2]Department of Methodology and Statistics, University Hospital and University of Maastricht, The Netherlands.

[3]Department of Pulmonology, University Hospital and University of Maastricht, The Netherlands.

*Correspondence to: J.J.E. Hendriks, Department of Paediatrics, University Hospital Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: jhe@skin.azm.nl

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the pancreatic juices, secondary to decreased or absent bicarbonate secretion by the pancreas. If duodenal pH is less than 5, breakdown of the enteric coating of the administered enzyme capsules is hindered.[1,2] In addition, low pH may inactivate pancreatic enzymes. Both processes result in suboptimal functioning of these enzymes, accompanied by incomplete digestion and absorption of nutrients like fat.

A favorable effect of a PPI on fat absorption in adult CF patients was demonstrated by Heijerman et al.[3] We confirmed this favorable effect in a pilot study in children.[4] In that short-term (3 months) study, the use of lansoprazole led to a significant increase of total body fat (TBF) or fat mass, while fat-free mass (FFM) or lean body mass did not improve. Although it has frequently been suggested that changes in body composition can affect lung function and especially respiratory mechanics, this has not been proven in CF patients. Research to support this hypothesis is sparse. Steinkamp and von der Hardt[5] demonstrated that nocturnal tube feedings improved nutritional status and lung function in malnourished CF patients. More recently, Ionescu et al.[6] demonstrated that in the last stages of CF, survival was negatively associated with a body mass index (BMI) <20 kg/m^2 and low FFM, while sustained maximum inspiratory pressure seemed to be more impaired than peak maximum inspiratory pressure. Nutritional growth retardation and suboptimal increases of body cell mass have also been associated with progressive lung dysfunction in CF.[7] In addition to its effect on fat absorption and body composition, a PPI could have a favorable influence on bronchial hyperresponsiveness (BHR) by decreasing gastroesophageal reflux (GER).

The present study was carried out in 14 children with stable CF, and was primarily designed to investigate the effect of long term addition of a PPI on body composition. Secondly, the relation between changes in body composition and changes of dynamic and static lung function, as well as of respiratory muscle strength, were examined. Thirdly, we evaluated the effect of decreased acid secretion and possibly decreased GER on BHR.

ABBREVIATIONS

BHR	Bronchial hyperresponsiveness
BMC	Bone mineral content
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane regulator
DEXA	Dual energy x-ray absorptiometry
ERV	Expiratory reserve volume
FFM	Fat-free mass
FEV_1	Forced expiratory volume in 1 sec
FIP-E	Federation International Pharmaceutic-Eenheden
FVC	Forced vital capacity
GER	Gastroesophageal reflux
NS	Not significant
$MEF_{25\%FVC}$	Maximal expiratory flow at 25% FVC
$MIF_{50\%VCin}$	Maximal inspiratory flow halfway in the VC
PEF	Peak expiratory flow
Pimax	Maximal inspiratory mouth pressure
PEmax	Maximal expiratory mouth pressure
PPI	Proton pump inhibitor
REE	Resting energy expenditure
RV	Residual volume
SDS	Standard deviation score
SGAW	Specific airway conductance
TBD	Total bone density
TBF	Total body fat
TGV	Thoracic gas volume
TLC	Total lung capacity
VCin	Inspiration vital capacity

MATERIALS AND METHODS

Patients

Fourteen stable CF patients (9 males) with pancreatic insufficiency and mild lung disease were studied before and during one year of treatment with 15 mg lansoprazole daily. Diet and exogenous pancreatic enzyme therapy did not change during the intervention. We conducted an open study for practical reasons, because we preferred to use our patients as their own control; every CF patient is unique and not exactly comparable to any other CF patient. We therefore compared our patients to large normal (Dutch) populations and expressed changes as changes of standard deviation scores (SDS). In order to reduce the chance of a placebo effect, only stable and mild patients were included in the study, as demonstrated by the high prestudy FEV_1, which was not different from the baseline FEV_1. Criteria for inclusion in the study were a mean prestudy stool acid steatocrit (an index of fat absorption) of more then 25% (normal $< 20\%$), despite an intake of at least 2,000 IU lipase/kg body weight/day (mean use, 4,020 IU/kg/day). Further, our CF patients had to be able to perform reliable lung function tests, and in the prestudy year their FEV_1 had to be above 70% of predicted values (mean prestudy year FEV_1 was $85.2 \pm 13.6\%$). Finally, they had to be able to use a peakflow meter and to fill in diary cards correctly. Informed consent was obtained before onset of the study; the study protocol was approved by the Medical Ethics Committee of the University Hospital of Maastricht. Patient characteristics at baseline are given in Table 1.

Anthropometry

Anthropometric measurements were performed in triplicate by one single investigator using the same instruments, a Harpenden stadiometer (Holtain Ltd., Crymych, UK) and an electronic weight scale (Seca delta, Model 707). Results are expressed as SDS, using Dutch reference values collected by Gerver and de Bruin.[8,9]

TABLE 1—Patient Characteristics Before Treatment With a Proton Pump Inhibitor

Item	Mean	SD	Range
Age (year)	9.74	3.38	4.6/17.2
Height (cm)	133.9	16.6	107.0/162.3
SDS	−1.068	0.590	−2.166/+0.003
Weight (kg)	27.7	9.9	15.5/52.3
SDS	−1.270	0.739	−2.393/+0.272
Steatocrit (%)	33.3	17.7	5.4/65.7
FEV_1 (% predicted)	83.9	17.2	58/112
FVC (% predicted)	86.6	13.0	64/109

SDS, standard deviation score.

Fecal Fat Content

Steatorrhea was monitored by measuring the fecal acid steatocrit as previously described;[10,11] results are expressed as fat/fat + solid layer in %. Fecal acid steatocrit has been shown to correlate well with chemical analyses of fecal fat ($r = 0.83$).[12] We chose this method in order to repetitively and easily monitor fecal fat content during the study.

Body Composition

Body composition was assessed by dual energy x-ray absorptiometry (DEXA).[13] This noninvasive method allows an easy and rapid (20 min) evaluation of body composition. During one assessment, TBF, FFM, bone mineral content (BMC), and total bone density (TBD) are measured. A software pediatric program (Paediatric Beta Software: Lunar 1.5) was used to calculate these parameters. The radiation dose of this examination is very low (< 5 mRem) when compared with the standard background radiation exposure of 82 mRem/year, and is therefore considered to be the method of choice to measure body composition in young children. Results were compared with those of a large ($n = 403$) age matched normal Dutch reference group,[14] and results are expressed as SDS.

Lung Function

Lung function tests were performed by an experienced lung function technician, using a Jaeger Masterlab pneumotachograph and plethysmograph. Calibration of the apparatus was performed twice daily. Only lung function data with FVC variability of less than 5% on 3 consecutive maneuvers were accepted. Lung function parameters were expressed as % of predicted values, based on Zapletal reference values.[15] Mouth pressures were measured at residual volume (RV) for maximum inspiratory pressure (Plmax) and at total lung capacity (TLC) for maximum expiratory pressure (PEmax) according the method of Black and Hyatt.[16]

Bronchial Hyperresponsiveness

Peak expired flow (PEF) was measured at home four times daily, using a Personal Best PEF meter (Respironics HealthScan Products, Europe, Belgium). Instruction was given regarding the correct technique and reading of the PEF meter. Three consecutive maneuvers were carried out at each session, and only the best of 3 was used to calculate BHR. In order to measure changes in BHR, several PEF characteristics were calculated each week for every month of the study period:[17]

- Mean diurnal variability (in L/min).
- Maximal diurnal variability: the difference between the worst morning and best evening PEF of that week (expressed as % of that week's best PEF).
- Minimal morning PEF (expressed as % of that week's best PEF).
- The difference between the best morning and the best evening PEF (in L/min).

Resting Energy Expenditure and Diet

Basal metabolic rate or resting energy expenditure (REE) was measured by indirect calorimetry, using a ventilated hood,[18] and was compared to Schofield's age-related normal values for children.[19] Dietary evaluation was carried out using a 3-day diary of the diet of these CF patients. From the recorded data, lipase intake Federation International Pharmaceutic-Eenheden (FIP-E), dietary fat (gram/day), protein intake (gram/day), and energy (KJ/day) content were calculated. FIP-E units indicate amount of pancreatic enzymes taken by a patient.

Experimental Protocol

The following measurements were obtained over a period of 1 year. Before starting the study and at each 3 monthly visit, anthropometric data were obtained (5×). Three fecal samples before start of the study, and then two samples monthly, were taken during the 12-month study period, providing 27 specimens for analysis of acid steatocrit.

TABLE 2—Mean Values and Statistics of Anthropometry, Resting Energy Expenditure, Body Composition, and Dietary Parameters Before and During Proton Pump Inhibitor Therapy[1]

Parameter (n = 14)	Mean(SD) before PPI	Mean (SD) during PPI	Wilcoxon *P*-value
Weight (SDS)	−1.270 (0.739)	−1.118 (0.817)	0.177
Height (SDS)	−1.068 (0.590)	−1.017 (0.608)	0.198
Body mass index (kg/m^2)	14.95 (1.81)	15.38 (1.92)	0.035
Steatocrit (%)	33.3 (17.8)	24.0 (9.8)	0.030
Total body fat (SDS)	−0.966 (0.489)	−0.707 (0.695)	0.011
Fat free mass (SDS)	−1.820 (0.673)	−1.843 (0.687)	0.826
Resting energy expenditure (% predicted)	111.7 (12.1)	110.7 (9.1)	0.778
Lipase intake (IU/kg/day)	4,020.0 (970)	3,580.0 (880)	0.198
Fat intake (gr/day)	90.5 (18.8)	81.9 (17.0)	0.056
Energy intake (kJ/day)	9,713.0 (1,966)	9,181.0 (1,913)	0.056

[1]PPI, proton pump inhibitor; SDS, standard deviation score; BMI, body mass index.

Total body DEXA was performed every 6 months (3×). Lung function tests included flow volume curve, body plethysmograph, and PI/PE-max performed at each visit (5×). REE was measured every 6 months (3×). Diary cards with PEF were recorded for 1 week during each month (13×). Dietary intake was recorded before starting the study, and at 6 and 12 months (3×).

Statistics

Data are presented in tables as means and standard deviations, while in the figures medians and quartiles are presented as changes from baseline. We tested the response to the treatment for all measured parameters. To maximize the power of the tests, we compared the mean of the whole intervention period to the pretrial (baseline) values. In that way, the power of the test is optimized, since measurement errors and within-subject variations tend to cancel out. A second advantage of this method is that we avoided doing 4 different tests for essentially the same hypothesis, which would inflate the type-1 error probability beyond the nominal 5%.[20] This may give a less detailed picture of trends within the trial period. However, in a small trial like the present one, we would not have the power to detect such trends. If a clear trend was apparent, we noted it in Results; the figures show some of these trends. By using the nonparametric Wilcoxon signed ranks test, we avoided the assumption of normality further, which is untestable with only 14 subjects. All data are summarized in the Tables 2–4. Differences with respect to baseline were considered significant when the two-sided *P*-value was 0.05 or less. The statistical package SPSS (version 7.5 for Windows, 1996) was used for data management and analysis.

TABLE 3—Mean Values and Statistics of Static and Dynamic Lung Function and Respiratory Muscle Strength Parameters Before and During Therapy With a Proton Pump Inhibitor[1]

Parameter	N	Mean (SD) before PPI	Mean (SD) during PPI	Wilcoxon *P*-values
Total lung capacity (TLC) (% predicted)	13	109.5 (16.6)	100.3 (7.3)	0.025
Residual volume (RV) (% predicted)	13	179.6 (73.1)	141.5 (29.9)	0.055
Thoracic gas volume (TGV) (% predicted)	13	128.0 (42.9)	111.0 (13.1)	0.209
Expiratory reserve volume (% predicted)	13	71.9 (15.6)	78.6 (20.6)	0.133
RV/TLC (% predicted)	13	40.1 (10.1)	35.2 (7.2)	0.173
TGV/TLC (% predicted)	13	55.7 (9.2)	54.0 (4.6)	0.753
Forced expired volume in 1 sec (% predicted)	14	83.9 (17.2)	81.8 (16.9)	0.234
Forced vital capacity (% predicted)	14	86.6 (13.0)	87.6 (13.1)	0.950
Max. expiratory flow 25%FVC (% predicted)	14	56.6 (53.7)	34.8 (16.6)	0.103
Max. inspiratory mouth pressure (cmH_2O)	13	−66.3 (18.9)	−81.3 (18.7)	0.002
Max. expiratory mouth pressure (cmH_2O)	13	75.9 (15.8)	83.7 (18.4)	0.069
Max. inspiratory flow 50%FVC (% predicted)	14	47.3 (14.9)	47.6 (13.8)	0.925
Specific airway conductance (1/kPa.s)	13	0.864 (0.257)	0.854 (0.219)	0.807
Peak expiratory flow (% predicted)	14	90.6 (18.7)	87.9 (15.4)	0.177

[1]PPI, proton pump inhibitor.

TABLE 4—Mean Values and Statistics of the Home Recordings of Derived Peak Expiratory Flow Parameters Before and During Proton Pump Inhibitor Therapy[1]

Parameter (n = 14)	Mean (SD) before PPI	Mean (SD) during PPI	Wilcoxon *P*-value
Mean diurnal variability (L/min)	24.6 (16.7)	26.6 (15.6)	0.722
Maximal diurnal variability (%)	27.6 (12.3)	21.3 (4.4)	0.041
Minimal morning PEF (%)	72.4 (12.3)	78.4 (4.2)	0.056
Mean difference PEF (L/min)	5.9 (27.6)	16.5 (19.3)	0.106

[1]PPI, proton pump inhibitor; PEF, peak expiratory flow.

RESULTS

Anthropometry

Mean (±1 SD) body weight SDS increased from −1.270 (±0.739) to −1.085 (±0.827) at 9 months ($P < 0.05$). The mean body weight SDS during the study was −1.118 (±0.817; NS). Mean height SDS showed a slight, but not significant, increase from a mean of −1.068 (±0.590) before to −1.017 (±0.608) during the study. BMI was considerably decreased 14.95 (±1.81 kg/m^2) before the study, but improved significantly to 15.38 (±1.92 kg/m^2; $P < 0.05$) (Table 2).

Fecal Fat Content

An immediate and significant decrease in fecal fat content (acid steatocrit) was noticed, shortly after the addition of lansoprazole. The mean acid steatocrit decreased from 33.3% (±17.8%) at the start to 23.7% (±11.0%) at 3 months ($P < 0.01$) and remained at that level thereafter. The mean acid steatocrit during treatment was 24.0% (±9.8%; $P < 0.05$).

Body Composition

Body fat assessed by DEXA performed at 6 months showed a significant improvement, persisting throughout the entire study. Mean TBF SDS increased from −0.966 (±0.489) before to −0.707 (±0.695) during PPI therapy ($P < 0.05$). In contrast, mean FFM SDS did not change, from −1.820 (±0.673) before to −1.843 (±0.687; NS) during PPI (Table 2 and Fig. 1).

Lung Function

Mean TLC decreased from 109.5% (±16.6%) of predicted value before to 100.3% (±7.3%; $P < 0.05$) during PPI. Mean RV showed a nearly significant decrease from 179.6% (±73.1%) before to 141.5% of predicted value (±29.9%; $P = 0.055$) during PPI. Mean ITGV decreased from 128.0% (±42.9%) before to 111.0% of predicted value (±13.1%; NS) during PPI. Mean ERV increased from 71.9% (±15.6%) to 78.6% of predicted value (±20.6%; NS) during PPI. When ratios of these static lung volumes were calculated, no significant changes were noted: the RV/TLC ratio changed from 40.1% (±10.1%) before to 35.2% (±7.2%) during PPI, while the ITGV/TLC ratio changed from 55.7% (±9.2%) before to 54.0% (±4.6%) during PPI (Table 3).

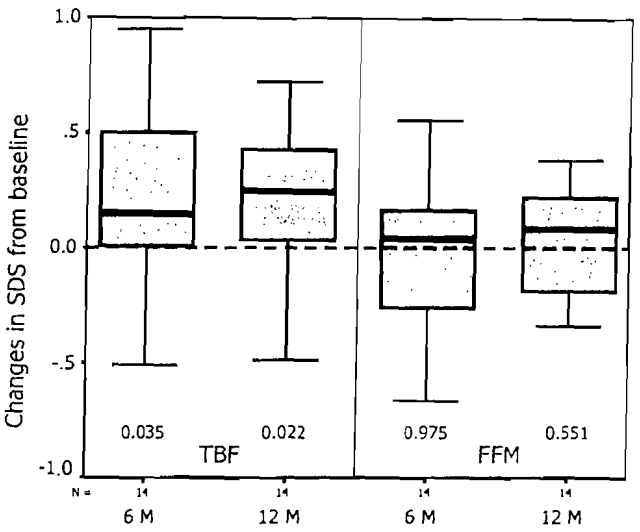

Fig. 1. Boxplots showing changes in standard deviation score for total body fat (TBF) and fat-free mass (FFM), 6 and 12 months after starting treatment with a proton pump inhibitor compared to the baseline value (at $t_0 \rightarrow Y = 0$) (*P*-values by Wilcoxon test).

Dynamic lung function parameters did not change significantly. Mean FEV_1 changed from 83.9% (±17.2%) to 81.8% of predicted value (±16.9%; NS) during PPI. Mean FVC from 86.6% (±13.0%) to 87.6% of predicted value (±13.1%; NS) during PPI. Mean sGAW did not change significantly, from 0.864 1/kPa.s (±0.257) to 0.854 (±0.219). Also, mean pneumotachographic PEF did not change, from 90.6% (±18.7%) to 87.9% of predicted value (±15.4%; NS) during PPI (Table 3).

Respiratory muscle strength parameters, especially mean PImax, improved markedly. PImax changed from −66.3 (±18.9 cmH_2O) to −81.3 (±18.7; $P = 0.002$) during PPI, and PEmax from 75.9 (±15.8 cmH_2O) to 83.7 (±18.4; $P = 0.069$) during PPI, while maximum inspired flow at 50% of inspired VC (MIF50%VCin) did not change during PPI, from 47.3% (±14.9%) to 47.6% of predicted value (±13.8%; NS) (Table 3 and Fig. 2).

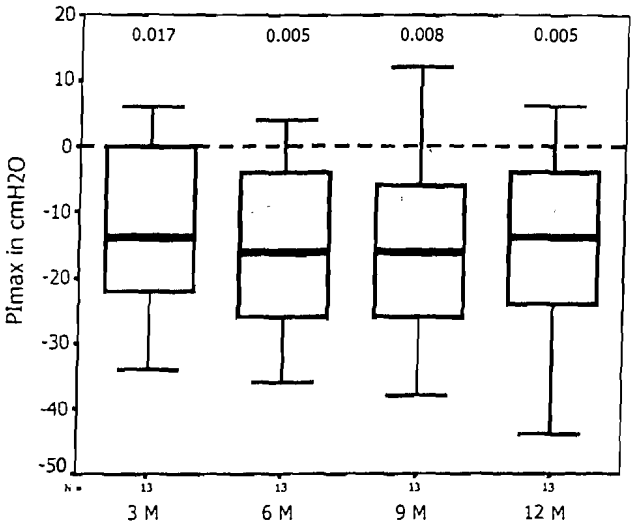

Fig. 2. Boxplots showing changes in maximal inspiratory pressure (PImax) comparing each 3-month period, during treatment with a proton pump inhibitor, with the baseline value (at $t_0 - Y = 0$) (*P*-values by Wilcoxon test).

Bronchial Hyperresponsiveness

The monthly recordings at home with the Personal Best PEF meter demonstrated variable changes. While mean diurnal variability increased slightly from 24.6 (± 16.7 L/min) before to 26.6 (± 15.6 L/min; NS) during PPI, maximal diurnal variability decreased significantly from 27.6% (± 12.3% of recent best) before to 21.3% of predicted value (± 4.4%; $P < 0.05$) during PPI. Minimal morning PEF increased from 72.4% (± 12.3%) before to 78.4% of predicted value (± 4.2%) during PPI ($P = 0.056$). Mean difference between best evening and best morning PEF increased from 5.9 (± 27.6) L/min before to 16.5 (± 19.3; NS) L/min under PPI (Table 4).

Resting Energy and Diet

REE did not change during PPI, from 111.7% of reference values (± 12.1%) to 110.7% (± 9.1%; NS). Dietary intake did not change significantly. Mean fat intake decreased from 90.5 (± 18.8) gram/day to 81.9 (± 17.0; NS) gram/day during PPI, and total daily energy intake decreased from 9,713 (± 1,966) kJ/day to 9,181 (± 1,913; NS) kJ/day during PPI (Table 2). The mean intake of lipase decreased from 4,020 (± 970) IU/kg to 3,580 (± 880; NS) IU/kg during PPI.

DISCUSSION

In the present study of 14 young CF patients, we evaluated the effect of lansoprazole on growth, fecal fat loss, body composition, and the consequences of possible changes in body composition on lung function and BHR. The decreased mean SDSs for weight, height, and BMI in our patients confirmed the well-known growth retardation of CF patients.[21] The use of a PPI resulted in a better increase in SDS for weight rather than height; however, despite a visible trend, both changes were not significant when averaged for the whole treatment period. BMI, which is derived from weight and height, did improve significantly. As this study was performed using an open design protocol, in a small group of CF patients, the results should be interpreted cautiously. But as our previous open study,[4] concerning the effect of a PPI on stool fat and body composition, showed similar results (decrease of stool fat and increase of TBF, with unchanged FFM), a placebo effect is unlikely. In the present study, performed in partly the same population and with more than 1 year off PPI in the interim, similar changes were measured and confirmed on several occasions during the treatment year. Repeated confirmation and progression of favorable changes during 1 year of follow-up are more likely to be due to treatment than to a placebo effect.

Our results show a significant and persistent decrease of the mean acid steatocrit during the entire study period. The finding that weight improved more than height can be explained by improved fat absorption and an increased TBF on treatment with PPI. Our body composition measurements are in line with this statement. Compared to normal Dutch children, our CF patients showed significant decreases of both mean TBF and FFM. Under treatment with a PPI and despite a nonsignificant decrease in fat and energy intake, mean TBF improved significantly, while mean FFM remained unchanged. The decreased steatocrit values could either be due to this slight decrease of fat intake or to improved fat absorption. Because the lipase intake also decreased, the second hypothesis seems more likely, as it also explains the significant increase of body fat and BMI. These results confirm previous findings showing a favorable effect of proton pump inhibitors on fecal fat losses in CF. An explanation for these diverging results concerning the improvement of TBF but not FFM could be the lack of an exercise program during the study.[22]

Despite a lack of improvement of FFM, we could demonstrate an improvement of static lung volumes (TLC and RV) and respiratory muscle performance, as shown by improvement of the expiratory and inspiratory forces, especially PImax.[23] Although we could demonstrate a significant decrease in TLC and a nearly significant decrease in RV, the ratio RV/TLC appeared not to change significantly. The initial mean RV/TLC ratio of 40% is, however, significantly increased when compared to that of normal individuals. The lack of a significant change of TGV is probably related to the large SD in that measurement at the start. The relation between decrease

of hyperinflation (TLC and RV) and improvement of respiratory muscle force is more difficult to interpret. Indeed, a decrease of hyperinflation can lead to a more favorable starting point for diaphragm muscle contraction, improving the contractile force and therefore maximal mouth pressures.[24] Lands et al.[25] demonstrated in their comparative study an effect of nutritional status on respiratory muscle strength in CF patients but not in asthmatic and anorexia nervosa patients, indicating that the combination of malnutrition and chronic hyperinflation gives rise to inefficient functioning of the diaphragm. On the other hand, Murciano et al.[26] demonstrated in malnourished anorexia nervosa patients a prompt improvement in diaphragmatic contractility with nutritional support. Ionescu et al.[6] demonstrated that in CF patients there is a significant relation between inspiratory muscle function and body composition. The decrease of TLC and RV with an increase of PI/PEmax in the present study points to such a beneficial effect of PPI on the diaphragm muscles. But since ITGV, ERV, and RV/TLC did not change, we could not demonstrate an improvement in elastic recoil. In the absence of absolute changes in body FFM, the improvement of PI/PEmax during the intervention period could hypothetically be explained by metabolic adaptations in the respiratory muscles rather than by changes in the mechanical properties of the diaphragm. As our protocol was not designed to investigate such metabolic muscle disturbances, we are unable to prove this statement. A growing number of studies on the functioning of the cystic fibrosis transmembrane regulator (CFTR) point to the presence of various cellular metabolic changes. As ventilatory muscle training was not part of the intervention procedure, training effects are not expected to be related to these changes in ventilatory muscle function. Besides the PImax, the *sustained* maximal inspiratory presure could have clinical significance in CF patients. Further studies are needed to assess the effects of PPI on *endurance* of the inspiratory muscles.

The reduction in lung volumes during lansoprazole treatment seems clinically relevant in view of the data of Kraemer et al.,[27] who recently showed in 60 infants with CF that differences in lung function within subgroups of mutations were mainly related to pulmonary hyperinflation. Hyperinflation seems to occur in a very early phase of the disease and may even precede inflammation and infection. This might, at least partly, be influenced by the type of mutation, as shown by Kraemer et al. Lung hyperinflation in CF patients have been related to surfactant deficiency.[28–31] The improved fat absorption might have a favorable effect on surfactant composition, but the relation between the use of a PPI and improvement of surfactant composition has yet to be demonstrated. Another factor contributing to hyperinflation could be the degree of inflammation, especially of the smaller airways. Bronchial inflammation is known to be present in CF, where it has been demonstrated even in very young CF patients.[32] The absence of effects on SGAW after PPI therapy does not exclude changes in small airways.

Body fat plays an important role in energy homeostasis by production of the adipocyte-derived leptin. Leptin seems to have a pleotrophic function in the body, and its administration has been shown to improve immune function.[33] Further studies are necessary in order to elucidate the relation between leptin metabolism and the observed changes in body composition in CF patients.

From the daily recordings of the PEF at home, maximal diurnal variability and minimal morning PEF are the most important indicators for the existence of BHR.[19] Both the maximal diurnal variability, being nearly 30% of recent best PEF, and the weekly minimal morning PEF, being only 72% of recent best PEF, support the conclusion that BHR is increased in CF. When compared to normal children, patients with CF show an increased prevalence of BHR.[34] BHR is directly related to bronchial inflammation, but also to GER. GER is common in CF patients,[35] and is often present in infants[36] and toddlers.[37] Consequently, administration of lansoprazole might affect both GER and BHR. Assessment of diurnal variability of PEF has been proposed as a surrogate for directly measuring the degree of BHR in asthmatic patients, even when asymptomatic,[38] but its usefulness has been limited because of its rather poor reproducibility.[39] However it remains the only available method to measure diurnal changes of airway obstruction in everyday life.[40] We demonstrated a significant decrease in maximal diurnal variability and a nearly significant change in minimal morning PEF. Mean diurnal variability did not improve at all, which points to the poor reproducibility of this method. The mean differences increased only slightly towards the end of the study, which demonstrates that evening PEF improved more than morning PEF, but this change was not significant. Although our results of PEF recordings do not allow us to conclude definitely that BHR in CF patients is decreased by therapy with a PPI, our results suggest that BHR is present in CF and that GER may contribute to it. More studies are necessary to confirm this finding.

In conclusion, we recommend regular assessment, even in young CF patients, of dynamic as well as static lung volumes. Further, our study shows that improvement of body composition and of some lung function parameters, particularly TLC and PImax, occur in parallel, as body composition improved with PPI therapy. We recommend that all possible effort be made to reduce fat malabsorption in young CF patients. The relationship between body composition and lung function in children with CF should be further studied in order to elucidate the mechanisms involved.

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