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Effects of Lung Volume Reduction Surgery for Emphysema on Glycolipidic Hormones*

Davide Mineo, MD; Vincenzo Ambrogi, MD; Luca Frasca, MD; Maria Elena Cufari, MD; Eugenio Pompeo, MD; and Tommaso Claudio Mineo, MD

Background: **Pulmonary emphysema is associated with cachexia and disregulation of the hormones regulating the glycolipid metabolism, insulin resistance, and altered substrate utilization. This study aimed at identifying the effects of lung volume reduction surgery (LVRS) on glycolipidic hormones compared to respiratory rehabilitation (RR).**

Methods: **Thirty-three patients with moderate-to-severe emphysema who were undergoing video-assisted thoracoscopic LVRS were compared to 31 similar patients who refused the operation and followed a standardized RR program. All patients were evaluated before and 12 months after treatment for respiratory function, body composition, glycolipidic hormones, metabolic parameters, and insulin resistance, which was calculated using the homeostatic model assessment index for insulin resistance (HOMA-IR). These groups were compared to a matched healthy control population.**

Results: **Only after LVRS significant improvements were obtained in respiratory function (FEV_1, + 25.2%; $p < 0.0001$; residual volume, −19.5%; $p < 0.0001$), metabolic parameters (total cholesterol, + 13.1%; $p < 0.01$; high-density lipoprotein cholesterol, + 11.2%; $p < 0.01$; triglycerides, +18.4; $p < 0.001$; nonesterified fatty acid, − 19.7%; $p < 0.001$), and body composition (fat-free mass [FFM], + 6.5%; $p < 0.01$; fat mass [FM], + 11.9%; $p < 0.01$). The leptin/FM ratio (− 6.1%; $p < 0.01$) and resistin/FM ratio (− 5.6%; $p < 0.01$) decreased, whereas the adiponectin/FM ratio (+ 6.9%; $p < 0.01$) and ghrelin (+ 9.2%; $p < 0.01$) increased, together with reductions in glycemia (− 8.8%; $p < 0.01$), insulin level (− 20.4%; $p < 0.001$), and HOMA-IR (− 27.2%; $p < 0.0001$). The decrement in residual volume was correlated with increment of FFM ($\rho = -0.49$; $p < 0.02$), FM ($\rho = -0.55$; $p < 0.009$), and ghrelin ($\rho = -0.52$; $p < 0.01$), and also with decreases in leptin corrected for FM ($\rho = 0.50$; $p < 0.02$) and, marginally, HOMA-IR ($\rho = 0.35$; $p = 0.07$).**

Conclusions: **After LVRS, glycolipidic hormone levels and nutritional status significantly improved, along with insulin resistance reduction and more physiologic utilization of substrates. Correlations between residual volume and body composition as well as glycolipidic hormone levels suggest that postoperative recovery in respiratory dynamics may induce favorable clinical changes when compared to RR.** ***(CHEST 2008; 134:30–37)***

Key words: COPD; ghrelin; insulin; leptin; lung volume reduction surgery; resistin

Abbreviations: FFM = fat-free mass; FM = fat mass; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment index for insulin resistance; LVRS = lung volume reduction surgery; NEFA = nonesterified fatty acid; RR = respiratory rehabilitation

Pulmonary emphysema causes significant systemic alterations including progressive tissue depletion, both fat mass (FM) and fat-free mass (FFM),[1–4] mainly due to persistent inflammation, chronic hypoxemia, and impaired respiratory dynamics. The so-called *respiratory cachexia* is associated with the elevation of inflammatory cytokine levels and the reduction of anabolic hormone levels. This condition is further worsened by long-term steroid therapy.[5,6] In particular, the hormones regulating the glycolipidic metabolism appear to be altered, with disregulation of insulin, leptin, and ghrelin secretion, and induction of insulin

resistance. These alterations, together with a shift from oxidative to glycolytic metabolism in peripheral skeletal muscles, secondary to the increased resting energy expenditure, favor a prevalent lipid substrate utilization and protein wasting.[1–9]

Compared to maximal medical therapy and standard respiratory rehabilitation (RR), lung volume reduction surgery (LVRS) has been shown to be effective in improving respiratory function, exercise tolerance, quality of life, nutritional status, resting energy expenditure, and substrate oxidation pattern in properly selected patients.[10–13] To date, little information is available regarding the effects of LVRS on glycolipidic hormone levels. The aim of this study was to analyze, in a prospective nonrandomized trial, the effects of LVRS in patients with moderate-to-severe emphysema on glycolipidic hormones, metabolism, and nutritional status, compared to those of RR.

Materials and Methods

Study Design and Populations

The study was a prospective nonrandomized trial of 33 consecutive male white patients with moderate-to-severe emphysema who were undergoing standard resectional videothoracoscopic LVRS[12] (*ie*, the LVRS group). They were compared to 31 similar patients who were eligible for surgery during the same time frame but had undergone a standardized RR program twice during the year (*ie*, the RR group) after having denied their final consent to undergo the operation for personal reasons.

The study population (*ie*, the LVRS group plus the RR group, designated as the emphysematous group) was compared to a matched control group of 30 male, white, healthy, never-smoker subjects, who were not receiving any drug that would interfere with the glycolipidic metabolism and underwent the same examinations at baseline and 12 months after treatment. No statistical differences were found in this group at reevaluation after 1 year (data not shown).

The analysis included intragroup evaluations (LVRS and RR groups, baseline vs 12 months after treatment) and intergroup evaluations (emphysematous group vs healthy group, at baseline and 12 months after treatment; LVRS group vs RR group, at baseline and 12 months after treatment). The study was approved by the ethics committee at our institution, was activated in July 2002, and patients were recruited up to July 2005. Written informed consent was obtained from all patients.

The observational period was set at 12 months, assuming that the maximal improvement should be reached for both treatments within this time frame. The inclusion criteria required the patients to be clinically stable, to be performing regular mild physical activity, and to be receiving an adequate balanced diet (1,800 kcal/d). All patients were receiving inhaled steroid and β_2-agonist therapy, with none having started oral steroid in the 6 months prior to study enrollment. Patients were excluded if they were receiving long-term oxygen therapy or had received RR in the last year; had concomitant endocrine, metabolic, or other chronic diseases; or were receiving any drugs that could interfere with the glycolipidic metabolism.

Respiratory and Body Composition Evaluations

Respiratory assessments included timed spirometry, plethysmography (Vmax22; SensorMedics; Yorba Linda, CA), single-breath diffusing capacity of the lung for carbon monoxide, and arterial blood gas analysis. Exercise tolerance was assessed with a standard 6-min walking test. Dyspnea was rated with the Medical Research Council index (best, 1; worst, 3).[14] Quality of life was assessed with the St. George Respiratory Questionnaire general score (best, 0; worst, 100).[15] Body composition, as body content of FM and FFM reported as absolute values and percentages, was measured using a dual-energy radiograph absorptiometry total body scanner (model QDR 2000; Hologic; Bedford, MA).[16]

Hormonal and Metabolic Evaluations

Blood samples were collected between 7:00 and 8:00 AM, after overnight fasting, were centrifuged, and were stored at − 80°C until processing. Leptin (normal male value, 0.5 to 13.8 ng/mL) [Human Leptin IRMA Kit; Diagnostic Systems Laboratories; Webster, TX], ghrelin (normal male value, 300 to 4,000 pg/mL) [radioimmunoassay; Mediagnost GmbH; Reutlingen, Germany], adiponectin (normal male value, 6.9 to 12.7 μg/mL) [enzyme-linked immunosorbent assay; BioVendor GmbH; Heidelberg, Germany], resistin (normal male value, 4 to 12 ng/mL) [enzyme-linked immunosorbent assay; BioVendor GmbH], and insulin (normal male value, 2.6 to 24.9 μU/mL) [electrochemical luminescence immunoassay; Roche Pharmaceuticals; Basel, Switzerland] were measured. Since leptin, adiponectin, and resistin are secreted from the adipose tissue, their levels positively correlate with body fat content. Their values were corrected for FM to better evaluate the effective posttreatment changes.

The homeostatic model assessment index for insulin resistance (HOMA-IR) was used to assess insulin resistance, according to the following formula: fasting glucose (in milligrams per deciliter) × fasting insulin (in micromoles per liter)/405 (cutoff ≥ 3 defining a state of insulin resistance).[17] Metabolic evaluation included biochemical parameters, such as fasting glucose, total cholesterol, and high-density lipoprotein (HDL) cholesterol, triglycerides, and nonesterified fatty acid (NEFA) [Randox Laboratories; Crumlin, UK].

Surgical Intervention

Four-port, video-assisted, thoracoscopic, resectional LVRS was performed in all surgical interventions, as has previously been reported.[12] The most damaged portions of the lung were reeval-

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uated by intraoperative inspection and resected using simple nonbuttressed suture lines, possibly excising a single strip of parenchyma to reduce the lung volume by approximately 30%.

Rehabilitation Therapy

The program entailed 3-h supervised sessions, 5 days per week for at least 6 weeks, twice a year.[18] The first half of each session included educational activity, such as breathing retraining, chest clearance, energy conservation, nutritional and medication education, and psychosocial support, while the second half included physical conditioning with inspiratory resistive exercises and upper and lower extremity training.

Statistical Analysis

Descriptive statistics were presented as the mean ± SD. Due to the nonnormal distribution of some variables and the limited sample size, nonparametric tests (SPSS, version 15.0; SPSS Inc; Chicago, IL) were used (Wilcoxon rank sum test for paired comparisons and Mann-Whitney tests for unpaired comparisons). Significance was set at $p < 0.05$. To study dependence among variables, a Spearman correlation analysis was performed in the surgical group, using the 12-month postoperative percentage changes. Data were presented with the ρ coefficient and relative significance.

Results

Baseline Intergroup Analysis

No significant differences in age, smoking history, disease severity, or medication use was found between emphysematous patients and healthy subjects (not shown). As expected, emphysematous patients had moderate-to-severe airway limitation with altered FEV_1, residual volume, dyspnea index, 6-min walking test results, and St. George respiratory questionnaire findings, whereas healthy subjects had normal values. Body composition revealed a poorer nutritional status (mean body mass index, 22.4 ± 1.7 vs 27.4 ± 2.1 kg/m^2, respectively; $p < 0.05$) in the emphysematous group than in the healthy group, with decrements in both FM (17.0 ± 4.2 vs 26.1 ± 2.5 kg, respectively;

Table 1—*Baseline Mean Values With Intergroup Comparisons

Variables	LVRS Group (n = 33)	RR Group (n = 31)	p Value†	Healthy Group (n = 30)	p Value‡
Age, yr	61 ± 7.9	60 ± 8.2	NS	63 ± 10	NS
Smoking history, pack-yr	31 ± 12	33 ± 10	NS		< 0.0001
FEV_1, % predicted	33 ± 7.1	34 ± 7.4	NS	82 ± 9.0	< 0.0001
Residual volume, % predicted	192 ± 34	189 ± 31	NS	112 ± 29	< 0.0001
DLCO, mmol/kPa/min	3.8 ± 0.8	3.9 ± 0.6	NS	8.7 ± 1.7	< 0.0001
PaO_2, kPa	9.6 ± 0.8	9.7 ± 0.7	NS	11.7 ± 1.8	< 0.0001
6-min walking test distance, m	410 ± 33	417 ± 43	NS	520 ± 60	< 0.0001
MRC dyspnea index	3.0 ± 0.8	2.9 ± 0.9	NS	0.5 ± 0.2	< 0.0001
St. George respiratory questionnaire quality of life index	26.6 ± 17.6	23.5 ± 18.9	NS	3.3 ± 2.5	< 0.0001
Body mass index, kg/m^2	22.5 ± 1.9	22.4 ± 1.6	NS	27.4 ± 2.1	< 0.05
FFM					
kg	49.6 ± 5.8	49.5 ± 6.0	NS	55.8 ± 7.0	< 0.05
%	74.5 ± 6.5	74.4 ± 5.9	NS	69.2 ± 4.2	< 0.05
FM					
kg	16.9 ± 4.3	17.1 ± 4.5	NS	26.1 ± 2.5	< 0.0001
%	22.4 ± 8.1	22.3 ± 7.7	NS	25.1 ± 5.8	< 0.01
Leptin, ng/mL	3.9 ± 1.3	4.1 ± 1.2	NS	6.0 ± 1.3	< 0.001
Leptin/FM ratio, ng/mL/kg	0.24 ± 0.1	0.25 ± 0.1	NS	0.23 ± 0.1	NS
Adiponectin, μg/mL	4.6 ± 1.8	4.6 ± 1.9	NS	8.3 ± 1.6	< 0.001
Adiponectin/FM ratio, μg/mL/kg	0.28 ± 1.2	0.29 ± 1.5	NS	0.32 ± 1.2	NS
Resistin, ng/mL	2.3 ± 1.1	2.3 ± 1.2	NS	3.5 ± 0.9	< 0.001
Resistin/FM ratio, ng/mL/kg	0.14 ± 0.1	0.14 ± 0.1	NS	0.13 ± 0.0	NS
Ghrelin, pg/mL	350 ± 77	357 ± 64	NS	541 ± 76	< 0.001
Glycemia, mg/dL	103 ± 6.3	102 ± 8.3	NS	92 ± 14	< 0.05
Insulin, μU/mL	23.2 ± 6.0	22.8 ± 5.9	NS	8.6 ± 2.7	< 0.0001
HOMA-IR	5.9 ± 1.5	5.7 ± 1.2	NS	1.9 ± 0.7	< 0.0001
Total cholesterol, mg/dL	153 ± 52	158 ± 47	NS	187 ± 44	< 0.01
HDL cholesterol, mg/dL	38.1 ± 14.1	39.1 ± 13.7	NS	53.7 ± 15.4	< 0.001
Triglycerides, mg/dL	130 ± 50	138 ± 43	NS	153 ± 36	< 0.01
NEFA, mg/dL	19.4 ± 8.1	18.9 ± 9.3	NS	11.6 ± 8.3	< 0.01

*Values are given as the mean ± SD, unless otherwise indicated. NS = not significant; DLCO = diffusing capacity of the lung for carbon monoxide; MRC = Medical Research Council.

†LVRS group vs RR group.

‡Emphysematous group (LVRS plus RR) vs healthy group.

$p < 0.0001$) and FFM (49.5 ± 5.9 vs 55.8 ± 7.0 kg, respectively; $p < 0.01$) corresponding to a lower FM percentage (22.3 ± 8.0% vs 25.1 ± 5.8%, respectively; $p < 0.01$) [Table 1].

Mean levels of leptin (4.0 ± 1.2 vs 7.2 ± 1.2 ng/mL, respectively; $p < 0.001$), resistin (2.3 ± 1.2 vs 3.5 ± 0.9 ng/mL, respectively; $p < 0.001$), and adiponectin (4.6 ± 1.8 vs 8.3 ± 1.6 μg/mL, respectively; $p < 0.001$) were significantly lower in emphysematous patients compared to healthy subjects. These significances disappeared when values were corrected for FM, as follows: leptin and resistin levels became relatively more elevated; whereas adiponectin levels remained lower in the emphysematous group compared to the control group. Similarly, mean ghrelin levels (354 ± 70 vs 541 ± 76 pg/mL, respectively; $p < 0.001$) were significantly lower in the emphysematous group.

Mean fasting glycemia levels were significantly higher in the emphysematous patients compared to the healthy subjects (102.9 ± 9.1 vs 92.3 ± 14 mg/dL, respectively; $p < 0.05$), as well as insulin levels (23.0 ± 6.2 vs 8.6 ± 2.7 μU/mL, respectively; $p < 0.0001$) and, accordingly, HOMA-IR values (5.8 ± 1.4 vs 1.9 ± 0.7, respectively; $p < 0.0001$). Conversely, mean total cholesterol levels (155 ± 49 vs 187 ± 44 mg/dL, respectively; $p < 0.01$), HDL cholesterol levels (38.5 ± 13.9 vs 53.7 ± 15.4 mg/dL, respectively; $p < 0.01$), and triglyceride levels (134 ± 46 vs 153 ± 36 mg/dL, respectively; $p < 0.01$) were considerably lower in the emphysematous group with respect to the healthy control group, while NEFA levels were higher (19.2 ± 8.6 vs 11.6 ± 8.3 mg/dL, respectively; $p < 0.01$).

Posttreatment Intragroup Analysis

In the LVRS group, all patients were available for the 12-month follow-up. In the RR group, one patient died, and the cause of death (car accident) apparently was unrelated to the lung disease.

All patients continued receiving combined inhaled therapy, with none of them requiring oral steroid

Table 2—*Posttreatment Mean Raw and Percentage Changes With Intragroup and Intergroup Comparisons

Variables	LVRS Group (n = 33)		RR Group (n = 30)			
	Raw Change (%)	p Value	Raw Change (%)	p Value	p Value†	p Value‡
FEV_1, % predicted	+ 7.9 (+ 25.2)	< 0.0001	+ 2.2 (+ 6.5)	< 0.05	< 0.01	< 0.001
Residual volume, % predicted	− 37.7 (− 19.5)	< 0.0001	+ 1.0 (+ 0.5)	NS	< 0.01	< 0.01
DLCO, mmol/kPa/min	+ 0.2 (+ 3.3)	< 0.05	+ 0.4 (+ 2.5)	NS	< 0.05	< 0.001
PaO_2, kPa	+ 0.7 (+ 7.4)	< 0.01	+ 0.1 (+ 4.3)	< 0.05	< 0.05	< 0.01
6-min walking test distance, m	+ 41.1 (+ 10.4)	< 0.01	+ 21 (+ 5.1)	< 0.01	< 0.01	< 0.001
MRC dyspnea index	− 1.8 (− 58.3)	< 0.0001	− 1.0 (− 33.3)	< 0.01	< 0.0001	< 0.001
St. George respiratory questionnaire quality of life index	− 10.8 (− 20.6)	< 0.001	− 1.8 (− 7.8)	< 0.01	< 0.0001	< 0.01
Body mass index, kg/m^2	+ 1.7 (+ 7.6)	< 0.01	− 0.8 (− 3.3)	NS	< 0.001	NS
FFM						
kg	+ 3.2 (+ 6.5)	< 0.01	− 1.6 (− 3.0)	NS	< 0.001	NS
%	− 0.9 (− 1.1)	NS	+ 0.1 (+ 0.1)	NS	< 0.01	NS
FM						
kg	+ 1.9 (+ 11.9)	< 0.01	− 0.6 (− 3.4)	NS	< 0.0001	NS
%	+ 0.8 (+ 4.0)	< 0.05	− 0.1 (− 0.2)	< 0.05	< 0.01	NS
Leptin, ng/mL	+ 0.1 (+ 4.5)	< 0.05	+ 0.05 (+ 1.2)	NS	< 0.05	< 0.01
Leptin/FM ratio, ng/mL/kg	− 0.1 (− 6.1)	< 0.01	+ 0.01 (+ 3.2)	NS	< 0.01	NS
Ghrelin, pg/mL	+ 28.7 (+ 9.2)	< 0.01	− 9.0 (− 2.4)	NS	< 0.001	< 0.01
Adiponectin, μg/mL	+ 0.8 (+ 19.8)	< 0.001	− 0.1 (− 2.5)	NS	< 0.001	NS
Adiponectin/FM, μg/mL/kg	+ 0.1 (+ 6.9)	< 0.01	− 0.01 (− 1.5)	NS	< 0.01	< 0.01
Resistin, ng/mL	+ 0.1 (+ 5.3)	< 0.05	+ 0.04 (+ 1.9)	NS	< 0.05	NS
Resistin/FM ratio, ng/mL/kg	− 0.1 (− 5.6)	< 0.01	+ 0.01 (+ 2.3)	NS	< 0.01	< 0.01
Glycemia, mg/dL	− 9.4 (− 8.8)	< 0.01	+ 1.1 (+ 1.1)	NS	< 0.01	NS
Insulin, μU/mL	− 4.9 (− 20.4)	< 0.001	+ 0.7 (+ 3.2)	NS	< 0.0001	< 0.01
HOMA-IR	− 1.6 (− 27.2)	< 0.0001	+ 0.3 (+ 4.9)	NS	< 0.0001	< 0.01
Total cholesterol, mg/dL	+ 5.0 (+ 13.1)	< 0.01	+ 2.6 (+ 1.7)	NS	< 0.01	NS
HDL cholesterol, mg/dL	+ 2.6 (+ 11.2)	< 0.01	− 0.2 (− 0.5)	NS	< 0.01	NS
Triglycerides, mg/dL	+ 16.3 (+ 18.4)	< 0.001	− 2.0 (− 1.4)	NS	< 0.001	NS
NEFA, mg/dL	− 5.3 (− 19.7)	< 0.001	+ 0.4 (+ 2.3)	NS	< 0.001	NS

*See Table 1 for abbreviations not used in the text.
†LVRS vs RR.
‡LVRS group vs healthy group.

therapy. After undergoing LVRS, significant improvements were observed in most of the respiratory, symptomatic, and nutritional parameters (Table 2). Significant increases were found in body mass index (+ 7.6%; $p < 0.01$), FFM (+ 6.5%; $p < 0.01$), FM (+ 11.9%; $p < 0.01$), and percentage of FM values (+ 4.4%; $p < 0.05$).

LVRS patients also showed significant decreases in the mean dosages of daily inhaled medications, as follows: beclomethasone, from 1.2 ± 0.2 to 0.7 ± 0.3 mg/d ($p < 0.001$); budesonide, from 630 ± 70 to 410 ± 80 μg/d ($p < 0.001$); salbutamol, from 360 ± 40 to 190 ± 50 μg/d ($p < 0.001$); or formeterol, from 38 ± 10 to 22 ± 11 μg/d ($p < 0.001$). Interestingly, the absolute value of leptin appeared slightly increased (+ 4.5%; $p < 0.05$) but resulted in a significant decrease as leptin corrected for FM (− 6.1%; $p < 0.01$). Resistin showed a similar trend with increment of the absolute value (+ 5.3%; $p < 0.05$) and a decrement when corrected for FM (− 5.6%; $p < 0.01$), whereas adiponectin levels significantly increased in both evaluations (+ 19.8% [$p < 0.001$] and + 6.9% [$p < 0.01$], respectively). Finally, ghrelin also showed a significant postoperative increase (+ 9.2%; $p < 0.01$). HOMA-IR significantly decreased (− 27.2%; $p < 0.0001$), mainly due to a significant decrease in insulin (− 20.4%; $p < 0.001$) that was greater than that of glycemia (− 8.8%; $p < 0.01$). Accordingly, there were increases in total cholesterol levels (+ 13.1%; $p < 0.01$) and HDL cholesterol levels (+ 11.2%; $p < 0.01$) as well as triglyceride levels (+ 18.4%; $p < 0.001$), while NEFA levels decreased (− 19.7%; $p < 0.001$). After RR, significant improvements were found only for some respiratory variables, whereas nutritional parameters and glycolipidic hormone levels showed mild but significant worsening, with medication requirements remaining substantially unchanged (Table 2).

Posttreatment Intergroup Analysis

At baseline, no statistical differences were observed between the LVRS and RR groups with regard to mean age, respiratory function, nutritional status, and glycolipidic hormone levels, confirming the homogeneity of the study sample (Table 1). Twelve months after treatment, LVRS patients showed significant improvements with regard to the respiratory and nutritional variables as well as glycolipidic hormone levels when compared to RR patients, thus approximating the levels in healthy subjects (Table 2). In particular, FM and FFM showed a substantial amelioration, and body mass index significantly increased. The glycolipidic hormone levels returned to a more physiologic balance, with a reduction in insulin resistance and more appropriate substrate utilization, as confirmed by the decrement in fasting glycemia, insulin, and NEFA levels.

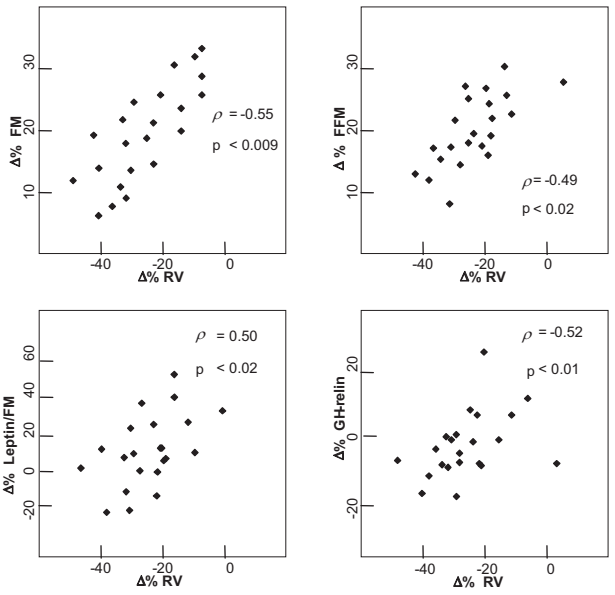

FIGURE 1. Correlation analysis (Spearman test) in LVRS group.

Correlation Analysis

In the LVRS group, the improvement in respiratory function appeared correlated with the amelioration of body composition and glycolipidic hormone values (Fig 1). As previously reported,[13] the reduction in residual volume was significantly correlated with the increment of FFM ($\rho = -0.49$; $p < 0.02$) and FM ($\rho = -0.55$; $p < 0.009$). In addition, the reduction of residual volume was significantly correlated with the increase in ghrelin ($\rho = -0.52$; $p < 0.01$), with the reduction in leptin corrected for FM ($\rho = 0.50$; $p < 0.02$), and only marginally with the decrease in the HOMA-IR ($\rho = 0.35$; $p = 0.07$).

DISCUSSION

In normal conditions, body composition and the glycolipidic metabolism are under a multihormonal control. Insulin, which is produced by pancreatic β cells, stimulates tissue glucose utilization, regulates fatty acid metabolism, and favors protein synthesis. In a state of insulin resistance, both muscle tissue and the liver are unable to utilize glucose as the energetic or deposit substrate and divert their metabolism to lipids. NEFAs are greatly available due to the concomitant increased lipid release from the

adipose tissue and liver, and the reduced lipid clearance in the peripheral tissues.[19]

Leptin, which is produced by the adipose tissue, informs the hypothalamus on body fat storage, suppressing food intake and increasing energy expenditure. Notably, its secretion is also stimulated by insulin in response to feeding and *vice versa*. Adiponectin and resistin, which also are secreted by the adipose tissue, are reciprocal antagonist hormones that regulate glycemia by decreasing or increasing insulin resistance, respectively.[20] Because of their common origins and peculiar roles they are called *adipokines*. Ghrelin, which is released by the gastric fundus, stimulates appetite, reduces energy expenditure, enhances glucose utilization, and prevents fat consumption, thus restoring body weight and composition, both FFM and FM.[21,22]

Several studies[1–9] have confirmed that emphysema can significantly affect glycolipidic hormones and metabolism. Insulin resistance and impaired glucose tolerance, with increased levels of insulin and HOMA-IR, but normal fasting glycemia, have been demonstrated in hypoxic patients.[23] Muscle protein depletion and preferential lipid substrate utilization with altered lipid profile (*ie*, low cholesterol and triglyceride levels, and high NEFA level) have been described in patients with a severe stage of disease.[24] The chronic elevation of inflammatory cytokine levels, which disrupts normal hormonal secretion and peripheral tissue substrate metabolism, is the main cause of such alterations.[25]

Several reports[26] have described reduced leptin levels in stable patients compared to control subjects, in accordance with a low body mass index and FM. On the contrary, leptin levels appeared to be increased and directly correlated to inflammatory cytokine levels, causing nutritional decay, in unstable or exacerbated patients.[27,28] To date, resistin and adiponectin levels in emphysema patients have been poorly investigated. Only one study[29] has reported reduced resistin levels in stable emphysematous patients, particularly if they were malnourished, when compared to healthy subjects. No data are available, so far, with regard to adiponectin levels in patients with pulmonary emphysema.

Most studies[30] describe increased ghrelin levels that are proportional to disease severity, as a compensation for the cachectic state. Conversely, it has been shown[31] that ghrelin levels may be decreased due to the high levels of inflammatory cytokines, thus explaining its efficacy in improving body composition when used as therapy for respiratory cachexia.[32]

When compared to maximal medical and rehabilitation therapy, LVRS provides an immediate and prolonged improvement of functional indexes, static volumes, exercise capacity, nutritional status, and quality of life.[12,13] After LVRS, the amelioration of gas exchange capacity and the reduction of the oxygen cost of breathing were correlated with weight gain[33] and FFM recovery.[34,35] We also showed that improvements in body weight and composition, bone mineral density, and resting energy expenditure correlated with the surgical reduction of residual volume.[13,36,37]

In this study, we evaluated whether LVRS could induce significant changes in glycolipidic hormone secretion, thus improving nutritional and clinical status. After LVRS, relevant changes in adipokine production were observed, suggesting a higher absolute secretion from the increased body fat content. However, after correction for FM, adiponectin levels showed even a greater increase, whereas leptin and resistin levels appeared to be decreased, revealing a lower relative release of adipokines from single adipose cells, with a preferential secretion for anabolic hormones rather than catabolic hormones. The significant increase of ghrelin reinforced this trend in the hormonal profile, favoring a recovery in body composition, both FFM and FM, and an amelioration of energy metabolism.

Likewise, the significant postoperative decrease in fasting insulin and glucose levels, and HOMA-IR, as well as the increase in levels of cholesterol and triglycerides and the decrease in NEFA indicated a healthier nutritional status and a reduction in insulin resistance. Hence, the increased insulin activity in the peripheral tissues induced a more appropriate utilization of glucose, instead of lipids, as the preferential energy substrate. The comparison with healthy subjects confirmed that the LVRS patients tended to approximate a more normal glycolipidic hormonal profile and substrate metabolism.

We hypothesized that LVRS, by reducing lung residual volume, decreases the thoracic hyperinflation and favors the recuperation of proper muscle respiratory function and dynamics.[2] Furthermore, by recruiting new anatomic spaces and supplementary pulmonary microcircles, LVRS increases both gas exchange capacity and oxygen tissue availability.[38] Such changes induced a reduction in breathing workload and energy expenditure, reversing the hypermetabolic-catabolic metabolism and tissue depletion, with restoration of body composition and hormonal profile. The reduction in respiratory medications and the prolonged cessation of tobacco smoking may also contribute to the improvement of the surgical patient.

A possible decrease in the chronic inflammatory status associated with emphysema due to the surgical reduction of the pulmonary source of the inflammatory cytokines could explain these postoperative hormonal changes, favoring a more physiologic metabolic and nutritional status. Correlation analysis

confirmed that the postoperative improvement of respiratory function positively influences glycolipidic metabolism and nutritional status. In particular, the surgical reduction of residual volume seemed to correlate with changes in levels of glycolipidic hormones, reducing the anorexigenic leptin levels and increasing the orexigenic ghrelin levels, with a recovery of body composition, increasing both FFM and FM.

The limitations of the study may be the relatively small sample size and the short follow-up. The changes in the levels of inflammatory mediators were not investigated, and their possible causal role needs further studies.

In conclusion, LVRS has demonstrated to steadily restore respiratory dynamics when compared to RR, with significant improvement of glycolipidic hormone levels and nutritional status, reduction in insulin resistance, and a more physiologic glucose utilization as the preferred energy substrate. The amelioration of glycolipidic hormone levels and body composition correlated with the surgical reduction of residual volume, suggesting that the recovery of respiratory function and mechanics may induce favorable hormonal and metabolic changes with nutritional recuperation. Such changes may represent a possible mechanism for the clinical improvements seen after LVRS when compared to RR.

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Effects of Lung Volume Reduction Surgery for Emphysema on Glycolipidic Hormones*

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