CLINICAL SCIENCE

The effect of acute magnesium loading on the maximal exercise performance of stable chronic obstructive pulmonary disease patients

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OBJECTIVE: The potential influence of magnesium on exercise performance is a subject of increasing interest. Magnesium has been shown to have bronchodilatatory properties in asthma and chronic obstructive pulmonary disease patients. The aim of this study was to investigate the effects of acute magnesium IV loading on the aerobic exercise performance of stable chronic obstructive pulmonary disease patients.

METHODS: Twenty male chronic obstructive pulmonary disease patients (66.2 ± 8.3 years old, FEV_1: 49.3 ± 19.8%) received an IV infusion of 2 g of either magnesium sulfate or saline on two randomly assigned occasions approximately two days apart. Spirometry was performed both before and 45 minutes after the infusions. A symptom-limited incremental maximal cardiopulmonary test was performed on a cycle ergometer at approximately 100 minutes after the end of the infusion. ClinicalTrials.gov: NCT00500864

RESULTS: Magnesium infusion was associated with significant reductions in the functional residual capacity (-0.41 l) and residual volume (-0.47 l), the mean arterial blood pressure (-5.6 mmHg) and the cardiac double product (-734.8 mmHg.bpm) at rest. Magnesium treatment led to significant increases in the maximal load reached (+8 w) and the respiratory exchange ratio (0.06) at peak exercise. The subgroup of patients who showed increases in the work load equal to or greater than 5 w also exhibited significantly greater improvements in inspiratory capacity (0.29 l).

CONCLUSIONS: The acute IV loading of magnesium promotes a reduction in static lung hyperinflation and improves the exercise performance in stable chronic obstructive pulmonary disease patients. Improvements in respiratory mechanics appear to be responsible for the latter finding.

KEYWORDS: Pulmonary Disease; Chronic Obstructive; Magnesium; Cardiopulmonary Exercise Test; Spirometry; Blood Pressure; Circulatory and Respiratory Physiology.

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INTRODUCTION

Magnesium (Mg) is involved in a great number of enzymatic reactions and may be involved in several biological processes, such as energy production, glycogen catabolism, control of neuronal activity, cardiac electric conduction, muscular contraction, vasomotor tone, and blood pressure (1,2). An increased interest in the potential influence of Mg on exercise performance has been observed in recent years (2-6).

Nutritional status is an important determinant of exercise performance in patients with chronic respiratory diseases (7). A potential role for Mg supplementation in regard to physical performance may be pronounced in these patients. Dietary Mg intake has been shown to be related to lung function, airway reactivity, and respiratory symptoms (8,9). Some studies have suggested that patients with chronic obstructive pulmonary disease (COPD) may exhibit decreased body levels of Mg (10-12). This abnormality may be related to the chronic use of medicines such as steroids and bronchodilators or the presence of food ingestion disorders. Inhaled Mg and IV Mg administration have been shown to promote bronchodilation and to improve lung function in asthmatic subjects (13-15). The IV administration of Mg during episodes of acute exacerbation of COPD in patients treated with albuterol leads to improvements in the peak flow (12). In another study, also involving COPD subjects with exacerbations, the effects of IV Mg were evident only after albuterol inhalation (16).

In a previous study, we have investigated the acute effects of the IV loading of Mg on the pulmonary function

No potential conflict of interest was reported.

parameters of stable COPD patients (17). The treatment was associated with a reduction in lung hyperinflation and an improvement in respiratory muscle strength. The objective of the present paper is to report the effects of acute Mg IV loading on the exercise performance of stable COPD subjects. We hypothesized that these patients would have a high frequency of hypomagnesemia and that Mg treatment would lead to improvements in their maximal exercise performance, primarily in the most stable subjects with low Mg levels.

MATERIALS AND METHODS

Patients

All patients had a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria (18). All individuals were former smokers who had quit smoking for at least 12 months. They also had been in a stable clinical condition for at least two months before admission to the study. Patients with a history of asthma or allergy, renal failure, heart failure, arrhythmias or cardiac electrical disturbances, or a significant disease other than COPD, were excluded. Individuals on chronic oral steroids, diuretics, or multimineral supplements were also excluded. The study was approved by the institutional medical ethics committee, and all of the volunteers gave their written informed consent at the initial visit. The protocol has also been registered at ClinicalTrials.gov (NCT00500864). The pulmonary function data from 18 of the present patients have been included in a previously published paper related exclusively to the evaluation of Mg effects on spirometric parameters and respiratory muscle strength (17).

Study design

This was a randomized, double-blinded, placebo-controlled crossover study. The patients attended an initial visit during which a clinical history was provided, pulmonary function tests were performed, basal arterial blood gases were determined, and blood for the Mg measurements was obtained. The volunteers were then randomized by drawing lots to receive one of two sequences of treatment: a placebo on day 1 and Mg on day 2, or Mg on day 1 and a placebo on day 2. Although we attempted to keep a fixed interval of two days between day 1 and day 2, the personal issues of some subjects led to the extension of this interval up to five days. The placebo or the Mg was administered slowly by an IV infusion through venous access in the arm. A total of 33 ml of a 20% Mg sulfate aqueous solution (Aster, Sorocaba, Brazil) was diluted in 67 ml of saline, corresponding to 2 g of the salt. This dose was given to the patients based on the recommendations in previously published papers (19). The placebo was similarly administered as 100 ml of saline. All researchers and technicians were blinded to the treatment administered, except for the pharmacist who prepared the solution immediately before the tests.

On the study days, the patients were subjected to the following procedures: (i) pulmonary function tests; (ii) an IV infusion of Mg or the placebo; (iii) blood venous sampling for plasma Mg measurements 30 minutes after the end of the infusion; (iv) a new set of pulmonary function tests performed 45 minutes after the end of the infusion; and v) a symptom-limited maximal cardiopulmonary exercise test performed within 90 and 120 minutes after the end of the IV infusion. All physiological and biochemical measurements were performed in the morning, with the patients abstaining from the use of bronchodilators and anti-inflammatory or any other type of medication for at least 18 hours prior to the experimental procedures.

Pulmonary function tests

Spirometry data were obtained using a water-sealed Godard spirometer (SensorMedics, Bilthoven, The Netherlands). The forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and the forced expiratory flow at 25–75% of the expiratory curve ($FEF_{25–75\%}$) were calculated employing representative curves. The total lung capacity (TLC) and residual volume (RV) were measured using the helium dilution technique. The procedures were performed according to the American Thoracic Society's recommendations, and the predicted normal values were based on Crapo et al. (20-22).

Exercise test

Symptom-limited incremental maximal cardiopulmonary exercise tests were performed in a cycle ergometer (Corival 400, Lode, Holland) according to the Brazilian Cardiology Society guidelines (23). All patients were submitted to a ramp protocol comprising one resting minute, four minutes biking at no load, and computer-driven automatic load increments every minute after that. The ramp increments were set in an individualized way, according to clinical estimates of the subject's exercise capacity. The exercise protocols were planned for test durations between 8 and 12 minutes. The patients were encouraged to maintain a velocity of 60 rpm, and the same protocol was applied on both occasions. The heart rate and rhythm were continuously monitored by an electrocardiogram and an analogic polygraph (HP 7754A, Palo Alto, CA, USA). Breath-by-breath respiratory measurements were registered using an ergospirometer (CPX/D MedGraphics, St. Paul, Minnesota). The arterial oxygen saturation was continuously monitored by a pulse oximeter (Moriya 1001, Japan). The arterial blood pressure was non-invasively measured at two-minute intervals. The perceptions of dyspnea and leg effort were measured at the end of the tests, using the modified Borg scale.

Magnesium levels

Basal plasma magnesium levels were measured in the venous blood samples collected into lithium-heparin tubes during an initial visit. Blood samples were also obtained from the arm that had not received the IV infusions on the two protocol days. The samples were stored at –80℃ after processing, and all analyses were performed on the same occasion using a Perkin Elmer model 3110 atomic absorption spectrometer (Waltham, MA, USA).

Statistical analysis

The data are reported as the means and the standard deviations. The data obtained on days 1 and 2 were compared according to the recommended methodology for investigations with a crossover design, including an assessment for period effects and treatment/period interactions (24,25). Paired t-tests were employed in this setting. Post hoc comparisons between the variables with the patients classified according to the degree of their response to the Mg infusion were performed employing non-paired t-tests. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

A total of 34 COPD patients were screened, 14 of whom were not admitted to the study due to the exclusion criteria. Twenty male patients were enrolled in the study (Table 1). According to the GOLD standards, nine (45%) patients were classified as having severe disease, seven (35%) were classified as having moderate disease, three (15%) were classified as having very severe disease, and one (5%) was classified as having mild disease. The mean plasma Mg level in the basal condition was within the normal range of the method for the whole group. However, when we analyzed the results considering the lower level of normality (1.5 Meq/L) as a limit, seven (35%) of the patients may be classified as exhibiting an Mg deficiency.

The mean time interval between the first and the second visit was 1.9 days, ranging from 1 to 5 days. Half of the volunteers received a placebo on day 1 and Mg on day 2. The statistical analysis showed no carryover effects, indicating that the order of the treatments and the variable washout period did not influence the final results. As expected, the infusion of 2 g of magnesium sulfate was associated with a significant increase in the mean plasma ion level compared with the placebo (Figure 1). The patients did not complain of serious side effects either during or immediately following the Mg infusion. Three (15%) patients noted a transitory hot wave sensation throughout their bodies. Another two (10%) patients described a short period of drowsiness.

The administration of Mg was not associated with significant changes in FVC, FEV_1, FEV_1/FVC or $FEF_{25–75\%}$ (Table 2). Magnesium infusion was associated with a non-significant decrease in TLC, but it was associated with significant reductions in the residual volume (RV) and functional residual capacity (FRC). The mean effects of the Mg treatment on the TLC, RV and FRC were, respectively, -0.30 l, -0.47 l, and -0.41 l. The inspiratory capacity (IC) improved to approximately 0.12 l, but this change did not reach statistical significance.

Table 1 - Characteristics of the 20 studied male COPD patients*.

Age (years)	66.2±8.3
TLC (% predicted)	121.4±17.9
FVC (% predicted)	89.0±22.7
FEV_1(% predicted)	49.3±19.8
FEV_1/FVC	43.8±11.4
$FEF_{25-75\%}$ (% predicted)	17.0±9.6
RV (% predicted)	169.7±52.6
FVC bd. response (% baseline)	7.7±8.0
FEV_1 bd. response (% baseline)	9.0±7.3
$FEF_{25-75\%}$ bd. response (% baseline)	13.9±18.6
pH	7.42±0.03
PaO_2 (mmHg)	76.3±7.8
$PaCO_2$ (mmHg)	40.3±3.9
$P(A\text{-}a)O_2$ (mmHg)	21.9±6.7
Plasma Mg level (mEq/l)	1.6±0.4

*TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; $FEF_{25-75\%}$: middle curve forced expiratory flow; $P(A\text{-}a)O_2$: alveolo-arterial oxygen gradient.

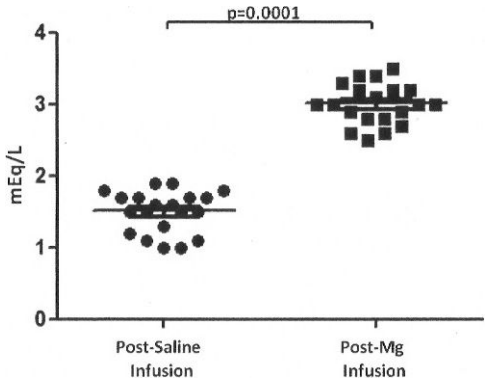

Figure 1 - Mg plasma levels after infusion of 2 g of magnesium sulfate or saline in 20 male COPD patients.

Among the several cardiorespiratory parameters measured with the patients seated on the cycle ergometer at rest, administration of Mg led to significant decreases only in the diastolic and mean arterial blood pressures (Table 3). In addition, the cardiac double product was significantly reduced as a result of Mg administration (-734.8 bpm.mmHg), and the arterial oxygen saturation evaluated by the pulse oximeter improved slightly (0.8%).

The use of Mg was associated with a significant increase in the duration of exercise (53 seconds) and of the maximal reached load (8.0 w) (Table 4). The respiratory exchange ratio (RER) showed a small but significant increase after Mg administration (0.06). Although Mg use led to a significant increase in the tidal volume at the peak of exercise (90.2 ml), there were no differences between the drug and the placebo treatments regarding the maximal ventilation.

The anaerobic threshold could be determined in only 12 subjects due to technical questions. There were no significant differences between the treatment and the placebo days, except that the time required to reach the anaerobic threshold after the Mg administration was significantly longer than that observed after the placebo was administered (10′23″ ±2′14″ ×9′43″ ±1′51″; $p=0.029$). The mean load reached at the anaerobic threshold was higher after the Mg administration than after the saline was administered, but the difference did not reach statistical significance (52.9±19.0 w×46.6±19.7 w; $p=0.083$).

To clarify the potential mechanisms related to the exercise improvements after Mg loading, we also analyzed the results with the patients divided in two subgroups based on changes in the maximal workloads that were lower than, or equal to or higher than 5 watts, respectively designated as Group I and Group II (Table 5). Ten patients were included in each group, and they did not differ in regard to age (64.9±9.6×67.5±7.0 years; $p=0.499$) or basal Mg plasma levels (1.6±0.4×1.6±0.3 mEq/l; $p=0.709$). These groups did not significantly differ regarding the treatment's effect on the Mg plasma levels or on the exercise hemodynamic parameters. However, the Group II patients showed a significantly better response of IC at rest and of the minute ventilation at the exercise peak.

DISCUSSION

This study detected low plasma Mg levels in 35% of a highly selective sample of COPD patients. This figure is consistent with the results of previous papers (10,11).

Table 2 - Effects of Mg loading on the pulmonary function parameters of 20 COPD patients*.

	Saline			Mg			Treatment effect (CI 95%) (Mg-Saline)	*p*-value
	Before	After	Before - After	Before	After	Before - After		
TLC (l)	6.35±1.16	6.47±0.95	0.12±0.80	6.19±0.85	6.01±1.04	-0.18±0.90	-0.30 (-0.73 – 0.13)	0.161
FVC (l)	2.85±0.80	2.88±0.88	0.03±0.24	3.11±0.72	3.18±0.80	0.07±0.19	0.03 (-0.08 – 0.14)	0.542
FEV_1 (l)	1.27±0.56	1.26±0.61	-0.01±0.10	1.28±0.53	1.31±0.56	0.03±0.13	0.04 (-0.03 – 0.11)	0.227
FEV_1/FVC (%)	43.4±10.4	42.4±11.1	-0.95±3.21	42.4±10.5	42.7±9.9	0.29±3.41	1.24 (-0.88 – 3.36)	0.235
$FEF_{25-75\%}$ (l)	0.44±0.27	0.40±0.22	-0.03±0.11	0.43±0.24	0.43±0.24	-0.01±0.10	0.03 (-0.04 – 0.09)	0.370
FRC (l)	4.34±1.07	4.38±0.83	0.04±0.84	4.12±0.83	3.75±1.01	-0.37±0.93	-0.41 (-0.82 – -0.01)	0.048
RV (l)	3.40±1.03	3.54±0.99	0.13±0.83	3.21±0.69	2.87±0.92	-0.34±0.97	-0.47 (-0.92 – -0.02)	0.042
ERV (l)	0.94±0.58	0.85±0.56	-0.09±0.23	1.02±0.72	0.87±0.50	-0.14±0.51	-0.05 (-0.29 – 0.19)	0.677
IC (l)	1.98±0.49	2.07±0.56	0.09±0.31	2.05±0.43	2.25±0.48	0.20±0.27	0.12 (-0.05 – 0.28)	0.148

*TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; $FEF_{25-75\%}$: middle curve forced expiratory flow; FRC: functional residual capacity; ERV: expiratory reserve volume; IC: inspiratory capacity.

Most important, this study also demonstrated that acute IV loading with 2 g of Mg sulfate attenuates static hyperinflation and positively affects the maximal exercise performance in stable COPD patients. We chose to investigate the effects of Mg on exercise performance following acute IV loading to guarantee similar stable clinical conditions for the COPD patients on both study days. Although the experimental conditions do not necessarily replicate results that would be obtained with the dietary supplementation of Mg for longer periods, they suggest that elevations in the body's Mg levels may be associated with meaningful physiological effects for COPD.

Static hyperinflation in COPD results mainly from the decreased elasticity of the lung parenchyma associated with emphysematous changes (26). In this study, treatment with Mg was associated with significant changes in the FRC and RV, indicating its substantial effect on lung hyperinflation approximately 45 minutes after the end of infusion. The decreases in the FRC and the RV are, most likely, secondary to the reductions in the expiratory airflow resistance because there is evidence that Mg antagonizes the action of calcium at the bronchial smooth muscle level, promoting relaxation and bronchodilatation (27). Other potential mechanisms leading to bronchodilatation may also include the inhibition of the release of acetylcholine at the nerve endings, stimulation of prostacyclin generation, and increases in the local synthesis of nitric oxide (28-30).

The Mg loading also led to significant changes in the cardiovascular parameters at rest. The mean blood pressure dropped approximately 5.6 mmHg, and this effect was secondary to a significant decrease of the diastolic measurement. The latter finding suggests that Mg-promoted peripheral arteriolar dilatation and the reduction of the systemic peripheral resistance are the most important mechanisms responsible for the decrease in the mean arterial blood pressure (31). The significant effect on the group's mean double product following Mg use indicates that the treatment was responsible for a reduction in the heart's work and in the level of myocardial oxygen consumption at rest.

A small but significant increase in SaO_2 has also been found at rest following Mg administration. Although this finding could actually represent an improvement in gas exchange, an alternative explanation may be found in the vasodilatory effect of Mg itself. Because pulse oximeters evaluate SaO_2 based on changes in skin color, improvements in peripheral perfusion associated with vasodilatation may lead to overestimated readings (32).

The most striking finding observed in the incremental maximal exercise test was the significant improvement in

Table 3 - Effects of Mg loading on the cardiorespiratory parameters of 20 COPD patients at rest*.

	Saline	Mg	Treatment Effect (CI 95%) (Mg-Saline)	*p*-value
HR (bpm)	74.6±11.2	72.8±9.8	-1.8 (-5.4 – 1.8)	0.308
SBP (mmHg)	137.8±25.5	131.0±17.1	-6.8 (-15.6 – 2.1)	0.127
DBP (mmHg)	87.5±13.3	82.5±8.7	-5.0 (-9.2 – -0.8)	0.023
MBP (mmHg)	104.3±15.6	98.7±10.5	-5.6 (-10.2 – -1.0)	0.019
SaO_2 (%)	95.2±2.3	95.9±2.0	0.8 (0.01 – 1.49)	0.048
Double product (bpm.mmHg)	10,261.3±2,291.9	9,526.5±1,638.5	-734.8 (-1,362.6 – -106.2)	0.024
RR (bpm)	19.0±5.4	19.3±3.7	0.3 (-2.1 – 2.7)	0.794
TV (ml)	517.0±150.7	575.4±222.4	58.4 (-62.8 – 179.5)	0.326
MV (l/min)	9.7±3.6	9.3±2.4	-0.4 (-2.0 – 1.2)	0.608
VO_2 (ml/min)	204.2±82.5	202.2±78	-2.0 (-46.9 – 43.0)	0.929
VCO_2 (ml/min)	167.6±66.4	167.5±67.2	-0.1 (-39.5 – 39.3)	0.996
RER	0.83±0.14	0.83±0.10	-0.01 (-0.072 – 0.062)	0.877
$PETO_2$ (mmHg)	101.9±5.4	100.9±4.9	-1.0 (-2.73 – 0.73)	0.240
$PETCO_2$ (mmHg)	30.1±4.2	30.2±3.1	0.05 (-1.14 – 1.24)	0.931

*HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean arterial blood pressure; SaO_2: peripheral arterial oxygen saturation; RR: respiratory rate; TV: tidal volume; MV: minute ventilation; VO_2: oxygen consumption; VCO_2: carbon dioxide production; RER: respiratory exchange rate; $PETO_2$: end tidal expiratory oxygen; $PETCO_2$: end tidal expiratory carbon dioxide.

Table 4 - Effects of Mg loading on the cardiorespiratory parameters of 20 COPD patients at maximal exercise*.

	Saline	Mg	Treatment Effect (CI 95%) (Mg-Saline)	*p*-value
HR_{peak} (bpm)	133.3±12.7	135.6±13.0	2.3 (-2.8 – 7.4)	0.355
$HR_{peak}/HR_{maxpred.}$	86.9±9.0	88.4±9.0	1.5 (-1.8 – 4.8)	0.353
SBP_{peak} (mmHg)	194.0±33.2	191.0±25.4	-2.5 (-9.3 – 4.3)	0.449
DBP_{peak} (mmHg)	103.0±18.7	99.5±16.1	-3.5 (-8.8 – 1.8)	0.185
MBP_{peak} (mmHg)	133.3±22.7	130.2±17.9	-3.2 (-8.2 – 1.9)	0.205
$SaO_{2\ peak}$ (%)	91.1±3.0	91.6±3.4	0.5 (-1.0 – 2.0)	0.480
Double product (bpm.mmHg)	25,900±5,375.7	25,876±3641.9	(-734.8 – 1,341.5)	0.982
RR_{peak} (bpm)	30.4±6.7	30.9±7.5	0.5 (-1,4 – 2,4)	0.593
TV_{peak} (ml)	1,318.4±314.8	1,408.5±286.8	90.2 (20.3 – 160.0)	0.014
MV_{peak} (l)	41.1±15.1	43.6±15.5	2.5 (-0.3 – 5.3)	0.078
MV_{peak} /MVV (%)	85.4±19.1	88.9±21.6	3.5 (-5.1 – 12.0)	0.405
Duration (min, sec)	12′42′′ ± 3′43′′	13′36′′ ±3′19′′	53′′ (14′′ – 1′33′′)	0.011
Maximal load (w)	73.4±37.8	81.4±33.7	8.0 (1.5 – 14.4)	0.018
$VO_{2\ peak}$ (ml/min)	1,110.6±342.5	1,110.3±319.8	8.7 (-54.6 – 72.0)	0.777
$VCO_{2\ peak}$ (ml/min)	1,216.8±433.2	1,288.0±410.6	71.3 (-27.0 – 169.5)	0.146
RER_{peak}	1.09±0.13	1.15±0.19	0.06 (0.01 – 0.11)	0.023
$PETO_{2\ peak}$ (mmHg)	98.1±10.0	98.6±10.6	0.5 (-0.9 – 1.9)	0.468
$PETCO_{2\ peak}$ (mmHg)	39.2±8.3	38.9±8.7	-0.4 (-1.6 – 0.9)	0.548
$Borg_{peak}$ dyspnea	6.2±2.6	6.0±2.6	-0.2 (-0.91 – 0.51)	0.560
$Borg_{peak}$ leg effort	5.1±2.8	5.1±3.0	0.03 (-0.63 – 0.68)	0.937

*HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean arterial blood pressure; SaO_2: peripheral arterial oxygen saturation; RR: respiratory rate; TV: tidal volume; MV: minute ventilation; VO_2: oxygen consumption; VCO_2: carbon dioxide production; RER: respiratory exchange rate; $PETO_2$: end tidal expiratory oxygen; $PETCO_2$: end tidal expiratory carbon dioxide.

the maximal achieved load associated with Mg treatment. This occurred although there were no significant differences in the peak oxygen consumption, or in Borg dyspnea and the leg fatigue scores, between treatment days. These results indicate that the overall exercise performance improved after Mg loading, as more work was performed with the same amount of VO_2 and corresponding levels of limiting symptoms. The cardiovascular measurements evaluated at the maximal exercise load also did not show significant changes with Mg treatment. Although the tidal volume measured at the peak of exercise was significantly higher after Mg administration, the observed elevation in peak ventilation did not reach statistical significance ($p = 0.078$).

Table 5 - Comparisons between Mg treatment effects with COPD patients classified according to the level of work load response *.

	Group I (n = 10)	Group II (n = 10)	*p*-value
Plasmatic Mg (mEq/L)	1.5±0.5	1.5±0.4	1
TLC (L)	-0.46±1.02	-0.14±0.82	0.447
FVC (L)	-0.03±0.21	0.10±0.26	0.209
FEV_1 (L)	-0.01±0.17	0.09±0.12	0.158
FRC (L)	-0.43±1.04	-0.40±0.72	0.947
RV (L)	-0.57±1.10	-0.37±0.85	0.647
ERV (L)	-0.07±0.70	-0.03±0.26	0.894
IC (L)	-0.06±0.29	0.29±0.32	0.020
HR_{peak} (bpm)	-0.4±9.7	5.0±11.7	0.278
MBP_{peak} (mmHg)	0.0±10.5	-6.3 10.6	0.197
$SaO_{2\ peak}$ (%)	1,3±3.2	-0.3±3.2	0.260
MV_{peak} (l)	-0.8±4.5	5.8±5.6	0.009
Duration (min, sec)	-21.8±20.9	128.1±45.4	<0.0001
Maximal load (w)	-2.6±5.8	18.5±11.0	<0.0001
$VO_{2\ peak}$ (ml/min)	-85.4±89.7	102.8±104.3	0.0004
$VCO_{2\ peak}$ (ml/min)	-48.5±91.5	191.0±229.8	0.007
RER_{peak}	0.1±0.1	0.1±0.1	0.785
$Borg_{peak}$ dyspnea	0.3±1.2	-0.7±1.7	0.142
$Borg_{peak}$ leg effort	0.4±1.0	-0.3 1.7	0.312

*Group I: Changes in work load <5 w; Group II; Changes in work load ≥5 w. TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FRC: functional respiratory capacity; RV: residual volume; ERV: expiratory reserve volume; IC: inspiratory capacity; HR: heart rate; MBP: mean blood pressure; SaO_2: peripheral arterial oxygen saturation; MV: minute ventilation; VO_2: oxygen consumption; VCO_2: carbon dioxide production; RER: respiratory exchange rate.

To further explore the potential mechanisms related to the improvement of exercise performance, we have compared the effects of the Mg treatment on the measurements of two sub-sets of patients, classified according to the level of work load responses. Neither basal Mg plasma levels, nor the degree of Mg plasma elevations after loading, differed between the groups. Additionally, there were no significant differences in the hemodynamic parameters during exercise. Both groups also exhibited decreases of similar proportions in TLC, RV, and FRC after treatment. The group with a positive exercise response, however, showed a substantial increase in IC after the Mg infusion. This finding strongly suggests that improvements in the respiratory mechanics played an important role in the genesis of improved exercise performance. This latter result is also compatible with the concept that progressive respiratory constraints are central limiting factors for maximal exercise capacity in COPD, and it highlights the importance of IC measurements in this setting (33-35).

It is worth noting that the minute ventilation at the peak of exercise in Group II was significantly higher than that in Group I. Although this finding might only reflect the higher level of work load reached, it may also be interpreted as the true mechanism responsible for an improved exercise performance. The use of Mg, most likely, was associated with reductions in dynamic hyperinflation during exercise in the responders. Unfortunately, measurements of IC during exercise, which is considered to be a proxy for dynamic hyperinflation, were not available to completely confirm this possibility (26).

The overall set of results indicates that the improvement in exercise performance that is associated with the Mg treatment does not appear to be secondary to changes in the heart function.

An additional potential contributing mechanism to the present findings is that the Mg treatment led to a higher efficacy of the exercise mechanism itself. The acute loading of Mg may have influenced the muscle contraction or the peripheral energy production process in this setting. Animal studies have shown that Mg administration leads to increases in the glucose available to tissues, decreases in lactate release and increases in pyruvate production (36-39). In addition, Mg oral supplementation in athletes has been shown to increase glucose blood levels during exercise via ACTH and cortisol discharge (39). Most importantly, because Mg is a cofactor that binds to ATP molecules, increases in intracellular Mg may also improve ATP production and glucose utilization (40). It has also been suggested that Mg supplementation may enhance the endothelial function by increasing the local NO availability, decreasing platelet aggregation, and reducing oxidative stress (41,42).

Although the VO_2 and VCO_2 of the overall group of patients did not differ between treatments, the RER showed a small but significant increase after the Mg infusion (0.06; $p = 0.023$). This finding could be better explained by a change in the metabolic profile, with an Mg-induced rise in glucose utilization, as previously suggested.

The present study has several limitations, including the small number of patients enrolled, the lack of a standard inquiry for dietary Mg ingestion, the lack of an adequate measurement of exercise dynamic hyperinflation, and the need for biochemical determinations during exercise. Dynamic inspiratory capacity evaluations and biochemical measurements, such as blood lactate and glucose levels, would permit less speculative explanations for the observed improvements in exercise performance. As Mg has substantial metabolic actions, it would be more informative if the present study had also measured intracellular Mg concentrations. In addition, technical problems did not permit the determination of the aerobic threshold in eight COPD patients, which precluded an adequate analysis of the data related to this parameter in the group.

The effects of Mg on peak exercise, although statistically significant, were small, with a mean load addition of 8 w. The clinical meaning of this finding is presently unknown, but it appears that it should be of little relevance. Additionally, this level of improvement was obtained with mean Mg plasma levels of approximately 3 mEq/L, which are substantially higher than in the typical physiological range (1.5–2.5 MEq/L). On the other hand, intracellular Mg levels may be more important than plasma measurements. Certainly, definitive answers to the questions generated by this paper will only be possible after clinical trials involving the oral supplementation of Mg in COPD patients for longer periods.

The acute IV loading of 2 g of Mg was associated with a reduction in static hyperinflation and increases in the load reached with incremental maximal exercise tests. Post-hoc analyses indicated that the positive exercise response was due to improvements in respiratory mechanics. The present results suggest that higher circulating levels of Mg may be beneficial for COPD patients. These findings also indicate the need for further studies investigating the effects of chronic dietary supplementation with Mg on the pulmonary function parameters and exercise tolerance of stable COPD patients.

AUTHOR CONTRIBUTIONS

Amaral AF and Crescêncio JC conceived the study and were responsible for the data collection and tabulating. Gallo Jr L and Vianna EO conceived the study and were responsible for the manuscript writing. Vannucchi H conceived the study and was responsible for the biochemical measurements. Martinez JA conceived the study and was responsible for the statistical analysis and manuscript writing.

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