INTRODUCTION

The pathophysiological mechanisms of COPD are largely expiratory and obstructive. However, their consequences are inspiratory and elastic. In other words, expiratory flow limitation and the resulting air trapping/lung hyperinflation tend to increase operating lung volumes, thus reducing inspiratory reserve volume (IRV). Pulmonary function tests show lower inspiratory fraction—inspiratory capacity (IC)/TLC—and relative inspiratory reserve—[1−(end-inspiratory lung volume/TLC)].

RESULTS: This was a prospective study involving 56 patients with COPD—24 (23 males/1 female) with COPD+CHF and 32 (28 males/4 females) with COPD only—who, after careful clinical stabilization, underwent spirometry (with forced and slow maneuvers) and whole-body plethysmography. Results: Although FEV₁ as well as the FEV₁/FVC and FEV₁/slow vital capacity ratios, were higher in the COPD+CHF group than in the COPD group, all major “static” volumes—RV, functional residual capacity (FRC), and TLC—were lower in the former group (p < 0.05). There was a greater reduction in FRC than in RV, resulting in the expiratory reserve volume being lower in the COPD+CHF group than in the COPD group. There were relatively proportional reductions in FRC and TLC in the two groups; therefore, IC was also comparable. Consequently, the inspiratory fraction was higher in the COPD+CHF group than in the COPD group (0.42 ± 0.10 vs. 0.36 ± 0.10; p < 0.05). Although the tidal volume/IC ratio was higher in the COPD+CHF group, the relative inspiratory reserve was remarkably similar between the two groups (0.35 ± 0.09 vs. 0.44 ± 0.14; p < 0.05).

CONCLUSIONS: Despite the restrictive effects of CHF, patients with COPD+CHF have relatively higher inspiratory limits (a greater inspiratory fraction). However, those patients use only a part of those limits, probably in order to avoid critical reductions in inspiratory reserve and increases in elastic recoil.

Keywords: Respiratory function tests; Pulmonary disease, chronic obstructive; Heart failure; Spirometry.

ABSTRACT

Objective: To evaluate the influence of chronic heart failure (CHF) on resting lung volumes in patients with COPD, i.e., inspiratory fraction—inspiratory capacity (IC)/TLC—and relative inspiratory reserve—[1−(end-inspiratory lung volume/TLC)].

Methods: This was a prospective study involving 56 patients with COPD—24 (23 males/1 female) with COPD+CHF and 32 (28 males/4 females) with COPD only—who, after careful clinical stabilization, underwent spirometry (with forced and slow maneuvers) and whole-body plethysmography.

Results: Although FEV₁, as well as the FEV₁/FVC and FEV₁/slow vital capacity ratios, were higher in the COPD+CHF group than in the COPD group, all major “static” volumes—RV, functional residual capacity (FRC), and TLC—were lower in the former group (p < 0.05). There was a greater reduction in FRC than in RV, resulting in the expiratory reserve volume being lower in the COPD+CHF group than in the COPD group. There were relatively proportional reductions in FRC and TLC in the two groups; therefore, IC was also comparable. Consequently, the inspiratory fraction was higher in the COPD+CHF group than in the COPD group (0.42 ± 0.10 vs. 0.36 ± 0.10; p < 0.05). Although the tidal volume/IC ratio was higher in the COPD+CHF group, the relative inspiratory reserve was remarkably similar between the two groups (0.35 ± 0.09 vs. 0.44 ± 0.14; p < 0.05).

Conclusions: Despite the restrictive effects of CHF, patients with COPD+CHF have relatively higher inspiratory limits (a greater inspiratory fraction). However, those patients use only a part of those limits, probably in order to avoid critical reductions in inspiratory reserve and increases in elastic recoil.

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interactions between COPD and CHF and their effects on the volumes available for inspiratory expansion in patients with COPD+CHF.

The objective of the present study was to compare inspiratory fraction and relative inspiratory reserve (and their determinants) between a carefully selected group of patients with COPD+CHF and a group of patients with COPD only. It was hypothesized that the characterization of the effect of CHF on these key physiological markers of COPD would advance the understanding of the mechanical and ventilatory constraints faced by patients with COPD+CHF.

METHODS

Sample
In the present cross-sectional study with consecutive data collection, we included all consecutive patients who underwent whole-body plethysmography between February of 2012 and March of 2014 at the COPD+CHF outpatient clinic of the Universidade Federal de São Paulo (UNIFESP, Federal University of São Paulo) Department of Pulmonary Function and Exercise Physiology, located in the city of São Paulo, Brazil, and who presented with FEV₁/FVC < 0.7 and left ventricular ejection fraction (LVEF) ≤ 45%. All patients had previously been selected from among those treated at the Myocardial Infarction Outpatient Clinic of the aforementioned institution or at the Left Ventricular Dysfunction Outpatient Clinic of the Instituto Dante Pazzanese de Cardiologia (IDPC, Dante Pazzanese Institute of Cardiology), also in the city of São Paulo, Brazil. The patients in the COPD group (FEV₁/FVC < 0.7 and LVEF > 45%) were selected from among those treated at the UNIFESP COPD Outpatient Clinic. Patients over 45 years of age with a smoking history of more than 10 pack-years were included. All patients were monitored by the same cardiologist and pulmonologist, undergoing standardized clinical assessment and receiving optimal treatment regimens for both diseases. Patients presenting with COPD exacerbation, decompensated CHF, or both in the month prior to study entry were excluded, as were those with unstable angina. The study was approved by the Research Ethics Committees of UNIFESP (Protocol no. 19595) and IDPC (Protocol no. 68612).

Measurements
Spirometry (with forced and slow maneuvers) and whole-body plethysmography were performed with a Platinum Elite™ body plethysmograph (Medical Graphics Corp., St. Paul, MN, USA), in accordance with current recommendations. The following variables were assessed: FEV₁; FVC; slow vital capacity (SVC); TLC; RV; thoracic gas volume, which was considered to be equivalent to functional residual capacity (FRC) in the present study; V₅₀ (the mean of three breaths taken before the inhalation preceding the SVC maneuver); and IC. All variables were expressed in liters. On the basis of the aforementioned variables, EILV (EILV = FRC + V₅₀), IRV (IRV = TLC – EILV), and expiratory reserve volume (ERV = FRC – RV) were calculated. The reference values were those obtained in a sample of Brazilian adults. The values that were analyzed in the present study were those obtained 20 min after the administration of 400 µg of inhaled albuterol.

Data analysis
Statistical analysis was performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used in order to verify the normality of the data. Data were presented as mean and standard deviation. The independent sample t-test was used in order to compare the results between the groups. For qualitative variables, the chi-square test was used in order to assess differences between the groups. The level of statistical significance was set at p < 0.05 for all tests.

RESULTS
A total of 86 patients (41 patients in the COPD+CHF group and 45 patients in the COPD group) were initially considered eligible for the present study. After exclusion of patients who were clinically unstable, those who were unable to perform advanced pulmonary function tests, and those whose tests were technically inadequate, 24 patients with COPD+CHF (23 of whom were male) and 32 patients with COPD only (28 of whom were male) were included.

The COPD+CHF and COPD groups were similar in terms of age (66 ± 9 vs. 64 ± 6 years), body mass index (26.5 ± 3.7 vs. 24.9 ± 4.1 kg/m²), and smoking history (51.7 ± 26.4 vs. 54.3 ± 38.2 pack-years). As expected, LVEF was significantly lower in the COPD+CHF group than in the COPD group (33 ± 7% vs. 68 ± 4%; p < 0.01). The most common cause of CHF was ischemic cardiomyopathy (n = 13), followed by idiopathic etiology (n = 6). Most of the patients in the COPD+CHF group were under treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (n = 21), diuretics (n = 20), or beta blockers (n = 18). There were no significant differences between the two groups regarding the frequency of use of long-acting bronchodilators, inhaled corticosteroids, or both (p > 0.05).

Although FEV₁ was higher in the COPD+CHF group than in the COPD group, FVC and SVC were similar between the two groups (Table 1). Therefore, FEV₁/FVC and FEV₁/SVC were higher in the COPD+CHF group (p < 0.05). In contrast, all major “static” lung volumes (RV, FRC, and TLC) were lower in the COPD+CHF group than in the COPD group. In the COPD group, there was a greater reduction in FRC than in RV, ERV therefore being lower in the COPD+CHF group. There were relatively proportional reductions in FRC and TLC in the two groups; therefore, IC was also comparable (p > 0.05; Table 1 and Figure 1A). A similar IC and a lower TLC resulted in a higher inspiratory fraction (IC/TLC) in the COPD+CHF group (p < 0.05; Table
It is of note that the patients in the COPD+CHF group used only part of the higher inspiratory fraction available. Therefore, despite a higher V\textsubscript{T}/IC ratio in the COPD+CHF group, IRV and relative inspiratory reserve—\([1 − (EILV/TLC)]\)—were similar between the two groups (\(p < 0.05\); Table 1 and Figure 1B).

### DISCUSSION

To our knowledge, this is the first cross-sectional study with prospective data collection to compare inspiratory fraction and relative inspiratory reserve—(IC/TLC) and \([1 − (EILV/TLC)]\), respectively\(^{3,4}\)—as well as their determinants, between patients with COPD+CHF and those with COPD only. The main findings of the present study were that a) in comparison with the patients with COPD only, those with COPD+CHF showed a relatively greater reduction in FRC than in TLC and RV; b) consequently, there was no difference between the two groups regarding IC, but there was an increase in inspiratory fraction (IC/TLC); c) the patients with COPD+CHF used only part of the higher inspiratory fraction available, given that relative inspiratory reserve—\([1 − (EILV/TLC)]\)—was similar between the two groups. Therefore, our results indicate that, despite the restrictive effects of CHF, there was not only a relative increase in inspiratory limits (a higher inspiratory fraction)\(^{3,4}\) but also an admirably judicious use of those limits, given that a “critical” IRV was preserved,\(^{2,22}\) i.e., a similar relative inspiratory reserve.

Over the last two decades, there have been considerable advances in the understanding of the crucial role that a precise regulation of operating lung volumes plays in reducing the metabolic demands associated with ventilation and the sensation of dyspnea in patients with COPD.\(^{2}\) The present study adds to this line of reasoning by showing that, even in the presence of comorbidities associated with reduced static lung volumes (i.e., CHF),\(^{13-16}\) the precise regulation of a “safe end-inspiratory reserve volume” for mechanical operation of the system at maximum capacity (i.e., TLC) appears to remain intact.\(^{23,24}\) Although our patients

| Variable | COPD (n = 32) | COPD + CHF (n = 24) |
|----------|---------------|---------------------|
| FEV\textsubscript{1}, L | 1.33 ± 0.55 | 1.78 ± 0.53* |
| FEV\textsubscript{1}, % predicted | 48.5 ± 18.2 | 58.4 ± 16.0* |
| FVC, L | 2.81 ± 0.67 | 2.90 ± 0.57 |
| FEV\textsubscript{1}/FVC | 0.46 ± 0.12 | 0.60 ± 0.10* |
| SVC, L | 3.05 ± 0.70 | 3.12 ± 0.53 |
| FEV\textsubscript{1}/SVC | 0.43 ± 0.14 | 0.57 ± 0.10* |
| V\textsubscript{E}, L | 0.81 ± 0.20 | 1.04 ± 0.34* |
| IC, L | 2.27 ± 0.52 | 2.34 ± 0.55 |
| FEF\textsubscript{25-75%}, L/s | 0.61 ± 0.44 | 1.00 ± 0.51* |
| TLC, L | 6.71 ± 1.10 | 5.91 ± 0.84* |
| TLC, % predicted | 108.9 ± 16.6 | 89.3 ± 15.5* |
| FRC, L | 4.42 ± 1.10 | 3.45 ± 0.79* |
| FRC, % predicted | 132.4 ± 28.5 | 104.4 ± 35.2* |
| RV, L | 3.36 ± 0.80 | 2.78 ± 0.79* |
| RV, % predicted | 165.4 ± 44.8 | 131.6 ± 42.6* |
| EILV, L | 5.13 ± 1.25 | 4.52 ± 0.99 |
| IRV, L | 1.60 ± 0.61 | 1.43 ± 0.51 |
| ERV, L | 0.99 ± 0.58 | 0.68 ± 0.43* |
| sRaw, cmH\textsubscript{2}O/s | 19.17 ± 14.80 | 11.02 ± 10.52* |
| EILV/TLC | 0.75 ± 0.10 | 0.75 ± 0.09 |
| V\textsubscript{E}/IC | 0.35 ± 0.12 | 0.44 ± 0.14* |
| IC/TLC | 0.36 ± 0.10 | 0.43 ± 0.10* |
| RV/TLC | 0.50 ± 0.08 | 0.46 ± 0.08 |
| FEF\textsubscript{25-75%}/FVC | 0.22 ± 0.11 | 0.34 ± 0.14* |
| FEF\textsubscript{25-75%}/TLC | 0.11 ± 0.07 | 0.18 ± 0.07* |

CHF: chronic heart failure; SVC: slow vital capacity; V\textsubscript{E}: tidal volume; IC: inspiratory capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; ERV: expiratory reserve volume; sRaw: specific airway resistance. *Values expressed as mean ± SD. *\(p < 0.05\) (independent sample t-test).
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Figure 1. Lung volumes and capacities expressed as absolute values (in A) and corrected for differences in total lung capacity (in B) in patients with COPD only and in those with COPD and chronic heart failure (CHF). TLC: total lung capacity; RV: residual volume; ERV: expiratory reserve volume; V_t: tidal volume; IRV: inspiratory reserve volume; FRC: functional residual capacity; EILV: end-inspiratory lung volume; and IC: inspiratory capacity. *p < 0.05 (independent sample t-test).

were not evaluated during exercise, the aforementioned strategy suggests that both groups had the same IRV available for consumption at higher ventilatory demands; however, because we did not directly measure the work of breathing in the present study, we cannot guarantee that the lower operating lung volumes observed in the COPD+CHF group would be enough to overcome the likely increase in elastic recoil associated with CHF.

The physiological mechanisms underlying the precise adjustment of IRV in patients with COPD remain largely unknown. However, the relative (i.e., fractional) nature of this adjustment is noteworthy; V_t increases only enough to maintain a "critical" IRV, even if there is still room for further increases. In fact, Faisal et al. have recently demonstrated that this adjustment remains precise in physiologically and structurally opposite diseases (COPD and interstitial lung disease). The way in which the respiratory system precisely defines this threshold appears to involve an awareness (either acquired by experience or innate) of the maximum capacity available. The price of excessive elastic recoil is clearly avoided. Although we do not know the extent to which the combination of COPD and CHF effectively increases dead space volume, this is a plausible hypothesis, given that lung perfusion might be reduced in areas in which ventilation is relatively preserved. Therefore, it makes sense that, in such patients, V_t is somewhat higher in order to reduce the dead space to tidal volume ratio (V_d/V_t). It is therefore possible that the limits to increases in V_t (with concomitant reduction in V_d/V_t) are also determined by humoral factors, i.e., the V_t required in order to reduce V_d/V_t thus allowing minute PaCO_2 variations that are close to its set point. In fact, given that PaCO_2 can be set at slightly lower values in patients with COPD+CHF, the dynamic regulation of V_d/V_t appears to be of particular relevance for such patients.

The fact that there was a reduction in FRC is of crucial importance for the understanding of our findings. Given that the reduction in FRC overcame the decrements in RV, there was a significant decrease in ERV. This confirmed the premise that, in order to maintain V_t and IRV, patients with COPD choose to pay the price of nearly reaching maximal expiratory volumes, despite the fact that this can affect the efficiency of pulmonary gas exchange and reduce flow reserves. However, it is of note that CHF probably increases lung elastic recoil and mean expiratory flow (the latter particularly during exercise). Therefore, at least in stable patients, reduced flow reserves might not necessarily be associated with increased expiratory flow limitation in COPD+CHF. The underlying reasons for a relatively greater reduction in FRC remain unclear and include the following: a) increased tonic activity of abdominal expiratory muscles; b) reduced small airway obstruction, the small airways being particularly relevant for determining volume balance in COPD patients; and c) increased rate of lung emptying in units with higher time constants, i.e., those particularly affecting "lower" lung volumes (near RV), as a result of a higher expiratory flow rate and cardiomegaly.

Given that there was no difference in body mass index between the two groups (and given that none of the patients had ascites), the hypothesis that TLC was lower in the COPD+CHF group because overweight and obesity were more common in that group does not seem plausible. In addition, lung volumes were nearly normal in the COPD+CHF group, whereas, in the COPD group, they were increased, as expected. Therefore, if we assume that the incidence of CHF is higher than its prevalence, CHF is likely to lead to a "pseudonormalization" of static lung volumes in COPD. However, longitudinal studies are needed in order to test this hypothesis.

What is the clinical applicability of our results? The remarkable maintenance of IRV in the COPD+CHF group demonstrates that it is particularly critical to maintain an adequate IC from a lower EELV in such patients. Therefore, although the patients with COPD+CHF were less hyperinflated (had a lower TLC) than those with COPD only, a reduction in air trapping appears to be fundamental to a downward shift in operating lung...
argued that CHF tends to overestimate the severity of COPD (as determined by FEV,
) because of reduced lung volumes. However, the increased airflow resulting from the increased elastic recoil induced by CHF tends to increase FEV,
. Another complicating factor is that the functional effects of CHF can be influenced by the relative predominance of emphysema or airway disease (chronic bronchitis). In the present study, the fact that there was no difference between the two groups in terms of the RV/TLC ratio suggests that they were somewhat comparable despite the differences in FEV,
. Further studies are needed in order to define the best approach to the functional pairing of patients with COPD+CHF and those with COPD only.

In conclusion, despite the significant restrictive effects of CHF (reduced TLC), reductions in FRC and ERV preserve IC and increase inspiratory fraction (IC/TLC) in patients with COPD+CHF. However, in order to preserve a “critical” IRV, such patients use only part of this higher inspiratory fraction, possibly in order to reduce elastic recoil and, consequently, the sensation of dyspnea. The present study lays the foundation for future studies comparing our findings regarding resting lung volumes with mechanical, ventilatory, and sensory responses during exercise in patients with COPD+CHF.

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