Objective: Diastolic dysfunction of the left ventricle is common in patients with chronic obstructive pulmonary disease (COPD). Dynamic hyperinflation has been suggested as a key determinant of reduced diastolic function in COPD. We aimed to investigate the effects of induced dynamic hyperinflation on left ventricular diastolic function in healthy subjects to exclude other confounding mechanisms associated with COPD.

Design: In this randomized controlled crossover trial (NCT03500822, https://www.clinicaltrials.gov/), we induced dynamic hyperinflation using the validated method of expiratory resistance breathing (ERB), which combines tachypnea with expiratory resistance, and compared the results to those of tachypnea alone. Healthy male subjects (n = 14) were randomly assigned to the ERB or control group with subsequent crossover. Mild, moderate, and severe hyperinflation (i.e., ERB1, ERB2, ERB3) were confirmed by intrinsic positive end-expiratory pressure (PEEPi) using an esophageal balloon catheter. The effects on diastolic function of the left ventricle were measured by transthoracic echocardiographic assessment of the heart rate-adjusted transmitral E/A-ratio and E/e'-ratio.

Results: We randomly assigned seven participants to the ERB group and seven to the control group (age 26 [24-26] vs. 24 [24-34], p = 0.81). Severe hyperinflation decreased the E/A-ratio compared to the control condition (1.63 [1.49–1.77] vs. 1.85 [0.95–2.75], p = 0.039), and moderate and severe ERB significantly increased the septal E/e'-ratio. No changes in diastolic function were found during mild hyperinflation. PEEPi levels during ERB were inversely correlated with the E/A ratio (regression coefficient = −0.007, p = 0.001).

Conclusions: Our data indicate dynamic hyperinflation as a determinant of left ventricular diastolic dysfunction in healthy subjects. Therapeutic reduction of hyperinflation might be a treatable trait to improve diastolic function in patients with COPD.

Keywords: heart failure, diastolic dysfunction, diastolic filling, dynamic hyperinflation, positive end-expiratory pressure, chronic obstructive pulmonary disease
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the most common causes of death worldwide (1). Despite decreasing mortality rates in some Western countries, the global mortality attributable to COPD has continued to rise over the last decades (2). Cardiovascular comorbidities are among the most relevant drivers of mortality in patients with COPD (3, 4).

Diastolic dysfunction of the left ventricle, along with systolic heart failure, coronary artery disease, and hypertension, has emerged as one of the most frequent comorbidities in COPD (5–7). The prevalence of diastolic dysfunction is variable and can reach as high as 90%, independent of disease severity, in COPD (8, 9). Patients with diastolic dysfunction are much more likely to have airflow limitation than patients with systolic dysfunction (10).

The current knowledge suggests that dynamic hyperinflation is a leading risk factor for diastolic dysfunction in COPD. Watz et al. (11) reported that the association of hyperinflation with left ventriculardiastolic dysfunction was stronger than that of airflow limitation or diffusion capacity. These findings are confirmed by longitudinal data indicating that increasing hyperinflation is a major determinant of diastolic impairment of the left ventricle in COPD (12). A reduction in preload was subsequently suggested as a link between hyperinflation and reduced diastolic filling (11, 13). However, the pathophysiologic interaction between COPD and compromised diastolic function is complex, and there are numerous possible mechanisms (14, 15). In addition to hyperinflation, hypoxic vasoconstriction (9), arterial stiffness (16), pulmonary hypertension (17), ventricular interdependence (7), and subendocardial ischemia (18) have been introduced as potential links in this cardiorespiratory interaction. Hence, the induction of hyperinflation in healthy subjects is used to study the effects of intrathoracic pressure changes on the heart as an isolated mechanism (19). However, no study has investigated diastolic function during the induction of dynamic hyperinflation in healthy subjects.

We aimed to induce dynamic hyperinflation in subjects without COPD to study its effects on echocardiographically assessed parameters of diastolic function. We hypothesized that induced hyperinflation, indicated by positive end-expiratory pressure (PEEPi), would significantly reduce the E/A ratio and increase the E/e’ ratio in subjects without cardiorespiratory diseases. Rejection of the null hypothesis would suggest that hyperinflation is a relevant mechanism for and a therapeutic target against diastolic dysfunction in patients with COPD.

MATERIALS AND METHODS

Participants

This study included healthy subjects younger than 40 years of age recruited from the Medical University of Vienna.

Subjects with obesity (i.e., body mass index ≥28), current or former cigarette smoking or respiratory disorders were excluded. Airflow limitation was ruled out via spirometry (Easyone, ndd medical technologies, Zurich, Switzerland). Further, exclusion criteria comprised arterial hypertension or overt cardiovascular diseases, including structural heart diseases. Finally, subjects with a baseline E/A ratio below 1.0 were excluded before randomization. After receiving detailed instructions about study-related procedures, each participant had to give written informed consent.

Study Design and Intervention

This randomized controlled investigator-blinded crossover trial was conducted at the Department of Respiratory and Critical Care Medicine at the Otto Wagner Hospital, Vienna. Participants were randomly assigned to start with ERB or tachypnea. Randomization was conducted in blocks of four participants via an online program (www.randomization.com). Dynamic hyperinflation in the study group was induced by means of the recently validated expiratory resistance breathing (ERB) method (20). Briefly, hyperinflation was induced via airflow limitation by means of an expiratory airway stenosis. Inspiration remained unmodified due to a one-way valve coupled via a T-connector. A metronome was used in order to standardize participants’ breathing pattern (i.e., respiratory rate and ratio of inspiration to expiration). Titration of hyperinflation was achieved via a stepwise reduction of the expiratory stenosis diameter (i.e., mild: 3.0 mm, moderate: 2.0 mm and severe: 1.5 mm). Standardized tachypnea, paced with a metronome (21), was used as the comparator intervention. After the first interventional phase (i.e., either ERB or tachypnea), the participants crossed over to the alternative intervention.

Measurements

Diastolic function was assessed via echocardiography with the apical four-chamber view (Vivid S9, GE Healthcare, Fairfield, USA), following current recommendations (22), and was subsequently analyzed by a blinded investigator. The velocity of transmittal flow during early and late diastole was measured to quantify the E-wave, A-wave, and E/A ratio. The E/A ratio was corrected for a heart rate of 60/min, as tachycardia can cause fusion of the E- and A-waves with a false-positive diastolic filling pattern. Hence, we excluded all measurements where the A- and E-waves met at a velocity of at least 0.2 m/s. Instead, we calculated the maximum A-velocity and the heart rate-corrected E/A-ratio, which resulted in a more conservative reduction of the E/A-ratio. Tissue Doppler imaging of the septal and lateral e’-waves was used to quantify the E/e’-ratio. Echo parameters were assessed during expiration, and the mean value was derived from three cardiac cycles.

Prior to the study intervention, an esophageal balloon catheter (Model C76050U, Marquat Génie Biomédical, Boissy-Saint-Léger, France) was inserted according to current standards (23). Via a pressure transducer, esophageal pressure was recorded by a validated pressure box (ICU-Lab, Kleistek Engineering, Bari, Italy). PEEPi was quantified by the negative deflection of...
esophageal pressure between the onset of inspiratory effort and
the beginning of inspiratory flow (24).

**Statistics and Ethics**

Data are presented as the means and 95% confidence intervals
or as medians and 1st–3rd quartiles. Normal distribution
was assessed by normal plots and were logarithm transformed
if required. For intergroup comparison of baseline data, we
used the Mann-Whitney U-test. Due to repeated observations,
we used a generalized estimation equation with a normal
probability distribution and an exchangeable correlation
structure, and robust standard errors. To rule out potential
confounding by randomization, we added a randomization
group to the model.

The sample size was calculated by means of the primary
outcome (i.e., E/A ratio) as a continuous variable from
matched pairs during spontaneous breathing and ERB. In a
pilot study, we found the effect size of matched pairs to be
normally distributed with a standard deviation of 0.15. With
an effect size of 0.17, we calculated a sample size of 10
participants to reject the null hypothesis with a probability
of 0.9. The level of significance (i.e., type-1 error) was set at
0.05. The number of dropouts was estimated at four, yielding
a final sample size of 14 participants. These calculations were
made using PS – power and sample size (free software,
version 3.0.43).

This trial was approved by the local Ethics
Committee/Institutional Review Board (EK 15-209-1015).
All study-related procedures were conducted in accordance with
the Declaration of Helsinki. The study was registered with http://
TABLE 1 | Baseline characteristics of study participants starting with expiratory resistance breathing (ERB, group 1) and tachypnea (TP, group 2).

| Anthropometrics               | Group 1 – ERB (n = 7) | Group 1 – TP (n = 7) | p-value |
|-------------------------------|-----------------------|---------------------|---------|
| Age, years                    | 26 (24–26)            | 24 (24–34)          | 0.805   |
| Height, cm                    | 184 (179–187)         | 178 (177–184)       | 0.128   |
| Weight, kg                    | 77 (75–85)            | 76 (75–86)          | 1.000   |
| BMI                           | 23.7 (22.1–25.1)      | 24 (21.4–27.1)      | 0.456   |
| BSA, m²                       | 1.95 (1.93–2.08)      | 2.00 (1.92–2.09)    | 1.000   |
| Lung function testing         |                       |                     |         |
| FEV1, L                       | 4.96 (4.55–5.23)      | 4.55 (3.57–5.05)    | 0.259   |
| FVC, % predicted              | 5.78 (4.97–6.43)      | 5.60 (4.66–5.73)    | 0.259   |
| FEV1/FVC ratio                | 0.86 (0.82–0.89)      | 0.81 (0.77–0.88)    | 0.318   |
| IC, L                         | 3.68 (3.46–3.90)      | 3.62 (3.21–4.02)    | 0.670   |
| MEF25, L/s                    | 2.57 (1.95–2.66)      | 1.89 (1.53–2.53)    | 0.730   |
| MEF50, L/s                    | 6.25 (5.14–6.38)      | 5.66 (3.86–6.10)    | 0.290   |
| MEF75, L/s                    | 9.28 (8.38–10.24)     | 8.99 (7.01–9.95)    | 0.560   |
| PEF, L/s                      | 11.58 (10.93–12.45)   | 10.77 (10.20–10.78)| 0.063   |
| Cardiovascular parameters     |                       |                     |         |
| Heart rate, bpm               | 70 (82–71)            | 71 (66–78)          | 0.620   |
| EF, percent                   | 60 (57–64)            | 59 (56–63)          | 0.731   |
| E/A ratio                     | 1.59 (1.43–2.28)      | 1.80 (1.27–2.20)    | 0.710   |

Data are presented as medians with 1st–3rd quartiles and were compared by a Mann–Whitney U-test. ERB, expiratory resistance breathing; TP, tachypnea; BMI, body mass index; BSA, body surface area; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, Inspiratory capacity; EF, ejection fraction; E/A ratio, ratio of E-wave to A-wave.

www.clinicaltrials.gov under NCT03500822 and is reported in accordance with the CONSORT statement (25).

RESULTS

Subject Characteristics

Recruitment started in July 2017, and data collection was completed in November 2017. Twenty-five subjects were assessed for eligibility, and 11 subjects did not meet the inclusion criteria or declined to participate. None of the participants had to be excluded during the study, and seven subjects per study group were available for inclusion in the analysis. Participant flow is depicted in Figure 1. Mean age, height and weight were equally distributed between the two randomization groups. Baseline echocardiography showed no structural or functional abnormalities and no significant differences between the groups. Detailed subject characteristics are presented in Table 1.

Cardiovascular Outcomes During Dynamic Hyperinflation

Hyperinflation, expressed as PEEPi, showed a non-parametric distribution. Log transformed PEEPi revealed stepwise increases from tachypnea to ERB1, ERB2, and ERB3 (delta PEEPi: 5.27 [4.96–17.13], p < 0.006; 21.33 [11.82–25.34], p = 0.002; 36.27 [26.13–43.58], p = 0.009). PEEPi correlated inversely with inspiratory capacity (regression coefficient = −1.04; p < 0.0001). The relationship between the two is displayed in Supplementary Figure 1. During hyperinflation, we observed a significant increase in heart rate. The E/A ratio was significantly reduced from tachypnea to ERB1 and ERB3. The reduction in the E/A ratio was predominantly maintained by increases in the A-wave, whereas the E-wave remained unchanged by hyperinflation. Even after correction for a heart rate of 60/min, the E/A ratio was significantly reduced during ERB2 and ERB3. Tissue Doppler showed significantly elevated septal and lateral E/e’ ratios during hyperinflation. The changes in E/A and E/e’ during hyperinflation are depicted in Figure 2. All echocardiographic parameters during spontaneous breathing, tachypnea and hyperinflation are listed in Table 2. No adverse events were observed during this study.

Association of Hyperinflation and Diastolic Function

The association between hyperinflation and the E/A ratio is illustrated in Figure 3. PEEPi showed a significant inverse correlation with the E/A ratio corrected for a heart rate of 60/min. As shown in Table 3, an increase of 1 cmH2O in PEEPi resulted in a reduction in the heart rate-corrected E/A ratio of 0.007. This association was independent of the randomization group (p = 0.936).

DISCUSSION

In this randomized controlled trial, we demonstrate that dynamic pulmonary hyperinflation causes diastolic dysfunction in healthy individuals. The induction of hyperinflation caused a significant impairment of diastolic function, expressed as the E/A ratio, and an increase in ventricular filling pressures, expressed as the E/e’ ratio. The amount of hyperinflation, as measured by PEEPi, was inversely associated with the E/A ratio. These findings indicate that diastolic dysfunction is determined by intrathoracic pressures and strengthen the role of hyperinflation as a therapeutic target for improving left ventricular diastolic filling and function in COPD.

The observed impairment of ventricular function and filling by induced hyperinflation is in concordance with previous studies in the field. Cheyne and colleagues (19) simulated COPD-specific hyperinflation in healthy subjects and found that left ventricular filling, quantified by end-diastolic volume, was significantly reduced following resistive loading of the respiratory system. Similarly, clinical observations of intubated patients with respiratory failure revealed reduced left ventricular end-diastolic volume and venous return via increasing extrinsic PEEP levels (26).

Our data extend this knowledge by providing a detailed description of the early- and late-diastolic transmural flow and E/e’ ratio during dynamic hyperinflation. The amount of dynamic hyperinflation during ERB is comparable to the values observed in patients with COPD (20). COPD patients at rest revealed modest PEEPi levels ranging from 2.4 to 4.8 cmH2O (27, 28) which evidently increase via voluntary tachypnea. During exercise, PEEPi was found to rise up to over 12 cmH2O (29), which is comparable to the 11.2 cmH2O during ERB with 3 mm stenosis diameter. Finally, during acute...
ventilatory failure, previous studies showed PEEPi levels of up to 20 cmH2O (30), which is in line with the 22.3 cmH2O of PEEPi measured during ERB with a stenosis diameter of 2 mm (20). Static hyperinflation and severe pulmonary emphysema have been identified as determinants of reduced end-diastolic volume by magnetic resonance imaging (31, 32). In the present study, we identified a significant negative association between the E/A ratio and dynamic hyperinflation, expressed via PEEPi. These observations are strengthened by the reports of Watz and colleagues, who found a diastolic filling pattern that was more strongly associated with static hyperinflation than with airway obstruction or diffusion capacity in patients with COPD (11). In our study, the E/A ratio was above the levels observed by Watz et al., even at the highest amount of hyperinflation. We found significant increases in the E/e' ratio during dynamic hyperinflation, which is in line with studies on patients with COPD indicating significant associations with E/e' and measures of hyperinflation in body plethysmography (7, 33). Diastolic dysfunction, expressed as E/e', was again more pronounced in patients with COPD than in the participants in our study. This might be a consequence of confounding mechanisms beyond hyperinflation in COPD, which we aimed to rule out by including otherwise healthy individuals. Hence, our investigations on transmural flow during the induction of dynamic hyperinflation in healthy subjects expands the current knowledge in the field of cardiopulmonary interaction by isolating hyperinflation from potential confounding factors in patients with COPD.

Potential mechanisms linking COPD to reduced diastolic filling and function comprise hypoxemia (18, 34), hypercapnia (35), systemic inflammation (36), arterial stiffness, pulmonary hypertension (17), and ventricular interdependence (37). Our investigation ruled out most of the abovementioned factors. Hence, potential mechanisms in our study might be limited...
to first, a direct connection of increased pulmonary pressure with augmented pleural stiffening. Pleural stiffness transfers to the cardiac fossa and compromises left heart dilatation due to an increased load on the ventricular wall (38). The observed increase in E/e’ in the present study might indicate increased filling pressures due to mechanical constraints on the heart. Furthermore, the decrease in the E/A ratio was predominately driven by A-velocity, which could be determined by either reduced left ventricular compliance or increased left atrial contractility (22). Second, impaired pulmonary vascular compliance (39) might reduce left ventricular preload and, consequently, cardiac output. Interpretations of ventricular interdependence remain speculative in our study as we did not account for the end-systolic volume or stroke volume of the left ventricle during ERB. Third, the existing literature describes pulmonary hypertension as a common feature in COPD, which increases right ventricular afterload (40). We can only speculate about a potential increase in pulmonary arterial pressure during dynamic hyperinflation as the validity of echocardiographic assessments of pulmonary artery pressure via tricuspid regurgitation is limited during hyperinflation. We did not conduct invasive measurement of pulmonary artery pressure in our sample. Indeed, recent observations have identified pulmonary hypertension during exercise as a distinct disorder that does occur in otherwise healthy subjects (41). However, exercise pulmonary hypertension is associated with substantial dyspnea and exercise limitation, which was not observed in any of our participants.

A strength of the present study is the robust design of the randomized controlled trial. We induced dynamic hyperinflation by means of a validated method, which accurately allows the investigation of cardiopulmonary interactions in isolation from other potential mechanisms present in diseased lungs. However, it is worth mentioning that we did not measure arterial blood gases during the induction of hyperinflation. In a simulation of COPD in healthy subjects, a recent study showed that hypoxemia resulted in increased right ventricular systolic pressures (14). We cannot fully rule out a potential influence of hypoxia and increased pulmonary vascular resistance on left ventricular dysfunction during our intervention. However, Cheyne and colleagues did not find substantial changes in arterial blood gases during the induction of hyperinflation.In a randomized controlled trial. We induced dynamic hyperinflation of our participants. Indeed, recent observations have identified exercise pulmonary hypertension as associated with substantial changes in arterial blood gases during the validation of ERB. However, during the validation of ERB we described a significant decrease in inspiratory capacity (20). In the current study, we further revealed a strong association between PEEPi and inspiratory capacity, as depicted in Supplementary Figure 1. Finally, we excluded a relevant amount of expiratory muscle activity via the application of a gastric balloon in one exemplary participant, illustrated by a gastric balloon in one exemplary participant, illustrated in Figure 3. The scatter plot of the association between left ventricular diastolic function and dynamic hyperinflation of the lungs is color coded. E/A, ratio of transmitral E- to A-wave corrected for a heart rate of 60/min; PEEPi log, log-transformed intrinsic positive end-expiratory pressure (cmH2O).

| Coefficient | p-value | Lower 95% CI | Upper 95% CI |
|-------------|---------|--------------|--------------|
| PEEPi dyn, cmH2O | −0.007 | 0.001 | −0.011 | −0.003 |
| Randomization | −0.015 | 0.936 | −0.386 | 0.360 |
| Constant | 1.903 | 0.360 | 2.561 |

Association between the diastolic function of the left ventricle, expressed as E/A ratio and corrected for heart rate, as the constant variable and dynamic hyperinflation, expressed as intrinsic positive end-expiratory pressure; E/A ratio, ratio of maximum early- to late-diastolic flow at the mitral valve; lower 95% CI, lower 95% confidence interval; upper 95% CI, upper 95% confidence interval; PEEPi dyn, dynamic changes in intrinsic positive end-expiratory pressure.
in Supplementary Figure 2 and Supplementary Table 1 as previously recommended (44).

Our study indicates that hyperinflation is a determinant of impaired diastolic filling and elevated ventricular filling pressures when isolated from previously identified confounding factors. Based on our findings, the reduction of hyperinflation via bronchodilation or bronchoscopic lung volume reduction might represent a promising tool for improving diastolic dysfunction in patients with COPD.

In summary, our findings strengthen the role of dynamic hyperinflation as a determinant of left ventricular diastolic dysfunction and favor hyperinflation, in contrast to other potential mechanisms, as a treatable trait for improving left ventricular diastolic function in COPD. Future studies should test the effects of pharmacologic or endoscopic lung volume reduction on echocardiographic parameters of diastolic function and their association with clinical endpoints, such as exercise capacity or dyspnea, in patients with chronic obstructive pulmonary disease.

DATA AVAILABILITY STATEMENT

Individual participant data referred to in this article (i.e., text, tables, figures) will be made available upon reasonable request. Other available documents comprise the study protocol and statistical analysis plan. Data will be made available for researchers who provide a methodologically sound proposal. Proposals should be directed to matthias.urban@gesundheitsverbund.at (ORCID: 0000-0002-7509-4983). Researchers are required to sign a data access agreement form before gaining access to the data.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Stadt Wien, Thomas-Klestil-Platz 8, A-1030 Vienna, Austria. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MU, G-CF, AM, OB, and IS: conception and design of the work. MU, G-CF, AM, and EG-S: acquisition, analysis, and interpretation of data. All authors: drafting and revising the manuscript, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

FUNDING

This work was supported by the Verein zur Forschung in der Pneumologischen Intensivmedizin and the Ludwig Boltzmann Institute for Lung Health.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.659108/full#supplementary-material

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. (2012) 380:2095–128. doi: 10.1016/S0140-6736(12)61728-0

2. Lorret-Tieulent J, Soerjomataram I, Lopez-Campos JL, Arocha J, Coebergh JW, Siriano JB. International trends in chronic obstructive pulmonary disease mortality, 1995-2017. Eur Respir J. (2019) 54:1901791. doi: 10.1183/13993003.01791-2019

3. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. (2012) 186:155–61. doi: 10.1164/rcrm.201201-0034OC

4. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest. (2005) 127:1952–9. doi: 10.1378/chest.127.6.1952

5. Farouk H, Albasmi M, El Chilali K, Mahmoud K, Nasr A, Heshmat H, et al. Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling. Respir Med. (2010) 104:996–1004. doi: 10.1016/j.rmed.2010.06.005

6. Cheyne WS, Williams AM, Harper MI, Eves ND. Heart-lung interaction in a model of COPD: importance of lung volume and direct ventricular interaction. Am J Physiol Heart Circ Physiol. (2013) 304:H1367–74. doi: 10.1152/ajpheart.00458.2016

7. Kubota Y, Arai S, Goto K, Hikosaka Y, Ushio Y, et al. COPD advances in left ventricular diastolic dysfunction. J Cardiol. (2016) 68:35–41. doi: 10.1016/j.jcc.2015.11.002

8. Caram LM, Ferrari R, Naves CR, Tanni SE, Coelho LS, Zanati SG, et al. Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease. Clinics. (2013) 68:772–6. doi: 10.6061/clinics/2013(06)08

9. Lopez-Sanchez M, Munoz-Esquerrre M, Huertas D, Gonzalez-Costello J, Ribas J, Manresa F, et al. High prevalence of left ventricle diastolic dysfunction in severe COPD associated with a low exercise capacity: a cross-sectional study. PLoS ONE. (2013) 8:e68034. doi: 10.1371/journal.pone.0068034

10. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Hauari A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. (2006) 355:260–9. doi: 10.1056/NEJMoa051530

11. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. (2010) 138:82–8. doi: 10.1378/chest.09-2810

12. Alter P, Mayerhofer BA, Kahnert K, Watz H, Waschki B, Andreas S, et al. Prevalence of cardiac comorbidities, and their underdetection and contribution to exertional symptoms in COPD: results from the COSYCONET cohort. Int J Chron Obstruct Pulmon Dis. (2019) 14:2163–72. doi: 10.2147/COPD.S209543

13. Alter P, Watz H, Kahnert K, Pfeifer M, Randerath WJ, Andreas S, et al. Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling. Respir Med. (2018) 137:14–22. doi: 10.1016/j.rmed.2018.02.011

14. Cheyne WS, Williams AM, Harper MI, Eves ND. Heart-lung interaction in a model of COPD: importance of lung volume and direct ventricular interaction. Am J Physiol Heart Circ Physiol. (2016) 311:H1367–74. doi: 10.1152/ajpheart.00458.2016

15. Zhyvotovska A, Yusupov D, Kamran H, Al-Bermani T, Abdul R, Kumar S, et al. Diastolic dysfunction in patients with chronic obstructive pulmonary disease: a meta-analysis of case controlled studies. Int J Clin Res Trials. (2019) 4:137. doi: 10.15344/2456-8007/2019/137
29. Tschernko EM, Gruber EM, Jaksch P, Jandrasits O, Jantsch U, Brack T, El Khawand C, Vanpee D, Rousseau L, Jamart J, Delaunois L.

31. Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE.

30. Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. *Chest.* (2008) 133:1354–9. doi: 10.1378/chest.07-2685

32. Barr RG, Blumeke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. *N Engl J Med.* (2010) 362:217–27. doi: 10.1056/NEJMoa0808836

33. Alter P, Jorres RA, Watz H, Welte T, Glaser S, Schulz H, et al. Left ventricular volume and wall stress are linked to lung function impairment in COPD. *Int J Cardiol.* (2018) 261:172–8. doi: 10.1016/j.ijcard.2018.02.074

34. Cargill RI, Kiely DG, Lipworth BJ. Adverse effects of hypoxaemia on diastolic filling in humans. *Clin Sci.* (1995) 89:165–9. doi: 10.1042/cs089165

35. Chhabra SK, De S. Cardiovascular autonomic neuropathy in chronic obstructive pulmonary disease. *Respir. Med.* (2005) 99:126–33. doi: 10.1016/j.rmed.2004.06.003

36. Paulus WJ, Tischce C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* (2013) 62:263–71. doi: 10.1016/j.jacc.2013.02.092

37. Sahit R, Bolten CE, Fraser AG, Edwards JM, Edwards PH, Ionescu AA, et al. Sub-clinical left and right ventricular dysfunction in patients with COPD. *Respir. Med.* (2010) 104:1171–8. doi: 10.1016/j.rmed.2010.01.020

38. Butler J. The heart is not always in good hands. *Clin. Chest.* (1990) 97:453–60. doi: 10.1378/chest.97.2.453

39. Krieger BP. Hyperinflation and intrinsic positive end-expiratory pressure: less room to breathe. *Respir. Physiol.* (2009) 77:344–50. doi: 10.1016/j.resp.2017.07.030

40. Marangoni S, Scalvini S, Schena M, Vitacca M, Quadri A, Levi G. Right ventricular diastolic dysfunction in chronic obstructive lung disease. *Eur Respir J.* (2010) 35:5438–43.

41. Lau EM, Chemla D, Whyte K, Kovacs G, Olszewski H, Herve P. Does exercise hyperpnea does exist? *Curr Opin Pulm Med.* (2016) 22:400–7. doi: 10.1097/MCP.000000000000292

42. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J.* (2006) 28:523–32. doi: 10.1183/09031936.06.0124605

43. Bouchard J, Testuz A, Blanche C. Gender aspects in cardiac imaging. *Cardiovasc Diagn.* (2019) 149:1–4. doi: 10.4144/cvm.2019.02069

44. Tobin MJ. Principles and Practice of Intensive Care monitoring. New York, NY: McGraw-Hill (1998). p. 1523.

Conflict of Interest: MU received grants from Nycomed Pharma as well as speaker fees and fees for advisory boards from Astra-Zeneca, Boehringer Ingelheim, Dräger, Sanitas, and Grünenthal. IS received personal fees for lectures from Astra-Zeneca, AOP, Orphan, Boehringer-Ingelheim and Chiesi. AM and EG-S have no conflicts of interest to declare. OB received unrestricted research grants from public governmental federal institutions and and from pharma industry (Menarini, Boehringer-Ingelheim, Chiesi, GSK, Pfizer, TEVA, Astra-Zeneca Air Liquide, MSD) as a member of the Ludwig Boltzmann Institute for Lung Health for the Austrian LEAD Study. He received personal fees for lecture and as member of advisory boards from Roche, Takeda, Nycomed and Astra-Zeneca. G- CF reports speaker fees and fees for advisory boards from Boehringer Ingelheim, Menarini, Janssen-Cilag, Novartis, Insmed Germany, Getinge, Draeger, CSL Behring, Orion Pharma, Astra Zeneca, Fresenius, Chiesi, Glaxo-Smith Kline, Roche; G-CF reports educational grants from Janssen-Cilag.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Urban, Mayr, Schmidt, Grasmuk-Sieg, Bubbhauer and Funk. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.