**Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling**

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# Abstract

Aims**.** Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases are thought to be linked through various factors. We aimed to assess the relationship between airway obstruction, lung hyperinflation and diastolic filling in COPD.

Methods**.** The study population was a subset of the COPD cohort COSYCONET. Echocardiographic parameters included the left atrial diameter (LA), early (E) and late (A) transmitral flow, mitral annulus velocity (e’), E wave deceleration time (E[dt]), and isovolumic relaxation time (IVRT). We quantified the effect of various predictors including forced expiratory volume in 1 second (FEV1) and intrathoracic gas volume (ITGV) on the echocardiographic parameters by multiple linear regression and integrated the relationships into a path analysis model.

**Results.** A total of 615 COPD patients were included (mean FEV1 52.6% predicted). In addition to influences of age, BMI and blood pressure, ITGV was positively related to e’-septal and negatively to LA, FEV1 positively to E(dt) (p<0.05 each). The effect of predictors was most pronounced for LA, e’-septal and E(dt), and less for E/A, IVRT and E/e’. Path analysis was used to take into account the additional relationships between the echocardiographic parameters themselves, demonstrating that their associations with the predictors were maintained and robust.

Conclusions. Airway obstruction and lung hyperinflation were significantly associated with cardiac diastolic filling in patients with COPD, suggesting a decreased preload rather than an inherently impaired myocardial relaxation itself. This suggests that a reduction in obstruction and hyperinflation could help to improve cardiac filling.

**Key words**: COPD; airway obstruction; hyperinflation; diastolic filling; dyspnea; heart failure; HFpEF

# Introduction

Cardiovascular comorbidities are frequent in COPD and associated with a worse prognosis [1, 2], while the presence of COPD has a negative impact on cardiovascular disease and heart failure [3-5]. For example, airflow limitation is associated with increased mortality in patients hospitalized for heart failure, independent of cigarette smoking [6]. It is unclear whether the overlap of cardiac diseases and COPD is due to the high prevalence of both diseases *per se*, or derived from shared risk factors, or based on causal pathophysiological links.

Heart failure can result from systolic or diastolic dysfunction. For clinical purposes, the terms heart failure with reduced or preserved ejection fraction were introduced (HFrEF, HFpEF). In the past, a reduction in systolic function has been viewed as the main cause for symptoms and outcome, but improved diagnostic and imaging techniques have underlined the importance of the diastolic component. Among patients with decompensated heart failure, a relevant contribution originates from diastolic heart failure [7, 8], the prognosis of whom is similar to those with systolic dysfunction [9].

The interplay between myocardial relaxation and filling appears crucial for diastolic heart failure. Frequent myocardial alterations are hypertrophy and increased stiffness, e.g. as a consequence of hypertension, which not only play a role in cardiovascular disorders such as atrial fibrillation, but are also related to respiratory disorders, such as sleep-disordered breathing [10]. Correspondingly, there is an increasing awareness that diastolic dysfunction may contribute to exercise intolerance and physical inactivity in COPD.

In the general population, the prevalence of diastolic dysfunction is associated with age, body weight and hypertension [11]. In patients with COPD, the available estimates of the prevalence of diastolic dysfunction vary widely, probably due to different diagnostic approaches and small sample sizes [12-18]. Single markers involved in diastolic function have been shown to correlate with the degree of airflow limitation [16, 19], underlining their potential contribution to dyspnea and exercise intolerance [20-24]. Direct pathophysiological links have also been hypothesized between heart failure and COPD [25, 26], but diastolic dysfunction in COPD has not been studied comprehensively. As direct assessment requires invasive measurements, clinical evaluations of diastolic dysfunction are largely based on echocardiographic composite criteria [18, 27].

We therefore aimed to quantify the association of echocardiographic indices of diastolic cardiac function with airflow limitation and lung hyperinflation, as well as age, body mass index (BMI), and systolic and diastolic blood pressure in patients with COPD. We incorporated the multiple relationships between the parameters in a comprehensive path analysis model. The study population was part of the large COPD cohort COSYCONET *(COPD and Systemic Consequences - Comorbidities Network*).

# Methods

COSYCONET is a prospective, observational, multicenter cohort study in patients with stable COPD that aims to evaluate severity and time course of comorbidities and their relationship to the lung disorder [28]. The study was approved by the Ethics Committee of the University of Marburg as coordinating center and the Ethics Committees of all study centers, and is registered on ClinicalTrials.gov (registration number NCT01245933).

## Study participants

The inclusion criteria for COSYCONET were [28]: at least 40 years of age; doctor-based diagnosis of COPD or chronic (non-obstructive) bronchitis. Exclusion criteria were: significant lung surgery in the past; moderate or severe exacerbation in the four weeks prior to entry; currently diagnosed lung tumor; and physical or cognitive impairment resulting in an inability to participate in the measurements. For the present analysis, additional exclusion criteria were: heart valve disease more than moderate or heart valve replacement; presence of an implanted pacemakers or cardioverter-defibrillator. Only patients with full and plausible lung function as well as echocardiographic data were included (for details see supplement). Additional inclusion criteria were airflow limitation of grade GOLD 1 to 4 [29], i.e. patients with chronic bronchitis not fulfilling these criteria, named as GOLD 0, were not included; and presence of ECG-documented sinus rhythm was required. An additional exclusion criterion was severe diastolic hypertension >110 mmHg, which may have unpredictable, long-term effects on diastolic function [30] (Figure 1).

## Assessments

Spirometry and body plethysmography maneuvers were performed as recommended by the American Thoracic Society (ATS), European Respiratory Society (ERS) and Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP) [31-34]. Lung function was determined after bronchodilation using 400 µg salbutamol and 80 µg ipratropium bromide [28]. Echocardiography used standard methodology as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [27, 35]. The endpoints evaluated were: left ventricular ejection fraction (LVEF), e’-septal, e’-lateral, left atrial (LA) diameter, the ratio of transmitral peak Doppler velocity in early (E) to late (A) diastolic LV filling (E/A), the E/e’ ratio (where e’ is the mean of e’-septal and e’-lateral) and, the ratio of pulmonary systolic (S) to diastolic (D) venous flow (S/D) (for details and explanations of the clinical implications of these assessments see supplement).

## Data analysis

The present analysis used the baseline data (visit 1, recruitment). Forced expiratory volume in 1 second (FEV1) and intrathoracic gas volume (ITGV) were evaluated as percent predicted values [36, 37], and the ratio of FEV1 to forced vital capacity (FVC) and effective airway resistance (Reff) as absolute values. The echocardiographic LA diameter was normalized to body surface area. For descriptive statistics, we used mean values and standard deviations (SD). Differences between groups were evaluated via t-tests or analysis of variance (ANOVA) in case of continuous variables, via chi-square tests in case of categorical variables. Multiple linear regression analyses were used to evaluate associations between age, BMI, systolic and diastolic blood pressure and lung function parameters, all of which were taken as independent variables, and single echocardiography parameters which were taken as dependent. The relationship between echocardiographic parameters was assessed via linear correlation coefficients. The level of statistical significance was assumed at p<0.05.

In order to integrate the various relationships found and to assess whether the dependence of echocardiographic parameters on the predictors was affected by their mutual relationships, we additionally established a path analysis model. Path analysis is commonly used in social sciences and econometrics [38] and has also been applied in recent medical research [39-43]. Its advantage over conventional regression analysis is that it can incorporate cross-talk between dependent variables and allows for the quantification of direct and indirect effects. It is therefore well suited to analyze complex networks of interdependences.

# Results

## Patient characteristics

A total of 2741 patients were enrolled in COSYCONET, 1591 of whom had full and plausible systolic echocardiographic and lung function data (Figure 1). After exclusion of patients formerly classified as GOLD 0 (symptoms of chronic bronchitis but FEV1/FVC>0.7), or without ECG-documented sinus rhythm, or with diastolic blood pressure >110 mmHg, or implausible diastolic data, 1259 patients remained, 615 of whom had complete diastolic echocardiographic data in terms of E/A, E/e’, e’-septal, E (dt), IVT, and LA.

Patient characteristics stratified for spirometric GOLD categories are given in Table 1. There were significant differences in age, body weight, BMI, and blood pressure across the GOLD grades. Furthermore, LA diameter, e’-septal and e’-lateral, E/e’ ratio, and E (dt) significantly differed across GOLD grades, with no obvious trend for the E/A ratio. Echocardiographic descriptive data are given in Table 2. There were no significant differences in LV mass across the GOLD grades; males exhibited greater LV mass than females, even though the data were normalized to body surface area. A normal (or near to normal, i.e. ≥ 50%) systolic LVEF was found in 587 of 615 patients (95.4%). Diastolic dysfunction was found in 24 patients (4.1%) with normal LVEF. In these, and in 28 patients with depressed LVEF (a total of 52 patients [8.5%]), the grading of diastolic function resulted in diastolic functional grades I/II/III in 35/2/2 patients, with 13 patients undetermined.

## Associations with echocardiographic parameters

For the multivariate analyses we used age, BMI, diastolic and systolic blood pressure, FEV1 and ITGV as statistical predictors potentially influencing echocardiographic parameters. Among the echocardiographic parameters, we excluded those being closely related by definition in order to reduce collinearity, which would result in models being statistically unreliable and difficult to interpret. On this basis we selected E/A, E/e’, e’-septal, E (dt), IVRT and LA for analysis. In the multiple multivariate regression analysis we accounted for the correlation between the predictors. Hyperinflation, indicated by an increased ITGV, was associated with a decreased LA diameter, and airway obstruction, indicated by a reduced FEV1, with a decreased E (dt). Results are shown in Table 3, which gives unstandardized regression coefficients and their 95% confidence intervals for all those relationships which were statistically significant. They are also illustrated in Figure 2, which shows standardized regression coefficients.

## Integrative path analysis model

To delineate the relationship between the echocardiography parameters beyond a conventional regression analysis we built a path analysis model (Supplemental Figure 1). The chosen structure fitted well, with a chi-squared of 5.787 (8 degrees of freedom, p=0.671; values above 0.05 indicate that the model does not significantly deviate from the data, thus indicating acceptance of the model. The RMSEA (see methods) was <0.001 (10/90% confidence limits, <0.001 and 0.038), with PCLOSE of 0.990 and CFI close to 1.000 (PCLOSE and CFI values above 0.95 indicate acceptability).

The model of echocardiographic parameters was then combined with the multiple regression results (Figure 2). The result is shown in Figure 3, with the corresponding regression and correlation coefficients in Supplemental Table 1. Importantly, the relationship between the echocardiographic parameters turned out to be robust and not substantially modified through the predictors. Regarding the dependence on predictors, the influence of diastolic blood pressure on e’-septal and that of systolic blood pressure on E/e’ lost their statistical significance. Obviously, these effects were now mediated indirectly via E/A and e’-septal, respectively (compare Figure 2 and 3). The final model fitted with a chi-square of 31.633 (38 degrees of freedom, p=0.757); the RMSEA was <0.001 (10/90% confidence limits, <0.001 and 0.021), while PCLOSE and CFI were close to 1.000. In accordance with the previous multivariate analysis, airway obstruction (reduction of FEV1) was correlated with a decreased E (dt), and hyperinflation (ITGV) with a reduced LA size.

When inverting the direction of the influences of age, BMI, blood pressure and lung function on the parameters of diastolic function, the model did not fit, thereby confirming the proper choice of influencing variables, of influenced variables and of model structure. Moreover, essentially the same model was obtained when including patients of the former GOLD grade 0 (n=727) in addition to those of grades 1-4. To assess the potential role of bodyplethysmographic airway resistance Reff, FEV1/FVC ratio and gender, additional analyses involving these parameters were performed. The resulting model was only slightly modified (for further sensitivity analyses see supplementary material).

# Discussion

Using data from a large, well-characterized cohort of patients with COPD, we found echocardiographic markers of diastolic function to be associated with airway obstruction and lung hyperinflation, in addition to age, BMI and blood pressure. Specifically, the degree of airflow limitation in terms of FEV1 was related to the E-wave deceleration time, while hyperinflation in terms of ITGV was related to mitral annulus velocity and a reduced LA diameter. These associations were statistically robust and not markedly dependent on the strong relationships between the echocardiography parameters themselves that reflected their pathophysiological interdependence.

The first novel finding of the present study is that the prevalence of myocardial diastolic dysfunction appears to be lower in COPD than expected. Moreover, although many studies have analyzed markers of diastolic function, the majority used either single or a small number of measures, particularly the E/A ratio [21, 44, 45]. Compared to these previous studies, we provide a comprehensive picture of diastolic dysfunction in COPD, which included both airway obstruction and lung hyperinflation among the influencing factors. Furthermore, the results of our path analysis suggest that the functional impairment of the lung itself exerts small but measurable effects on diastolic parameters, presumably as consequence of a decreased left heart preload. This causal mechanism is an alternative to the assumption of an inherently impaired myocardial relaxation, or of systemic inflammation in COPD [46].

As there is no single echocardiographic parameter that changes in a monotonic manner with the severity of the disease, the diagnosis of diastolic dysfunction is challenging. For example diastolic heart failure is characterized by increased ventricular filling pressure that can only be measured invasively [47]. Therefore a bundle of markers have been recommended that can be obtained by echocardiography, including changes in cardiac cavity dimensions, Doppler magnitude flow and duration signals, and tissue Doppler velocities, e.g., of the mitral annulus [27]. The American Society of Echocardiography and the European Association of Cardiovascular Imaging [27] recommend the use of a panel of parameters for the echocardiographic evaluation of diastolic ventricular function (which is why we analyzed a set of six parameters to describe diastolic function). Consistent with the recommendation to use a panel of parameters, in our analyses, there was no clear relationship between COPD grades or lung function and E/A ratio [48].

The presence of comorbid conditions such as COPD may complicate the evaluation of diastolic dysfunction, e.g., a decrease of LV chamber size has been observed with increasing airflow limitation and lung hyperinflation [21, 49]. Furthermore, in patients with COPD right heart load can be increased which might exert an influence on the left heart. The consequence is that in patients with manifest heart failure, alterations of echocardiographic parameters could be predominantly a function of heart disease itself and not of lung function. Recognizing this, we excluded patients with certain cardiac entities from our analyses, and so we were able to demonstrate the influence of alterations in lung function, both obstruction and hyperinflation, on diastolic function.

Age, BMI and blood pressure are known to be associated with heart function and morphology in the general population [27]. In our COPD population age was related to E/A, e’-septal, E/e’ and LA diameter, BMI to E/A, E/e’ and LA diameter, and blood pressure to E/A, IVRT and e’-septal.

Regarding hyperinflation of the lung, ITGV positively correlated with e’-septal but inversely with LA diameter suggesting that lung hyperinflation has a negative impact on LV filling. This is compatible with reduced left heart filling, i.e. reduced preload. In contrast, reductions in LA filling and diameter can be linked to a reduction in pulmonary vein area as found in COPD independently of the transmitral flow pattern, whereas an abnormal transmitral flow has been associated with an increased vein area in subjects without COPD [46]. This emphasizes the necessity both for a comprehensive picture of diastolic function beyond measurement of single parameters and a consideration of the modulating effect of the lung disorder when evaluating diastolic dysfunction.

Regarding airway obstruction, a lower FEV1, was associated with a lower E (dt), suggesting a link between airway resistance and LV diastolic pressure, relaxation, and/or stiffness. Animal studies have shown that large negative intrathoracic pressure amplitudes can influence left ventricular afterload [47]. Furthermore, positive intrathoracic pressure during expiration, combined with prolonged expiration time, could maintain an elevated intrathoracic pressure for a greater fraction of the respiratory cycle, thereby reducing venous return and impairing ventricular filling and cardiac output [47]. These observations are consistent with observations of decreased LV chamber size in severe COPD [21, 49] and of histological alterations [47] such that the junction points from right to left ventricle at the septal insertion are prone to increased load and distending forces [50-52].

When measuring a broad panel of parameters it has to be taken into account that some of them are very closely related to each other. Therefore we had to be selective in terms of which were included in the path analysis. Various models could be constructed that were in accordance with pathophysiological considerations and statistically valid. The final model of the echocardiographic parameters alone showed the best fit and statistical robustness. This was emphasized by the fact that the addition of the predictors in the final model did not alter the relations between the echocardiographic parameters. Moreover, the links between the echocardiographic outcomes and the predictors age, BMI, FEV1 and ITGV remained stable. This stability underlined that airway obstruction and lung hyperinflation have a small, but robust effect on the echocardiographic indices of diastolic function.

If obstruction and hyperinflation in COPD are linked to a decreased preload and thus influence cardiac filling, as suggested by our data, a decreased preload might be more frequent in COPD patients than a genuine myocardial relaxation disorder itself. A clinical implication might be that bronchodilator therapy could improve diastolic function in COPD, in accordance with the finding that lung deflation can improve cardiac filling [26, 53]. It might be speculated that this therapy antagonizes the decreased LA size in COPD, improves early left ventricular filling, which leads to an increase in left heart preload and filling. Whether this has therapeutically relevant consequences needs to be explored in interventional studies.

Our study has the strength that we could analyze quality-controlled data from a large COPD cohort. However, a potential limitation is that the examined subgroup was less than one quarter of the total number of patients included in COSYCONET [28]. This reduction was due to the fact that echocardiography had not been performed in all patients, with the data set incomplete in others. It is difficult to estimate whether this selection introduced a bias but we preferred to restrict the analysis to patients with complete data instead of introducing statistical difficulties based on incomplete data. The disease characteristics of our population were similar to the overall COSYCONET population [28], which is (in turn) consistent with broad COPD populations [54-65]. However, as we excluded patients with reported cardiac diseases or manifest cardiac alterations, direct comparisons of the occurrence of diastolic dysfunction with that in an unselected population of COPD patients are not possible. A further strength was the availability of bodyplethysmographic data that permitted the direct quantification of lung hyperinflation, which turned out to be a significant influencing factor. We also consider it as a strength that the data allowed the formulation and statistical confirmation of a comprehensive picture of echocardiographic indices and lung function via path analysis. Despite this, the cross-sectional character does not permit truly causal inferences, for which follow-up data are more suitable. A method-inherent limitation of our study is that we relied on echocardiographic measurements, which therefore meant that we obtained surrogate markers of diastolic dysfunction only. Alternative, direct measurements include invasive pressure measurement or cardiac magnetic resonance imaging [66]; such techniques are either not indicated in the majority of patients with COPD, or are not widely available. We cannot completely exclude the possibility that the presence of hyperinflation *per se* could have impacted the echocardiographic data, in terms of variability, patient selection bias, or distortion of the measured values. However, we used data that are typical of those collected in clinical practice, and so we do not believe that this has impact on the potential clinical implications of our findings.

# Conclusions

The present cross-sectional study suggests that airway obstruction and lung hyperinflation in COPD are associated with impaired left heart diastolic filling that can be detected by echocardiography. This association resulted in small but significant shifts in the distributions of echocardiographic parameters. The findings are consistent with the hypothesis that a decreased left heart preload is a mechanical consequence of alterations in the cardiac environment caused by the lung disorder, and suggest that reductions of airway obstruction and hyperinflation could improve cardiac forward volume.

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# References

[1] M. Divo, C. Cote, J.P. de Torres, C. Casanova, J.M. Marin, V. Pinto-Plata, J. Zulueta, C. Cabrera, J. Zagaceta, G. Hunninghake, B. Celli, B.C. Group, Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease, Am J Respir Crit Care Med 186(2) (2012) 155-61.

[2] L.E. Vanfleteren, M.A. Spruit, M. Groenen, S. Gaffron, V.P. van Empel, P.L. Bruijnzeel, E.P. Rutten, J. Op 't Roodt, E.F. Wouters, F.M. Franssen, Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease, Am J Respir Crit Care Med 187(7) (2013) 728-35.

[3] N.M. Hawkins, Z. Huang, K.S. Pieper, S.D. Solomon, L. Kober, E.J. Velazquez, K. Swedberg, M.A. Pfeffer, J.J. McMurray, A.P. Maggioni, I. Valsartan in Acute Myocardial Infarction Trial, Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), European journal of heart failure 11(3) (2009) 292-8.

[4] F. Bursi, R. Vassallo, S.A. Weston, J.M. Killian, V.L. Roger, Chronic obstructive pulmonary disease after myocardial infarction in the community, American heart journal 160(1) (2010) 95-101.

[5] K.A. Fisher, M.S. Stefan, C. Darling, D. Lessard, R.J. Goldberg, Impact of COPD on the mortality and treatment of patients hospitalized with acute decompensated heart failure: the Worcester Heart Failure Study, Chest 147(3) (2015) 637-645.

[6] K.K. Iversen, J. Kjaergaard, D. Akkan, L. Kober, C. Torp-Pedersen, C. Hassager, J. Vestbo, E. Kjoller, E.L.F.S. Group, The prognostic importance of lung function in patients admitted with heart failure, European journal of heart failure 12(7) (2010) 685-91.

[7] T.E. Owan, D.O. Hodge, R.M. Herges, S.J. Jacobsen, V.L. Roger, M.M. Redfield, Trends in prevalence and outcome of heart failure with preserved ejection fraction, The New England journal of medicine 355(3) (2006) 251-9.

[8] M.M. Redfield, Heart Failure with Preserved Ejection Fraction, The New England journal of medicine 375(19) (2016) 1868-1877.

[9] C.W. Yancy, M. Lopatin, L.W. Stevenson, T. De Marco, G.C. Fonarow, A.S.A. Committee, Investigators, Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database, J Am Coll Cardiol 47(1) (2006) 76-84.

[10] R. Wachter, L. Luthje, D. Klemmstein, C. Luers, R. Stahrenberg, F. Edelmann, V. Holzendorf, G. Hasenfuss, S. Andreas, B. Pieske, Impact of obstructive sleep apnoea on diastolic function, Eur Respir J 41(2) (2013) 376-83.

[11] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, V. Falk, J.R. Gonzalez-Juanatey, V.P. Harjola, E.A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J.T. Parissis, B. Pieske, J.P. Riley, G.M. Rosano, L.M. Ruilope, F. Ruschitzka, F.H. Rutten, P. van der Meer, M. Authors/Task Force, R. Document, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European journal of heart failure 18(8) (2016) 891-975.

[12] A. Boussuges, C. Pinet, F. Molenat, H. Burnet, P. Ambrosi, M. Badier, J.M. Sainty, J. Orehek, Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study, Am J Respir Crit Care Med 162(2 Pt 1) (2000) 670-5.

[13] N. Ozer, L. Tokgozoglu, L. Coplu, S. Kes, Echocardiographic evaluation of left and right ventricular diastolic function in patients with chronic obstructive pulmonary disease, Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 14(6) (2001) 557-61.

[14] G.C. Funk, I. Lang, P. Schenk, A. Valipour, S. Hartl, O.C. Burghuber, Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure, Chest 133(6) (2008) 1354-1359.

[15] R. Sabit, C.E. Bolton, A.G. Fraser, J.M. Edwards, P.H. Edwards, A.A. Ionescu, J.R. Cockcroft, D.J. Shale, Sub-clinical left and right ventricular dysfunction in patients with COPD, Respiratory medicine 104(8) (2010) 1171-8.

[16] L.M. Caram, R. Ferrari, C.R. Naves, S.E. Tanni, L.S. Coelho, S.G. Zanati, M.F. Minicucci, I. Godoy, Association between left ventricular diastolic dysfunction and severity of chronic obstructive pulmonary disease, Clinics (Sao Paulo, Brazil) 68(6) (2013) 772-6.

[17] X. Freixa, K. Portillo, C. Pare, J. Garcia-Aymerich, F.P. Gomez, M. Benet, J. Roca, E. Farrero, J. Ferrer, C. Fernandez-Palomeque, J.M. Anto, J.A. Barbera, P.-C.S. Investigators, Echocardiographic abnormalities in patients with COPD at their first hospital admission, Eur Respir J 41(4) (2013) 784-91.

[18] H. Farouk, M. Albasmi, K. El Chilali, K. Mahmoud, A. Nasr, H. Heshmat, S. Abdel-Moneim, E. Baligh, Left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease: Impact of methods of assessment, Echocardiography 34(3) (2017) 359-364.

[19] Y.S. Huang, Y.C. Feng, J. Zhang, L. Bai, W. Huang, M. Li, Y. Sun, Impact of chronic obstructive pulmonary diseases on left ventricular diastolic function in hospitalized elderly patients, Clin Interv Aging 10 (2015) 81-7.

[20] H. Watz, B. Waschki, C. Boehme, M. Claussen, T. Meyer, H. Magnussen, Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study, Am J Respir Crit Care Med 177(7) (2008) 743-51.

[21] H. Watz, B. Waschki, T. Meyer, G. Kretschmar, A. Kirsten, M. Claussen, H. Magnussen, Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation, Chest 138(1) (2010) 32-8.

[22] M.M. Schoos, M. Dalsgaard, J. Kjaergaard, D. Moesby, S.G. Jensen, I. Steffensen, K.K. Iversen, Echocardiographic predictors of exercise capacity and mortality in chronic obstructive pulmonary disease, BMC Cardiovasc Disord 13 (2013) 84.

[23] R. Faludi, M. Hajdu, V. Vertes, A. Nogradi, N. Varga, M.B. Illes, V. Sarosi, G. Alexy, A. Komocsi, Diastolic Dysfunction Is a Contributing Factor to Exercise Intolerance in COPD, Copd 13(3) (2016) 345-51.

[24] S. Inoue, Y. Shibata, H. Kishi, J. Nitobe, T. Iwayama, Y. Yashiro, T. Nemoto, K. Sato, M. Sato, T. Kimura, A. Igarashi, Y. Tokairin, I. Kubota, Decreased left ventricular stroke volume is associated with low-grade exercise tolerance in patients with chronic obstructive pulmonary disease, BMJ open respiratory research 4(1) (2017) e000158.

[25] Y. Kubota, K. Asai, K. Murai, Y.T. Tsukada, H. Hayashi, Y. Saito, A. Azuma, A. Gemma, W. Shimizu, COPD advances in left ventricular diastolic dysfunction, Int J Chron Obstruct Pulmon Dis 11 (2016) 649-55.

[26] I.S. Stone, N.C. Barnes, W.Y. James, D. Midwinter, R. Boubertakh, R. Follows, L. John, S.E. Petersen, Lung Deflation and Cardiovascular Structure and Function in Chronic Obstructive Pulmonary Disease. A Randomized Controlled Trial, Am J Respir Crit Care Med 193(7) (2016) 717-26.

[27] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd, 3rd, H. Dokainish, T. Edvardsen, F.A. Flachskampf, T.C. Gillebert, A.L. Klein, P. Lancellotti, P. Marino, J.K. Oh, B.A. Popescu, A.D. Waggoner, Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 29(4) (2016) 277-314.

[28] A. Karch, C. Vogelmeier, T. Welte, R. Bals, H.U. Kauczor, J. Biederer, J. Heinrich, H. Schulz, S. Glaser, R. Holle, H. Watz, S. Korn, N. Adaskina, F. Biertz, C. Vogel, J. Vestbo, E.F. Wouters, K.F. Rabe, S. Sohler, A. Koch, R.A. Jorres, C.S. Group, The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline, Respiratory medicine 114 (2016) 27-37.

[29] C.F. Vogelmeier, G.J. Criner, F.J. Martinez, A. Anzueto, P.J. Barnes, J. Bourbeau, B.R. Celli, R. Chen, M. Decramer, L.M. Fabbri, P. Frith, D.M. Halpin, M.V. Lopez Varela, M. Nishimura, N. Roche, R. Rodriguez-Roisin, D.D. Sin, D. Singh, R. Stockley, J. Vestbo, J.A. Wedzicha, A. Agusti, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary, Am J Respir Crit Care Med 195(5) (2017) 557-582.

[30] J.Y. Jung, S.K. Park, C.M. Oh, J.G. Kang, J.M. Choi, J.H. Ryoo, J.H. Lee, The influence of prehypertension, controlled and uncontrolled hypertension on left ventricular diastolic function and structure in the general Korean population, Hypertens Res 40(6) (2017) 606-612.

[31] J. Wanger, J.L. Clausen, A. Coates, O.F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. Macintyre, R. McKay, M.R. Miller, D. Navajas, R. Pellegrino, G. Viegi, Standardisation of the measurement of lung volumes, Eur Respir J 26(3) (2005) 511-22.

[32] C. Vogelmeier, R. Buhl, C.P. Criee, A. Gillissen, P. Kardos, D. Kohler, H. Magnussen, H. Morr, D. Nowak, D. Pfeiffer-Kascha, W. Petro, K. Rabe, K. Schultz, H. Sitter, H. Teschler, T. Welte, R. Wettengel, H. Worth, A. Deutsche, B. Deutsche Gesellschaft fur Pneumologie und, [Guidelines for the diagnosis and therapy of COPD issued by Deutsche Atemwegsliga and Deutsche Gesellschaft fur Pneumologie und Beatmungsmedizin], Pneumologie 61(5) (2007) e1-40.

[33] C.P. Criee, S. Sorichter, H.J. Smith, P. Kardos, R. Merget, D. Heise, D. Berdel, D. Kohler, H. Magnussen, W. Marek, H. Mitfessel, K. Rasche, M. Rolke, H. Worth, R.A. Jorres, P. Working Group for Body Plethysmography of the German Society for, C. Respiratory, Body plethysmography--its principles and clinical use, Respiratory medicine 105(7) (2011) 959-71.

[34] B.R. Celli, M. Decramer, J.A. Wedzicha, K.C. Wilson, A. Agusti, G.J. Criner, W. MacNee, B.J. Make, S.I. Rennard, R.A. Stockley, C. Vogelmeier, A. Anzueto, D.H. Au, P.J. Barnes, P.R. Burgel, P.M. Calverley, C. Casanova, E.M. Clini, C.B. Cooper, H.O. Coxson, D.J. Dusser, L.M. Fabbri, B. Fahy, G.T. Ferguson, A. Fisher, M.J. Fletcher, M. Hayot, J.R. Hurst, P.W. Jones, D.A. Mahler, F. Maltais, D.M. Mannino, F.J. Martinez, M. Miravitlles, P.M. Meek, A. Papi, K.F. Rabe, N. Roche, F.C. Sciurba, S. Sethi, N. Siafakas, D.D. Sin, J.B. Soriano, J.K. Stoller, D.P. Tashkin, T. Troosters, G.M. Verleden, J. Verschakelen, J. Vestbo, J.W. Walsh, G.R. Washko, R.A. Wise, E.F. Wouters, R.L. ZuWallack, A.E.T.F.f.C. Research, An official American Thoracic Society/European Respiratory Society statement: research questions in COPD, Eur Respir J 45(4) (2015) 879-905.

[35] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F.A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.H. Picard, E.R. Rietzschel, L. Rudski, K.T. Spencer, W. Tsang, J.U. Voigt, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography 28(1) (2015) 1-39 e14.

[36] P.H. Quanjer, G.J. Tammeling, J.E. Cotes, O.F. Pedersen, R. Peslin, J.C. Yernault, Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society, Eur Respir J Suppl 16 (1993) 5-40.

[37] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S. Ip, J. Zheng, J. Stocks, E.R.S.G.L.F. Initiative, Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur Respir J 40(6) (2012) 1324-43.

[38] R.H. Hoyle, Handbook of Structural Equation Modeling, 2014.

[39] J.V. Pottala, G.D. Djira, M.A. Espeland, J. Ye, M.G. Larson, W.S. Harris, Structural equation modeling for analyzing erythrocyte fatty acids in Framingham, Comput Math Methods Med 2014 (2014) 160520.

[40] D. Silove, S. Rees, A.K. Tay, Z.M. da Costa, E.S. Savio, C. Soares, W. Tol, Pathways to perinatal depressive symptoms after mass conflict in Timor-Leste: a modelling analysis using cross-sectional data, Lancet Psychiatry 2(2) (2015) 161-7.

[41] A. Tawakol, A. Ishai, R.A. Takx, A.L. Figueroa, A. Ali, Y. Kaiser, Q.A. Truong, C.J. Solomon, C. Calcagno, V. Mani, C.Y. Tang, W.J. Mulder, J.W. Murrough, U. Hoffmann, M. Nahrendorf, L.M. Shin, Z.A. Fayad, R.K. Pitman, Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study, Lancet 389(10071) (2017) 834-845.

[42] K. Kahnert, T. Lucke, R.M. Huber, J. Behr, F. Biertz, A. Vogt, H. Watz, P. Alter, S. Fahndrich, R. Bals, R. Holle, S. Karrasch, S. Sohler, M. Wacker, J.H. Ficker, K.G. Parhofer, C. Vogelmeier, R.A. Jorres, C. consortium, Relationship of hyperlipidemia to comorbidities and lung function in COPD: Results of the COSYCONET cohort, PLoS One 12(5) (2017) e0177501.

[43] A.H. Ribeiro, P.A. Lotufo, A. Fujita, A.C. Goulart, D. Chor, J.G. Mill, I.M. Bensenor, I.S. Santos, Association Between Short-Term Systolic Blood Pressure Variability and Carotid Intima-Media Thickness in ELSA-Brasil Baseline, Am J Hypertens 30(10) (2017) 954-960.

[44] K. Jorgensen, E. Houltz, U. Westfelt, F. Nilsson, H. Schersten, S.E. Ricksten, Effects of lung volume reduction surgery on left ventricular diastolic filling and dimensions in patients with severe emphysema, Chest 124(5) (2003) 1863-70.

[45] M. Lopez-Sanchez, M. Munoz-Esquerre, D. Huertas, J. Gonzalez-Costello, J. Ribas, F. Manresa, J. Dorca, S. Santos, High Prevalence of Left Ventricle Diastolic Dysfunction in Severe COPD Associated with A Low Exercise Capacity: A Cross-Sectional Study, PLoS One 8(6) (2013) e68034.

[46] M. Lopez-Sanchez, M. Munoz-Esquerre, D. Huertas, A. Montes, M. Molina-Molina, F. Manresa, J. Dorca, S. Santos, Inflammatory markers and circulating extracellular matrix proteins in patients with chronic obstructive pulmonary disease and left ventricular diastolic dysfunction, Clin Respir J 11(6) (2017) 859-866.

[47] J.A. Simpson, K.R. Brunt, C.P. Collier, S. Iscoe, Hyperinflation-induced cardiorespiratory failure in rats, J Appl Physiol (1985) 107(1) (2009) 275-82.

[48] B.M. Smith, M.R. Prince, E.A. Hoffman, D.A. Bluemke, C.Y. Liu, D. Rabinowitz, K. Hueper, M.A. Parikh, A.S. Gomes, E.D. Michos, J.A.C. Lima, R.G. Barr, Impaired left ventricular filling in COPD and emphysema: is it the heart or the lungs? The Multi-Ethnic Study of Atherosclerosis COPD Study, Chest 144(4) (2013) 1143-1151.

[49] R.G. Barr, D.A. Bluemke, F.S. Ahmed, J.J. Carr, P.L. Enright, E.A. Hoffman, R. Jiang, S.M. Kawut, R.A. Kronmal, J.A. Lima, E. Shahar, L.J. Smith, K.E. Watson, Percent emphysema, airflow obstruction, and impaired left ventricular filling, The New England journal of medicine 362(3) (2010) 217-27.

[50] P. Alter, H. Rupp, P. Adams, F. Stoll, J.H. Figiel, K.J. Klose, M.B. Rominger, B. Maisch, Occurrence of late gadolinium enhancement is associated with increased left ventricular wall stress and mass in patients with non-ischaemic dilated cardiomyopathy, European journal of heart failure 13(9) (2011) 937-44.

[51] P. Alter, Mystery of myocardial midwall late enhancement?, Int J Cardiovasc Imaging 30(8) (2014) 1569-70.

[52] P. Alter, C.F. Vogelmeier, A.R. Koczulla, Late gadolinium enhancement in sarcoidosis: ventricular wall stress should not be overlooked, Chest 147(3) (2015) e118.

[53] J.M. Hohlfeld, J. Vogel-Claussen, H. Biller, D. Berliner, K. Berschneider, H.C. Tillmann, S. Hiltl, J. Bauersachs, T. Welte, Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial, Lancet Respir Med *in print* (2018).

[54] T.M. Eagan, T. Ueland, P.D. Wagner, J.A. Hardie, T.E. Mollnes, J.K. Damas, P. Aukrust, P.S. Bakke, Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study, Eur Respir J 35(3) (2010) 540-8.

[55] B. Gjerde, P.S. Bakke, T. Ueland, J.A. Hardie, T.M. Eagan, The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway, Respiratory medicine 106(3) (2012) 361-6.

[56] M. Nishimura, H. Makita, K. Nagai, S. Konno, Y. Nasuhara, M. Hasegawa, K. Shimizu, T. Betsuyaku, Y.M. Ito, S. Fuke, T. Igarashi, Y. Akiyama, S. Ogura, C.C.S.I. Hokkaido, Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease, Am J Respir Crit Care Med 185(1) (2012) 44-52.

[57] A.R.C. Patel, G.C. Donaldson, A.J. Mackay, J.A. Wedzicha, J.R. Hurst, The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD, Chest 141(4) (2012) 851-857.

[58] L.J. Persson, M. Aanerud, P.S. Hiemstra, J.A. Hardie, P.S. Bakke, T.M. Eagan, Chronic obstructive pulmonary disease is associated with low levels of vitamin D, PLoS One 7(6) (2012) e38934.

[59] A. Jochmann, A. Scherr, D.C. Jochmann, D. Miedinger, S.S. Torok, P.N. Chhajed, M. Tamm, J.D. Leuppi, Impact of adherence to the GOLD guidelines on symptom prevalence, lung function decline and exacerbation rate in the Swiss COPD cohort, Swiss Med Wkly 142 (2012) w13567.

[60] P.R. Burgel, R. Escamilla, T. Perez, P. Carre, D. Caillaud, P. Chanez, C. Pinet, G. Jebrak, G. Brinchault, I. Court-Fortune, J.L. Paillasseur, N. Roche, I.B.S. Committee, Impact of comorbidities on COPD-specific health-related quality of life, Respiratory medicine 107(2) (2013) 233-41.

[61] M.K. Han, H. Muellerova, D. Curran-Everett, M.T. Dransfield, G.R. Washko, E.A. Regan, R.P. Bowler, T.H. Beaty, J.E. Hokanson, D.A. Lynch, P.W. Jones, A. Anzueto, F.J. Martinez, J.D. Crapo, E.K. Silverman, B.J. Make, GOLD 2011 disease severity classification in COPDGene: a prospective cohort study, Lancet Respir Med 1(1) (2013) 43-50.

[62] M. Suzuki, Y. Torii, J. Kawada, H. Kimura, H. Kamei, Y. Onishi, K. Kaneko, H. Ando, T. Kiuchi, Y. Ito, Immunogenicity of inactivated seasonal influenza vaccine in adult and pediatric liver transplant recipients over two seasons, Microbiol Immunol 57(10) (2013) 715-22.

[63] J. Bourbeau, W.C. Tan, A. Benedetti, S.D. Aaron, K.R. Chapman, H.O. Coxson, R. Cowie, M. Fitzgerald, R. Goldstein, P. Hernandez, J. Leipsic, F. Maltais, D. Marciniuk, D. O'Donnell, D.D. Sin, G. Cancold Study, Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the need for longitudinal observational studies in COPD, Copd 11(2) (2014) 125-32.

[64] G.C. Donaldson, M. Law, B. Kowlessar, R. Singh, S.E. Brill, J.P. Allinson, J.A. Wedzicha, Impact of Prolonged Exacerbation Recovery in Chronic Obstructive Pulmonary Disease, Am J Respir Crit Care Med 192(8) (2015) 943-50.

[65] W.C. Tan, D.D. Sin, J. Bourbeau, P. Hernandez, K.R. Chapman, R. Cowie, J.M. FitzGerald, D.D. Marciniuk, F. Maltais, A.S. Buist, J. Road, J.C. Hogg, M. Kirby, H. Coxson, C. Hague, J. Leipsic, D.E. O'Donnell, S.D. Aaron, C.C.R.G. Can, Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study, Thorax 70(9) (2015) 822-9.

[66] P. Alter, A.R. Koczulla, C. Nell, J.H. Figiel, C.F. Vogelmeier, M.B. Rominger, Wall stress determines systolic and diastolic function--Characteristics of heart failure, Int J Cardiol 202 (2016) 685-93.

***Table 1. Patients' characteristics overall and stratified by GOLD grade and gender***

|  | **All Patients****N = 615** | **GOLD 1****N = 46** | **GOLD 2****N = 270** | **GOLD 3****N = 243** | **GOLD 4****N = 56** | **Male****N = 357** | **Female****N = 258** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Age, years | 64.3±8.3 | 63.8±9.9 | 65.3±8.3 | 64.2±8.0 | 61.1±7.8\*\* | 65.1±8.3 | 63.3±8.3\*\* |
| Male, n (%) | 357 (58.0) | 29 (63.0) | 153 (56.7) | 139 (57.2) | 36 (64.3) | - | - |
| Body height, cm | 170.6±9.1 | 172.1±8.3 | 170.4±9.2 | 170.5±9.4 | 170.8±8.6 | 175.9±6.9 | 163.2±6.3\*\*\* |
| Body weight, kg | 76.8±16.3 | 77.5±14.0 | 78.5±16.5 | 76.5±16.2 | 69.4±15.2\*\*  | 82.7±15.1 | 68.6±14.1\*\*\* |
| Body mass index, kg/m2 | 26.3±4.7 | 26.1±4.0 | 26.9±4.7 | 26.2±4.8 | 23.7±4.3\*\*\* | 26.7±4.5 | 25.7±5.0\* |
| **Lung function** |  |  |  |  |  |  |  |
| FEV1, % predicted | 52.6±17.7 | 87.0±5.8 | 63.3±8.6 | 40.7±5.7 | 24.8±4.2\*\*\* | 52.3±18.4 | 53.1±16.8 |
| FVC, % predicted | 77.8±17.8 | 104.8±8.0 | 86.1±11.8 | 69.1±12.8 | 52.8±13.1\*\*\* | 77.7±18.2 | 77.8±17.3 |
| FEV1/FVC | 0.52±0.11 | 0.64±0.04 | 0.57±0.08 | 0.47±0.09 | 0.38±0.10\*\*\* | 0.51±0.12 | 0.53±0.10\* |
| Reff, kPa\*s/l | 0.43±0.19 | 0.24±0.15 | 0.33±0.15 | 0.50±0.22 | 0.74±0.27\*\*\* | 0.39±0.21 | 0.48±0.25\*\*\* |
| ITGV, % predicted | 149.6±34.5 | 125.5±24.4 | 134.0±25.9 | 160.8±29.9 | 195.7±34.7\*\*\* | 146.0±35.0 | 154.5±33.3\*\* |
| **Blood pressure**  |  |  |  |  |  |  |  |
| Systolic, mmHg | 140.0±18.4 | 133.7±14.8 | 142.0±19.3 | 139.8±18.0 | 136.8±16.9\* | 140.9±17.9 | 138.7±19.0 |
| Diastolic, mmHg | 74.6±10.1 | 72.0±8.8 | 74.8±10.1 | 74.7±10.4 | 75.7±10.0 | 76.3±9.6 | 72.4±10.5\*\*\* |
| **Pulmonary medication, n(%)** |  |  |  |  |  |  |  |
| LABA | 530 (86.2) | 34 (73.9) | 221 (81.9) | 223 (91.8) | 52 (92.9)\*\*\* | 313 (87.7) | 217 (84.1) |
| LAMA | 469 (76.3) | 24 (52.2) | 182 (67.4) | 209 (86.0) | 54 (96.4)\*\*\* | 269 (75.4) | 200 (77.5) |
| ICS | 409 (66.5) | 30 (65.2) | 157 (58.1) | 182 (74.9) | 40 (71.4)\*\* | 242 (67.8) | 167 (64.7) |
| **Cardiovascular Medication, n (%)** |  |  |  |  |  |  |  |
| Betablockers | 121 (19.7) | 5 (10.9) | 49 (18.1) | 58 (23.9) | 9 (16.1) | 74 (20.7) | 47 (18.2) |
| ACE / renin inhibitors,AT antagonists | 276 (44.9) | 16 (34.8) | 126 (46.7) | 114 (46.9) | 20 (35.7) | 174 (48.7) | 102 (39.5)\* |
| Diuretics | 104 (16.9) | 3 (6.5) | 38 (14.1) | 48 (19.8) | 15 (26.8)\* | 65 (18.2) | 39 (15.1) |

Data are given as mean ± standard deviation, unless specified otherwise. Differences between GOLD grades I to IV or gender:\* <0.05, \*\*<0.01, \*\*\*<0.001.

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Reff = effective airway resistance; ITGV = intrathoracic gas volume; LABA = long-acting beta2 receptor agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; ACE = angiotensin converting enzyme; AT = angiotensin II, Pulmonary and cardiovascular medication includes any use of the drug, i.e. as single substance as well as in combined formulations. Diuretics include aldosterone antagonists.

***Table 2. Echocardiographic characteristics overall and stratified by GOLD grade and gender***

|  | **All Patients****N = 615** | **GOLD 1****N = 46** | **GOLD 2****N = 270** | **GOLD 3****N = 243** | **GOLD 4****N = 56** | **Male****N = 357** | **Female****N = 258** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| LVEF, % | 62.2±8.5 | 62.7±8.2 | 62.5±8.8 | 62.1±8.4 | 60.3±7.9 | 61.3±8.4 | 63.4±8.6\*\* |
| LVEDD, mm | 47.7±6.9 | 48.4±6.0 | 48.4±6.7 | 47.3±7.2 | 46.1±6.7 | 49.5±6.8 | 45.3±6.2\*\*\* |
| LV mass, g/m² | 108.1±43.1 | 105.9±28.6 | 112.5±43.9 | 104.8±43.8 | 103.4±44.9 | 115.2±42.0 | 98.4±42.7\*\*\* |
| LA, mm | 34.7±5.9 | 35.7±5.7 | 35.5±5.6 | 34.2±6.3 | 31.8±5.0\*\*\* | 35.9±5.9 | 33.0±5.5\*\*\* |
| LA, mm/m2 | 18.5±3.0 | 18.8±2.7 | 18.8±2.8 | 18.3±3.2 | 17.8±3.0\* | 18.1±3.0 | 19.1±3.0\*\*\* |
| E/A ratio | 0.91±0.28 | 0.94±0.22 | 0.89±0.27 | 0.92±0.30 | 0.92±0.28 | 0.91±0.30 | 0.91±0.25 |
| e’-septal, cm/sec | 8.0±2.5 | 7.8±2.0 | 7.9±2.4 | 8.0±2.6 | 9.0±3.1\* | 7.9±2.5 | 8.2±2.6 |
| e’-lateral, cm/sec | 9.6±2.8 | 9.9±2.9 | 9.4±2.7 | 9.6±2.9 | 10.7±2.8\* | 9.6±2.8 | 9.6±2.8 |
| E/e’ ratio | 8.3±2.8 | 8.2±2.1 | 8.3±2.7 | 8.5±2.9 | 7.2±2.7\* | 8.1±2.8 | 8.5±2.7\* |
| E (dt), msec | 208±75 | 220±66 | 217±77 | 205±74 | 166±61\*\*\* | 208±77 | 207±72 |
| IVRT, msec | 100±29 | 97±24 | 102±30 | 100±28 | 94±27 | 100±29 | 100±28 |
| S/D ratio | 1.22±0.38 | 1.27±0.36 | 1.18±0.38 | 1.26±0.40 | 1.26±0.27 | 1.23±0.39 | 1.21±0.37 |
| Ar – A, msec | -42.4±60.5 | -43.1±67.8 | -54.6±49.2 | -33.3±69.8 | -22.0±40.7 | -40.5±59.7 | -44.5±61.5 |

Data are given as mean ± standard deviation, unless specified otherwise. Differences between GOLD grades I to IV or gender: \* <0.05, \*\*<0.01, \*\*\*<0.001. LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LA = left atrial diameter; E/A = ratio of transmitral peak Doppler velocity in early (E) and late (A) diastolic LV filling; e’-septal/lateral = peak velocity in early diastole of the septal/lateral mitral annulus; E/e’ ratio = ratio of E and e’ that is the mean of e’-septal and e’-lateral; E (dt) = E-wave deceleration time; IVRT = isovolumic relaxation time; S/D = ratio of the pulmonary systolic (S) and diastolic (D) venous flow; Ar – A = difference of the duration of pulmonary venous flow (Ar) and of the mitral inflow during atrial contraction. For detailed explanation of parameters see supplement.

***Table 3. Regression weights of the model given in Figure 2***

| **Relationship** | **Estimate** | **S.E.** | **95% CI** **lower upper** | **p** |
| --- | --- | --- | --- | --- |
| E/A | **←** | Age | -0.006 | 0.001 | -0.008 | -0.004 | <0.001 |
| E/e’ | **←** | Age | 0.007 | 0.001 | 0.005 | 0.009 | <0.001 |
| e’-septal | **←** | Age | -0.004 | 0.001 | -0.006 | -0.002 | <0.001 |
| LA | **←** | Age | 0.072 | 0.014 | 0.045 | 0.099 | <0.001 |
| E/A | **←** | Diastolic  | -0.002 | 0.000 | -0.002 | -0.002 | <0.001 |
| e’-septal | **←** | Diastolic  | -0.001 | 0.001 | -0.003 | 0.001 | 0.038 |
| IVRT | **←** | Diastolic  | 0.016 | 0.006 | 0.004 | 0.028 | 0.006 |
| E/e’ | **←** | Systolic  | 0.001 | 0.001 | -0.001 | 0.003 | 0.045 |
| e’-septal | **←** | Systolic  | -0.001 | 0.000 | -0.001 | -0.001 | 0.039 |
| E/A | **←** | BMI | -0.002 | 0.001 | -0.004 | 0.000 | 0.045 |
| E/e’ | **←** | BMI | 0.009 | 0.003 | 0.003 | 0.015 | <0.001 |
| LA | **←** | BMI | -0.065 | 0.026 | -0.116 | -0.014 | 0.012 |
| E (dt) | **←** | FEV1 | 0.025 | 0.006 | 0.013 | 0.037 | <0.001 |
| e’-septal | **←** | ITGV | 0.000 | 0.000 | 0.000 | 0.000 | 0.001 |
| LA | **←** | ITGV | -0.011 | 0.004 | -0.019 | -0.003 | 0.002 |

Numerical results of the multiple multivariate regression analysis (Figure 2). The table describes the linear regression coefficients. The first columns show the dependent and independent variables, the next ones the non-standardized estimate and its standard error (S.E.), the next ones the 95% confidence interval (95%CI) and the corresponding p value. The regression analysis was performed taking into account the correlations between predictors as indicated by lines with two arrows in Figure 2. The corresponding covariances are the same as in Supplemental Table 1.The standardized regression coefficients and the correlations coefficients corresponding to the non-standardized estimates are indicated in Figure 2.

FEV1 = forced expiratory volume in 1 second; ITGV = intrathoracic gas volume; LA = left atrial diameter; E/A = ratio of transmitral peak Doppler velocity in early (E) and late (A) diastolic LV filling; e’-septal/lateral = peak velocity in early diastole of the septal/lateral mitral annulus; E/e’ ratio = ratio of E and e’ that is the mean of e’-septal and e’-lateral; E (dt) = E-wave deceleration time; IVRT = isovolumic relaxation time; diastolic and systolic denotes blood pressure, respectively.

# Legends

**Figure 1.** Participants included in the analysis.

**Figure 2.** Results of multivariate multiple linear regression analysis of predictors versus echocardiographic parameters, while including the correlations between the influencing variables (double-headed arrows). Each line is labelled by the standardized regression coefficient or correlation coefficient. Details of the numerical results are shown in Table 3.

**Figure 3.** Final path analysis model describing the relationship between predictors and echocardiographic parameters as well as the relationships between echocardiographic parameters. This model was constructed as an overlay of the models shown in Figures 2 and Supplemental Figure 1 and adapted according to changes in statistical significance in the combined model. The regression coefficients describing each of the relationships between two variables (unidirectional arrows for regression and bidirectional arrows for correlation), their confidence intervals and significance levels are given in Table 3. Each line is labelled by the standardized regression coefficient or correlation coefficient.