



Original Contribution

Prevalence and predictors associated with severe pulmonary hypertension in COPD

Mitra Samareh Fekri, MD^a, Mehdi Torabi, MD^{b,*}, Sara Azizi Shoul, MD^c, Moghaddameh Mirzaee^d^a Associate Professor of Pulmonology Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran^b Assistant Professor of Emergency Medicine, Department of Emergency Medicine, Kerman University of Medical Sciences, Clinical Research Center, Afzalipour Hospital, Kerman, Iran^c Department of Emergency Medicine, Kerman University of Medical Sciences, Kerman, Iran^d Department of Biostatistics and Epidemiology, School of Public Health, University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Article history:

Received 4 June 2017

Received in revised form 27 July 2017

Accepted 4 August 2017

Keywords:

Pulmonary hypertension

COPD

Body mass index

Cachexia

ABSTRACT

Background: Pulmonary hypertension (PH) is one of the most common complications of COPD (chronic obstructive pulmonary disease), but its severe form is uncommon. Various factors play an important role in the occurrence and severity of pulmonary hypertension in patients.

Methods: This cross-sectional study was performed on patients with COPD referred to an emergency department over a one-year period. The tests—including complete blood count (CBC) and arterial blood gas (ABG), pulmonary functional test (PFT) and echocardiography—were performed for all patients to measure mPAP (mean pulmonary artery pressure), ejection fraction (EF) and body mass index (BMI). The prevalence of severe pulmonary hypertension and its associated factors were investigated in these patients.

Results: A total of 1078 patients was included in the study, of whom 628 (58.3%) were male and 450 (41.7%) were female. The mean age of the patients undergoing the study was 70.1 ± 12.2 . A total of 136 (13.7%) of them had mPAP (mm Hg) ≥ 40 mm Hg as severe pulmonary hypertension. Following multivariable analysis by using the backward conditional method, it was shown that seven variables had a significant correlation with severe PH.

Conclusions: The results showed that there is an independent correlation between hypoxia, hypopnea and compensatory metabolic alkalosis, polycythemia, left ventricular dysfunction, emaciation, and cachectic with severe pulmonary hypertension. The prevalence of severe PH in these patients was 13.7%.

© 2017 Published by Elsevier Inc.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an irreversible bronchial inflammation that involves the lung airways and parenchyma and causes mucociliary dysfunction. Pulmonary hypertension (PH) is a common complication of COPD, which occurs in the wake of the development and exacerbation of the disease in the patients. PH is defined by a resting mean pulmonary arterial pressure >25 mm Hg, which is measured via right heart catheterization [1–4]. The prevalence of PH in these patients is different and depends on the severity of the disease, but is usually mild to moderate, and worsens by exercise, sleep and exacerbation of the disease. Approximately 5–10% of patients have “disproportionate” PH, which is the severe form of the disease. In these patients, resting PH is above 40 mm Hg. Such patients—because of the right

ventricular failure—have worse prognosis compared with those who have mild to moderate pulmonary hypertension [4–7].

A method of choice for the diagnosis of PH is right-heart catheterization, but because its nature is aggressive, Transthoracic Doppler Echocardiography can be used as a noninvasive method to screen these patients. In this method, mean pulmonary artery pressure (mPAP) ≥ 40 mm Hg is considered severe PH [3,5]. The most important factors that can contribute to the occurrence or exacerbation of PH include forced expiratory volume 1 (FEV1), ejection fraction (EF), and body mass index (BMI).

BMI is a measure of body fat and weight. It is calculated by dividing a person's weight in kilograms by the square of their height in meters. A correlation has been established between a high BMI and the increased risk of cardiovascular complications. It has been observed that lower levels of BMI can increase the risk of COPD complications and is inversely related to the survival of these patients, such that a lower BMI increases the risk of mortality caused by COPD [8,9].

Ejection fraction (EF) is used to assess left ventricular function and is calculated using the biplane Simpson's technique. An EF $<50\%$ is considered left ventricular dysfunction. Patients with COPD are at risk for left ventricular dysfunction; however, the results regarding the association of LV dysfunction in COPD patients has been the subject of much

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; FEV1, forced expiratory volume 1; FVC, forced vital capacity; mPAP, mean pulmonary artery pressure; MPV, mean platelet volume; PDW, platelet distribution width; PFT, pulmonary function test; PH, pulmonary hypertension; RDW, red cell distribution width.

* Corresponding author.

E-mail address: me_torabi@kmu.ac.ir (M. Torabi).

controversy. Nevertheless, the risk of mortality increases in patients with left ventricular dysfunction [10–12]. It seems that this left ventricular dysfunction is caused by right ventricular heart failure [11].

Lung function in patients with COPD is measured by FEV1 using Spirometry, which enables the assessment of the degree and severity of airway obstruction. A lower value of FEV1 is correlated with a severity of obstruction. In addition, there is a direct correlation between FEV1 levels with the prognosis of these patients [13,14].

The aim of this study was to assess the prevalence of severe PH in COPD patients referred to the emergency department of Afzalipour hospital and to monitor the relationship between PH with other variables.

2. Materials and methods

2.1. Study design

This cross-sectional study was performed at the internal medicine referral center of Kerman Afzalipour Hospital, located in the southeast of Iran, on patients with exacerbated COPD referred to the emergency department from June 21, 2014 through June 21, 2015. In the primary stage of the study, before starting the treatment process, vital signs were measured and complete blood count (CBC) and arterial blood gas (ABG) tests were performed on all the patients. After the patients were stabilized, pulmonary function test (PFT) and echocardiography for measurement of mean pulmonary artery pressure (mPAP) and ejection fraction (EF) were conducted. The inclusion criteria for the study were all COPD exacerbation patients whose airway obstruction, based on spirometric results, had an FEV1/FVC ratio <0.7; also, they were given two puffs of salbutamol inhaler and, after 15 min, if there was not a 12% or 200 cm³ increase in FEV1, and the possibility of all other obstructive pulmonary diseases, such as bronchiectasis, were ruled out, then that patient was qualified to enter the study as a COPD patient. Patients who had increased thrombotic events like pulmonary emboli, malignancies, chronic kidney disease, thyroid disorder, sarcoidosis, vasculitis, obstructive sleep apnea, HIV infection, idiopathic PAH, pregnant women or patients unwilling to cooperate were excluded from the study (Fig. 1).

CBC and its related tests were performed by SYSMEX KX-21N Automated Hematology Analyzer (SYSMEX, Japan). Blood was collected in laboratory tubes containing potassium citrate and tests were run no later than an hour after the blood sampling. ABG test was done by the model 995-Hb blood gas analyzer (AVL Medical Instruments, Japan). The use of ethylenediaminetetraacetic acid (EDTA) in lab tubes was avoided during the study to eliminate the risk of obtaining confounded results due to the probability of increased platelet volume. A pulmonary function test was performed for all the patients using spirometer, SPIRO

LAB II S/N A23–050.912 model (MIR, Italy), by an experienced technician, after the complete process was thoroughly explained to them. The results were interpreted and approved by a pulmonary subspecialist. Echocardiography was performed by cardiologists using the SAMSUNG MEDISON EKO 7 device (SAMSUNG MEDISON, South Korea) in order to measure mean pulmonary artery pressure (mPAP) and ejection fraction (EF). Patients were divided into two groups on the basis of the EF: LV ejection fraction <50%, which was considered left ventricular dysfunction, and EF ≥ 50% a normal heart function. Also, patients were divided into two groups based on the mean PAP: mPAP = 25–39 mmHg. This was considered mild to moderate pulmonary hypertension and mPAP ≥ 40 mm Hg as severe pulmonary hypertension. A check-list was collected and maintained by an emergency medicine resident. Frequent supervision for data collection was performed by the emergency medicine specialist.

This study is based on the Helsinki Accords (1975), revised in Hong Kong (1989); it was performed and approved by the Ethics Committee of Kerman University of Medical Sciences. Oral consent was obtained from each patient before entry into trial.

2.2. Variables and outcome

CBC and its related tests (WBC, PMN, HCT, MPV, PDW, RDW, PLT), FEV1, EF, ABG (PaO₂, PaCO₂, PH, HCO₃), vital signs (HR, BP, RR, SI, O₂ saturation) and BMI were the variables considered to be potentially correlated with mPAP. These variables are quantitatively considered for their association with mPAP.

2.3. Statistical analysis

For description of quantitative variables with normal and nonnormal distributions, respectively mean (± SD) was used. For qualitative (categorical) variables, percentage of frequency was used. Odds ratio (OR) and 95% confidence interval (CI) for expressing the severity of this association were used. A *P*-value < 0.05 was considered statistically significant in all statistical tests. All variables with a *P*-value of <0.25 in the *t*-tests and χ^2 tests were included in the logistic regression model (both univariate and multivariate) [15]. The final multivariate model was created by the backward conditional method (SPSS Version 16.0) (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Basic characteristics

Of a total of 1477 patients diagnosed with exacerbated COPD referring to the hospital within one year, 399 of them were excluded from the study and 1078 of them included in the study, in which 628 (58.3%) were male and 450 (41.7%) were female. The mean age of the patients undergoing the study was 70.1 ± 12.2. The youngest patient was 39 and the oldest was 93 years old. A total of 136 (13.7%) of them had mPAP (mm Hg) ≥ 40 mm Hg as severe pulmonary hypertension. Also, 129 (12.5%) of them had ejection fraction (EF) < 50% as LV

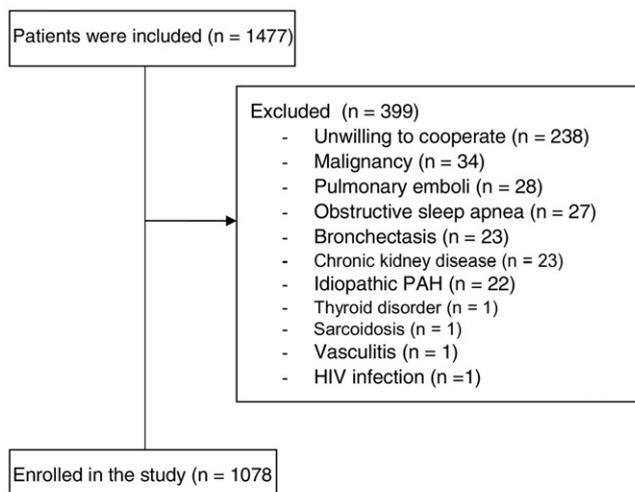


Fig. 1. Flow chart showing enrollment of patients.

Table 1
Patients' characteristics

Variables	Number (%)
Gender	
Male, N (%)	628 (58.3)
Female, N (%)	450 (41.7)
Age(y), mean ± SD	70.14 ± 12.26
mPAP (mm Hg)	
≥40	136 (13.7)
<40	854 (86.3)
Ejection fraction(EF)	
<50	129 (12.5)
≥50	907(87.5)
Hospital mortality	93(8.6)

dysfunction. Table 1 shows descriptive information for the variables relevant to these patients.

3.2. Univariate analysis

Using univariable analysis, all the quantitative variables that carried the potential possibility of pulmonary hypertension (PH) were statistically analyzed. In this statistical model, there is a significant difference between some of the variables and pulmonary hypertension. Then, to evaluate the severity of this association, odds ratio (OR) analysis was performed on the same variables (Table 2). As depicted, each 1% decrease in EF would result in an increase of 4% in the odds of severe PH. As well as in those with a BMI of <18.5, compared with BMI of over 25, the odds of severe PH would be increased 8.69-fold. Other variables showing significant associations can also be similarly considered.

3.3. Multivariate analysis

The multivariable analysis was then conducted by using the backward conditional method. In the final model, it was shown that seven variables had a significant correlation with the severe PH of the patients undergoing the study: As depicted, each 1% decrease in EF, would result in an increase of 11% in the odds of severe PH. As well as in those with a BMI of <18.5, the odds of severe PH would be increased 5.61-fold (Table 3).

3.4. Limitations

The most important limitation of our study is that there is no right heart catheterization to confirm PH in these patients. Another limitation is the fact that it is a unicenter study. However, since the hospital in which the study was run is the referral center for internal medicine patients in the southeast region of Iran, and since the prevalence of COPD patients is extremely high in this region—as well as the fact that there was a large sample size—this limitation became less significant. In addition, patients who were unwilling to cooperate were eliminated from the study. Also, patients who did not have the possibility of EF, mPAP or BMI measurement, or no acceptable PFT, were excluded from the study.

Table 2
Univariate analysis of variables according to their association with PH.

Variables	mPAP		OR(95%CI)	P value
	25–39 mm Hg	≥40 mm Hg		
Age	70.47 ± 12.35	68.01 ± 11.01	0.98(0.96–0.99)	0.03
HR	98.71 ± 21.77	87.80 ± 28.33	0.99(0.98–1.00)	0.17
RR	25.67 ± 7.04	21.30 ± 6.70	0.87(0.84–0.90)	<0.0001
O ₂ saturation	67.72 ± 12.75	64.69 ± 11.34	0.98(0.96–0.99)	0.03
WBC	8447.98 ± 5150.32	7723.26 ± 4875.752	1	0.14
PMN	78.19 ± 10.02	76.07 ± 11.68	0.99(0.97–1.00)	0.27
HCT	43.44 ± 8.19	48.79 ± 12.58	1.06(1.03–1.08)	<0.0001
Plt	136,122.74 ± 80,355.544	134,471.85 ± 79,577.332	1	0.83
MPV	9.09 ± 1.05	9.27 ± 1.08	1.00(0.84–1.20)	0.94
RDW	13.81 ± 2.31	14.12 ± 2.42	1.06(0.99–1.15)	0.07
PDW	11.86 ± 1.76	12.24 ± 2.08	1.07(0.97–1.18)	0.17
HCO ₃	24.57 ± 6.86	26.10 ± 5.15	1.02(0.92–1.05)	0.09
FEV1	48.91 ± 7.08	48.67 ± 5.44	1.03(1.00–1.05)	0.02
EF	54.77 ± 6.15	52.91 ± 6.82	0.96(0.94–0.99)	0.02
BMI <18.5	20.62 ± 3.56	19.30 ± 3.58	8.69(3.44–21.91)	<0.0001
18.5–24.99			2.80(1.09–7.20)	0.032
≥25			1	

HR; heart rate, RR; respiratory rate, HCT; hematocrit, Plt; platelete, MPV; mean platelete volume, RDW; red cell distribution width, PDW; platelet distribution width; FEV1; forced expiratory volume 1, EF; ejection fraction, BMI; body mass index.

Table 3
Multivariate regression analysis of variables according to their association with sever PH.

Variable	OR(95%CI)	P value
O ₂ saturation	0.92(0.89–0.94)	<0.0001
RR	0.84(0.78–0.97)	<0.0001
HCO ₃	1.05(1.00–1.09)	0.017
HCT	1.05(1.02–1.09)	0.001
EF	0.89(0.85–0.93)	<0.0001
BMI (<18.5)	5.61(1.85–17.03)	0.002

4. Discussion

In this study, the prevalence and predictors associated with severe PH in patients with COPD were examined. According to the results, the prevalence of severe PH in these patients by noninvasive echocardiographic evaluations was 13.7%. Moreover, there was an independent correlation between severe PH, with variables such as hypoxia, hypopnea and compensatory metabolic alkalosis, polycythemia, left ventricular dysfunction, emaciation, and cachectic as well.

The prevalence of severe PH in COPD patients range from 5 to 13.5% and, in most cases, the prevalence has been <10% [16–18]. Nevertheless, the prevalence increases substantially under certain conditions, such as exacerbations of COPD and impaired left ventricular function [3]. In this study, this rate was reported at 13.7%.

Patients with COPD, in the course of their disease, experience several complications. PH is one of the most common complications. The rate of progression of PH in these patients is <1 mm Hg per year and is calculated by echocardiography as a noninvasive diagnostic modality [5]. Pulmonary hypertension is usually mild to moderate, but a severe form of the disease can occur in a small percentage of the patients. The rate of mortality increases with increasing severity of the disease [1,18,19]. In this condition, pulmonary artery pressure exceeds 40 mm Hg (out-of-proportion) [5]. The patients with advanced COPD and acute exacerbation of the disease experience acute respiratory failure, which manifests as hypertension and hypoxemia deterioration [5–7]. In this stage with disease progression, the patient experiences resting hypoxemia which, in turn, can exacerbate the PH. Therefore, PH in patients with COPD can be caused by multiple factors including functional (hypoxia alveolar) and morphological (destruction of the lung parenchyma and vascular reconstruction) factors that through increased pulmonary vascular resistance can cause PH. Acute hypoxemia through the release of cytokines and mediators causes vasoconstriction of pulmonary vessels, especially small arteries, which results in PH. Moreover, chronic hypoxia through remodeling of pulmonary vascular bed and high-grade intimal lesions can cause PH [6,7,19]. Furthermore, chronic hypoxia through reactive oxygen species (ROS), vascular remodeling and enhanced vasoreactivity can increasingly induce and exacerbate PH [6,20]. Resting hypoxemia in these patients is significantly higher compared with those who do not have PH and they also have a worse prognosis [19,21]. In addition to hypoxia, the number of effective breaths gradually dwindles in the patients and causes chronic hypercapnia. Metabolic alkalosis is also generated by renal compensation to chronic respiratory acidosis [17]. At this stage, with PAP of above 40 mm Hg, a sharp reduction in the FEV1 is expected, but not only does FEV1 not decrease, but its level might be even higher than that of COPD patients without pulmonary hypertension (PH). But the point is that with exercise, the FEV1 is reduced drastically due to the mixed circulatory and ventilatory impairment [5]. These people may have less severe bronchial obstruction with an average FEV1 of 50%, but hypoxemia and hypocapnia are detectable as obvious in these patients. Despite moderate decline in FEV1, these patients have a poor prognosis and, so, their prognosis is not predictable by FEV1 [6,22]. Following prolonged and chronic hypoxia, polycythemia gradually occurs in these patients [23]. Increased blood viscosity due to polycythemia can increase pulmonary vascular resistance such that this process eventually causes the hypoxia-induced pulmonary hypertension [6,24]. The results of this study also confirm the progressive

development of PH in patients with COPD and its relationship with hypoxia, hypopnea, compensatory metabolic alkalosis and polycythemia. The findings also indicate that in a resting state, a substantial decrease of FEV1 cannot be expected.

Pulmonary hypertension is commonly observed in patients with heart failure and low EF and this mutual connection is associated with a poor outcome [25,26]. However, EF may be normal in 36–44% of patients (heart failure with preserved ejection fraction [HFpEF]) [26–28]. As pulmonary arterial pressure and right ventricular pressure gradually increase, function and RV output decline. This reduced blood flow delivery impairs preload and left ventricular filling and ultimately reduces stroke volume and left cardiac function. Therefore, it is expected that EF is further reduced by increasing pulmonary arterial pressure. It has been shown that the gradual decline in EF and increase in PAP can worsen the disease prognosis [4,25,26,29]. In this study, there was a significant relationship between the severity of pulmonary hypertension with decreased left ventricular function. In addition, there was a significant relationship between mortality, with both EF below 50% and PAP above 40 ($P < 0.0001$).

The body mass index (BMI) is used to define increased body fat and BMI is regarded as a good indicator to measure obesity by WHO. A high BMI—in particular, equal to or higher than 30—is an indicator for increased risk of cardiovascular complications and mortality, but in patients with COPD, there is an inverse relationship between mortality and obesity, which referred to as the “obesity paradox” and protective marker. Therefore, obesity in patients with PH through its protective effect can reduce patients’ mortality and vice versa [30]. PH is also associated with cachectic, so that people with PH gradually lose weight and their BMI decreases due to depletion of body fat. Low BMI increases the risk of developing pulmonary hypertension [31]. In this study, the BMI cut-off was considered to be 18.5. The results indicated that in patients with BMI below 18.5, there was a significant difference between patients with severe PH and patients with moderate to low PH, so that the incidence of PH was greater in cachectic and emaciated patients.

5. Conclusion

The prevalence of severe pulmonary hypertension in this study was reported in 13.7% of patients. The independent factors associated with PH include hypoxia, hypopnea and compensatory metabolic alkalosis, polycythemia, left ventricular dysfunction, emaciation and cachectic in patients.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgment

This study was supported by the Clinical Research Center of Afzalipour Hospital [grant number 94.427], Kerman University of Medical Science, Kerman, Iran.

References

- Adir Y, Harari S. Pulmonary hypertension associated with chronic obstructive lung disease and idiopathic pulmonary fibrosis. *Curr Opin Pulm Med* 2014;20(5):414–20.
- Galiè N, Hooper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009;30(20):2493–537.
- Moreira EM, Gall H, Leening MJ, Lahousse L, Loth DW, Krijthe BP, et al. Prevalence of pulmonary hypertension in the general population: the Rotterdam study. *PLoS One* 2015;10(6):e0130072.
- Minai OA, Chaouat A, Adnot S. Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective. *CHEST J* 2010;137(6_suppl):39S–51S.
- Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013;62(25):D109–16.
- Pulmonary hypertension in chronic obstructive pulmonary disease and interstitial lung diseases. In: Weitzenblum E, Chaouat A, Canuet M, Kessler R, editors. *Seminars in Respiratory and Critical Care Medicine*. © Thieme Medical Publishers; 2009.
- Pugliese SC, Poth JM, Fini MA, Olschewski A, El Kasmi KC, Stenmark KR. The role of inflammation in hypoxic pulmonary hypertension: from cellular mechanisms to clinical phenotypes. *Am J Physiol Lung Cell Mol Physiol* 2015;308(3):L229–52.
- Harik-Khan RI, Fleg JL, Wise RA. Body mass index and the risk of COPD. *Chest J* 2002;121(2):370–6.
- 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(2):155–61.
- Flu W-J, van Gestel YR, van Kuijk J-P, Hoeks SE, Kuiper R, Verhagen HJ, et al. Co-existence of COPD and left ventricular dysfunction in vascular surgery patients. *Respir Med* 2010;104(5):690–6.
- Funk G-C, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. *Chest J* 2008;133(6):1354–9.
- Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998;113(3):576–83.
- Ong K, Lu S, Soh C. Does the multidimensional grading system (BODE) correspond to differences in health status of patients with COPD? *Int J Chron Obstruct Pulmon Dis* 2006;1(1):91.
- Celli BR, Cote CG, Lareau SC, Meek PM. Predictors of survival in COPD: more than just the FEV1. *Respir Med* 2008;102:S27–35.
- Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med* 2008;3(1):17.
- Chaouat A, Bugnet A-S, Kadaoui N, Schott R, Enache I, Ducoloné A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172(2):189–94.
- Andersen KH, Iversen M, Kjaergaard J, Mortensen J, Nielsen-Kudsk JE, Bendstrup E, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *J Heart Lung Transplant* 2012;31(4):373–80.
- Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008;32(5):1371–85.
- Funke-Chambour M, Geiser T, Schoch OD. Pulmonary hypertension associated with chronic lung diseases. *Swiss Med Wkly* 2016;146.
- Liu JQ, Zelko IN, Erbynn EM, Sham JS, Folz RJ. Hypoxic pulmonary hypertension: role of superoxide and NADPH oxidase (gp91phox). *Am J Physiol Lung Cell Mol Physiol* 2006;290(1):L2–L10.
- Gologanu D, Stanescu C, Ursica T, Balea MI, Ionita D, Bogdan MA. Prevalence and characteristics of pulmonary hypertension associated with COPD-A pilot study in patients referred to a pulmonary rehabilitation program clinic. *Maedica* 2013;8(3):243.
- Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. *Eur Respir J* 2013;41(6):1292–301.
- Pesto S, Begic Z, Prevrljak S, Pecar E, Kukavica N, Begic E. Pulmonary hypertension—new trends of diagnostic and therapy. *Medical Archives* 2016;70(4):303.
- Zhou Y, Zhou T, Qiao L, Wang X, Xu H, Liu H, et al. Effect of polycythemia on hypoxia induced pulmonary hypertension and pulmonary vascular remodeling in rats. *Sichuan da xue xue bao Yi xue ban = J Sichuan Univ Med Sci Ed* 2009;40(4):619–22.
- Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. *Clin Chest Med* 2007;28(1):233–41.
- Bonderman D, Ghio S, Felix SB, Ghofrani HA, Michelakis ED, Mitrovic V, et al. Riociguat for patients with pulmonary hypertension due to systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. *Circulation* 2013;CIRCULATIONAHA 113.001458.
- Farr G, Shah K, Markley R, Abbate A, Salloum FN, Grinnan D. Development of pulmonary hypertension in heart failure with preserved ejection fraction. *Prog Cardiovasc Dis* 2016;59(1):52–8.
- Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction. *Circ Heart Fail* 2014;7(2):367–77.
- Marcus JT, Noordegraaf AV, Roeleveld RJ, Postmus PE, Heethaar RM, Van Rossum AC, et al. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. *Chest J* 2001;119(6):1761–5.
- Zafir B, Adir Y, Shehadeh W, Shteinberg M, Salman N, Amir O. The association between obesity, mortality and filling pressures in pulmonary hypertension patients: the “obesity paradox”. *Respir Med* 2013;107(1):139–46.
- Kawamoto A, Kato T, Minamino-Muta E, Okano Y, Shioi T, Kimura T. Relationships between nutritional status and markers of congestion in patients with pulmonary arterial hypertension. *Int J Cardiol* 2015;187:27–8.