Pulmonary emphysema and heart: separated but living together?

Dina Visca
Alfredo Chetta

Department of Clinical and Experimental Medicine, Respiratory Disease Unit, University of Parma, Parma, Italy

Address for correspondence:
Dina Visca, MD
Department of Clinical and Experimental Medicine
Respiratory Disease Unit
University of Parma
Padiglione Rasori, via G. Rasori 10
43100 Parma, Italy
Phone: +39 0521 703414
Fax: +39 0521 292615
E-mail: dinavisca@gmail.com

Summary

Pulmonary and cardiovascular diseases have a strong influence on each other. It is well known that cardiac diseases play a leading role as main cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD). Systemic inflammation has considered as the main linkage between pulmonary diseases and co-morbidities, especially as far as the cardiovascular risk in presence of smoking habit. The impairment in lung mechanics may also markedly affect the cardiac performance in COPD. Notably, static and dynamic hyperinflation that are specially represented in pulmonary emphysema, may influence cardiac function. We reviewed the emerging evidence that highlights the role of impaired lung mechanics on ventricular volumes, stroke volume and stroke work at rest and on exercise in presence of pulmonary emphysema.

KEY WORDS: pulmonary emphysema; respiratory mechanics; hyperinflation; cardiac performance.

Introduction

Pulmonary emphysema is a common pathologic condition characterized by abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles that leads to airspace walls destruction and usually to progressive airflow limitation. Emphysema is therefore considered as a subtype of Chronic Obstructive Pulmonary Disease (COPD).
Such as asthma and chronic bronchitis, emphysema is associated with enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases and his development is influenced by genetic predisposition. Systemic inflammatory status has been considered as the main linkage between COPD and co-morbidities.

Systemic inflammatory status is considered as the main link between COPD and co-morbidities.

Even if it is well known that cardiovascular disease is a common co-morbidity in COPD patients because of smoking habit, little has been described concerning the interaction between lung and heart in pulmonary emphysema from a lung mechanics point of view.
The aim of this overview is to describe about how much the lung mechanics could affect cardiac performance in presence of irreversible airflow obstruction.

COPD and cardiovascular risk

Suspect of COPD should be considered in patients complaining dyspnoea, chronic cough or sputum production, especially when exposure to risk factors such as smoking and air pollution is present. Next, spirometry is basic to diagnose COPD. The entity of bronchial obstruction, as assessed by the Forced Expiratory Volume at 1st second (FEV1), symptoms and exacerbations per year are useful parameters in order to stratify COPD severity and look for the best therapeutic approach (1). In addition, co-morbidities contribute to the overall health status in COPD patients and usually influence quality of life (1). Even if skeletal muscle wasting, osteoporosis, normocytic anemia, diabetes, metabolic syndrome and depression may commonly affect COPD patients, cardiovascular diseases have always played a leading role among co-morbidities. Indeed, it is well recognized that patients with COPD have a higher risk for congestive cardiac failure, arrhythmia and acute myocardial infarction if compared to control subjects (2). On the other hand, beta-blockers (3), angiotensin-converting enzyme inhibitors and statins (4) have the potential to reduce mortality and exacerbations in COPD population.

Beside the systemic inflammation, the impairment in lung mechanics may be a further deep linkage between heart and lung in chronic respiratory disease.

A chronic inflammatory status that characterizes bronchial and lung parenchymal damage in COPD seems to be the bridge to co-morbidities, especially to heart diseases. The mechanism responsible for in-

creased risk of cardiovascular disease in COPD has not been completely understood, however more attention has recently paid to inflammatory mediators that could also have a widespread action on other organs and apparatus leading to chronic and intermittent hypoxia, systemic inflammation and oxidative stress (5). Beside the systemic inflammation, the impairment in lung mechanics may be a further deep linkage between heart and lung in chronic respiratory disease. FEV_1, as percentage of predicted value was found to be an independent predictor of cardiovascular mortality in COPD (6) and a risk factor for cardiovascular events among general population (7) even in never-smokers (8). The FEV_1/Forced Vital Capacity (FVC) ratio was found to correlate to coronary events as well (9).

Lung Hyperinflation and Heart

In pulmonary emphysema, the loss of elastic recoil leads not only to the irreversible bronchial obstruction, but also to the lung hyperinflation, that implies an increased volume over the normal tidal breathing range and an increase in functional residual capacity (FRC). In addition, the more lung function is impaired the more the airway collapsibility affects lung mechanic, leading to an high intrinsic positive end-expiratory pressure (PEEPi) that increases intrapleural pressure.

In patients with pulmonary emphysema, the lung mechanics impairment may significantly affect the cardiac function. In 2007 Jorgensen et al. (10) studied 13 patients with severe emphysema with magnetic resonance technique and found decreased intrathoracic blood volume and left ventricular and right ventricular end-diastolic volumes, impaired stroke volume and stroke work in hyperinflated lungs compared to healthy patients. The authors argued that there are at least two main explanations of these findings (10). In presence of hyperinflated lungs, a high PEEPi could cause intrathoracic hypovolemia and small end-diastolic dimensions of both left and right ventricular chambers. The redistribution of pulmonary circulation in emphysema may occur not only because of a direct parenchimal destruction or hypoxia vasoconstriction, but also because of a decreased compliance of pulmonary vascular bed, that tends to push blood to the periphery borne down by a high PEEPi. Secondly, right and left ventricular chambers could be mechanically compressed by hyperinflated lungs that could worse end-diastolic stiffness. According to Frank-Starling law, a low preload finally reduces ventricular performance in terms of stroke volume (SV) and stroke work.

The redistribution of pulmonary circulation in emphysema tends to push blood to the periphery borne down by a high PEEPi.

Afterward, Watz et al. (11) in 2010 studied 138 COPD patients, ranging from GOLD I to IV class, and observed that the degree of COPD severity was directly correlated to heart dysfunction. Of interest, in this study the cardiac chamber sizes and impaired left ventricular diastolic filling pattern correlated more to the degree of static hyperinflation, as assessed by inspiratory-to-total lung capacity ratio (IC/TLC), than to the degree of airway obstruction, expressed as FEV_1 % predicted, or to diffusion capacity for carbon monoxide. Furthermore, IC/TLC was an independent predictor of cardiac chamber sizes after adjustment for body surface area.

Interestingly, as the pulmonary hyperinflation may have negative effects, so the pulmonary deflation has the potential to improve the cardiac function in patients with pulmonary emphysema. The NETT (National Emphysema Treatment Trial) Research Group recently found (12) that the decreased hyperinflation through lung volume reduction surgery was significantly associated with an improvement in oxygen pulse, that is considered as a non invasive marker of cardiovascular efficiency and a measure of SV.

It is of note that the extent of emphysema, as detected on computed tomography (CT), is associated to an impaired cardiac function, even in patients without very severe lung disease (12). In a recent population-based study, a greater extent of emphysema on CT scanning was linearly related to impaired left ventricular filling, reduced stroke volume and lower cardiac output without changes in the ejection fraction (13). The smoking status significantly worsened these associations. Accordingly, the authors hypothesized that the mechanisms of the impaired left ventricular filling in early, mild emphysema might be the subclinical loss of capillary bed due to the apoptotic effect of smoking on pulmonary endothelium.

Dynamic Hyperinflation and Cardiovascular Response to Exercise

In healthy subjects at rest, FRC physiologically equals the relaxation volume (V_r), at which all respiratory muscles are relaxed and the outward elastic recoil of the chest wall precisely balances the inward recoil of the lungs. By contrast, in patients with pulmonary emphysema changes in ventilation, such as an increase in flow and/or in breathing frequency, can elevate FRC above V_r. The condition characterized by FRC which does not equal, but it is greater than V_r is called dynamic hyperinflation and, in COPD patients, may typically occur during exercise. In addition to the static lung hyperinflation, dynamic hyperinflation is responsible for limitation to exercise in COPD patients and for onset of exertion dyspnoea. Accordingly, it is conceivable that during exercise dynamic hyperinflation can further worsen a poor resting cardiac function in patients with pulmonary emphysema. Both ventilatory and cardiac response to exercise can be well studied through cardiopulmonary exercise test (CPET). CPET is a relatively non invasive method to test tolerance to maximal exercise and gives several information about how cardiovascular, respiratory and muscle apparatuses respond to exercise. Notably, the assessment of the dynamic hyperinflation is based on the comparison of the IC performed at rest and during exercise and a positive difference between them is putative of dynamic hyperinflation, assuming that TLC remains constant during exercise.

We found that the extent of dynamic hyperinflation was inversely related not only to oxygen pulse, but also the product of systolic blood pressure and heart rate, the so-called double product (DP).

It has been recently shown that in patients with pulmonary emphysema the reduction in dynamic hyperinflation after LVRS was significantly associated to an improvement in cardiac response to exercise, both in term of oxygen pulse pressure, which is the difference between systolic and diastolic blood pressure.

Dynamic hyperinflation may significantly affect cardiac performance during rapidly incremental CPET. Vassaux et al. (14) first observed that dynamic hyperinflation is negatively associated to oxygen pulse at peak of exercise in patients with severe COPD. These results were confirmed and extended by our group in COPD patients with different degree of severity, by showing a significant relationship between dynamic hyperinflation and a battery of non-invasive measures of cardiovascular function during exercise (15). Notably in these patients, we found that the extent of dynamic hyperinflation was inversely related not only to oxygen pulse, but also to the product of systolic blood pressure and heart rate, the so-called double product (DP). Interestingly, DP reflects myocardial oxygen uptake during exercise because the three major determinants of myocardial oxygen uptake are the ventricular wall tension, the contractile state of the heart and the heart rate (16). Secondly, our group observed that the oxygen uptake efficiency slope (OUES), a parameter that integrates the functional capacities of several organ systems (cardiovascular, musculoskeletal and pulmonary) and represents the rate of increased O_2 consumption in response to a given ventilation during incremental exercise (17), was negatively associated with dynamic hyperinflation.

Importantly, it has been recently shown that in patients with pulmonary emphysema the reduction in dynamic hyperinflation after LVRS was significantly associated to an improvement in cardiac response to exercise, both in term of oxygen pulse and pulse pressure, which is the difference between systolic and diastolic blood pressure (18). It is of note that pulmonary rehabilitation may lower the ventilatory demand during exercise, resulting in the prolongation of the expiration time and, in turn, in the reduction of dynamic hyperinflation (19). Accordingly, one may hypothesized that in COPD patients, pulmonary rehabilitation may improve the cardiovascular response to exercise by enhancing the ventilatory function. In line with this assumption, our group has recently reported an improvement of cardiovascular response during exercise at submaximal exercise independent of the external work after a standard pulmonary rehabilitation program (20). This change was associated with an enhancement in ventilator function during exercise.

Closing remarks

Lung mechanics and cardiac performance are deeply dependent on each other and both may be responsible for exercise limitation, exertion dyspnoea and poor quality of life in presence of irreversible airflow limitation and lung hyperinflation.

Notably, in patients with pulmonary emphysema both static and dynamic hyperinflation may significantly affect the cardiovascular function.

Lung mechanics and cardiac performance are deeply dependent on each other and both may be responsible for exercise limitation, exertion dyspnoea and poor quality of life in presence of irreversible airflow limitation and lung hyperinflation.

Clinicians should take in consideration that any therapeutic approach, such as the use of inhaled bronchodilators, lung volume reduction surgery, and pulmonary rehabilitation, that aim to improve lung mechanics may in turn improve cardiac performance as well.

References

1. Pauwels RA, Buist AS, Calverley PM, Jenkins, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256-76.
2. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan, Canada Cardiovascular Disease in COPD patients. Ann Epidemiol 2006; 16:63-70.
3. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of β blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. BMJ 2011;342:d2549.
4. Mancini GB, Etminan M, Zhang B, Levesque LE, FitsGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 2006;47(12):2554-60.
5. Macnee W, Maclay J, McAllister D. Cardiovascular injury and repair in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5(8):824-33.
6. Tockman MS, Pearson JD, Fleg JL, Metter EJ, Kao SY, Rampal KG, et al. Rapid decline in FEV1. A new risk factor for coronary heart disease mortality. Am J Respir Crit Care Med 1995; 151:390-398.
7. 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;107:1514-1519.
8. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley Prospective Population Study. BMJ 1996;313(7059):711-715.
9. Engstrom G, Hedblad B, Janzon L, Valind S. Respiratory decline in smokers and ex-smokers an independent risk factor for cardiovascolar disease and death. J Cardiovasc Risk 2000;7(4):267-272.
10. Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in pa-

tients with severe emphysema. Chest 2007;131(4): 1050-1057.
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 (1):32-38.
12. Come CE, Divo MJ, San José Estépar R, Sciurba FC, Criner GJ, Marchetti N, et al. Lung deflation and oxygen pulse in COPD: results from NETT randomized trial. Respir Med 2012;106(1):109-19.
13. Barr RG, Bluemke 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(3):217-27.
14. Vassaux C, Torre-Bouscoulet L, Zeineldine S, Cortopassi F, Paz-Dìaz H, Celli BR, et al. Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. Eur Respir J 2008; 32(5):1275-82.
15. Tzani P, Aiello M, Elisa D, Boracchia L, Marangio E, Olivieri D, et al. Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients. Respir Res 2001;12:150.
16. Le V-V, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. Prog Cardiovasc Dis 2008;51(2):135-60.
17. Hollemberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 2000;36(1): 194-201.
18. Lammi MR, Ciccolella D, Marchetti N, Kohler M, G. J. Criner GJ. Increased oxygen pulse after lung volume reduction surgery is associated with reduce dynamic hyperinflation. Eur Respir J 2012; 40(4): 837-843.
19. Casaburi R, ZuWallack R. Pulmonary Rehabilitation for Management of Chronic Obstructive Pulmonary Disease. N Engl J Med 2009;360(13): 1329-1335.
20. Ramponi S, Tzani P, Aiello M, E. Marangio, E. Clini, A. Chetta. Pulmonary rehabilitation improve cardiovascular response to exercise in COPD. Respiration 2013;86(1):17-24.