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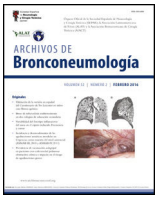

Editorial

The Heart–Lung Dilemma in COPD: A Tale of Two Cities☆

El dilema entre el pulmón y el corazón en EPOC: historia de dos ciudades

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The heart and the lung are 2 different organs that develop differently in the embryo, yet the anatomical and functional relationships of both are so interrelated that the physiology of one cannot be fully understood without understanding the physiology of the other. This relationship is even more pronounced in the context of chronic obstructive pulmonary disease (COPD) for several reasons: many cardiac diseases share risk factors and, in part, have a similar clinical expression; the pathophysiology of disease in one organ can ultimately affect the other; and there is the potential for treatment interaction.[1] Consequently, the study of interaction between the heart and the lung is of particular relevance in the study of COPD comorbidities.

Until recently, there were 2 main issues in the debate about the heart–lung relationship in COPD patients. Firstly, interactions between oral beta-blockers and inhaled beta-adrenergic drugs posed significant challenges for clinicians,[2] both because their potential for drug interaction, and because of the possible effect of beta-blockers in the prevention of COPD exacerbations and the potential usefulness of these drugs during exacerbations.[3] Secondly, the cardiovascular safety of bronchodilators was, and still is, widely discussed. Despite the results of large clinical safety trials,[4] studies with contrasting results are still appearing.[5]

Discussions of both these issues examine the possible detrimental effects that these treatments may have on the other organ. However, a third question has recently emerged in the heart–lung dilemma: whether inhaled treatments might not only be harmless to the heart, but may also benefit COPD patients with pulmonary hyperinflation. The suggested hypothesis for this observation is that improving cardiological physiological parameters also improves hyperinflation.[6] At least 4 studies have been published recently on this topic, all of which had a crossover design.

Two of these studies used echocardiography to explore the effect of a long-acting bronchodilator on cardiac function. The first evaluated the acute cardiological response to indacaterol (IND) versus placebo, 60 and 180 min after a single administration, in a series of 40 COPD patients.[7] The second compared tiotropium with placebo over 28 days with no washout period between treatments in 40 COPD patients.[8] Interestingly, both studies gave different results. In the tiotropium study, the authors observed a significant improvement in left ventricular ejection fraction of between 5% and 5.5% according to the randomization group, while in the indacaterol study, no significant improvements were found in any of the right heart parameters, with the exception of tricuspid annular plane systolic excursion, which increased by 0.41 mm at 180 min, and tricuspid E-wave deceleration which increased by 11.9 ms at 180 min. However, no left heart changes were detected with indacaterol. Studies directly comparing both families of bronchodilators would therefore be necessary to better explore these differences.

The other 2 crossover studies evaluate the effect of drug combinations administered in a single inhalation device on cardiac function assessed by magnetic resonance imaging (MRI). The first of these studies examined the effect of the combination of fluticasone furoate with vilanterol (FF/VI) compared to placebo over 7 days, with a 7-day washout between treatments, using right end-diastolic volume index as the main variable in 45 COPD patients.[9] The second study also evaluated IND with glycopyrronium bromide (GB) over 14 days using magnetic resonance imaging, with a 14-day washout between treatments and left end-diastolic volume index as the main variable in 60 COPD patients.[10] The benefits obtained with FF/VI were 5.35 ml/m^2 compared to the baseline value of 78.6 ml/m^2, and 5.83 ml/m^2 versus placebo for the right heart; and 3.66 ml/m^2 compared to the baseline value of 65.3 ml/m^2, and 3.63 ml/m^2 versus placebo for the left heart. The benefits of IND/GB were 6.36 ml/m^2 compared to the baseline value of 56.16 ml/m^2; and 4.61 ml/m^2 versus placebo for the right heart, and for the left heart, 6.30 ml/m^2 compared to the baseline value of 55.46 ml/m^2, and 5.23 ml/m^2 versus placebo. Although no direct comparisons are available, the results seem similar.

These studies have helped alert clinicians to the importance of hyperinflation and its cardiological impact in COPD. Although echocardiography remains the most widely used modality for the evaluation of myocardial function, technological advances and new measurement methods, such as MRI, have allowed this parameter to be assessed more accurately.[11,12] However, these findings should raise some questions. In the first place, the magnitude of

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the improvement should be assessed in the context of the patient's clinical condition. The baseline values described in the magnetic resonance imaging studies are within normal limits,[13] as might be expected from the inclusion criteria. The clinical implications of the improvements in end-diastolic volumes are difficult to determine in patients with no significant cardiac abnormalities. These issues leave the potential effect of bronchodilators in patients with COPD, hyperinflation, and cardiac disease open to question. A longitudinal study following up these changes would also be required to evaluate if they are maintained or if they are associated with future acute events or progression of acute lung or heart disease. In addition, a required objective of these longitudinal studies should be to assess cardiovascular safety in patients with hyperinflation and a history of heart disease. The cardiovascular safety of bronchodilators remains a subject of debate,[4,5] and the impact of these drugs on patients with hyperinflation has not been sufficiently explored. Finally, this impact needs to be evaluated in real-life studies that include patients with more advanced cardiovascular comorbidity and altered cardiac physiology at baseline. To this end, randomized controlled clinical trials must be performed in an adequate number of patients to monitor at least the aspects mentioned above.

In summary, the relationship between cardiac and respiratory drugs is a present day dilemma, and the potential benefit/safety balance is delicate. Like the title of Charles Dickens' book (1812–1870) "A Tale of Two Cities", the lung and heart follow parallels paths in health and disease. Future research should elucidate the potential efficacy and safety of treatments in different types of patients with COPD and heart disease, so that we can offer the most personalized medicine possible.

Conflict of Interests

J.L. Lopez-Campos has received honoraria for speaking engagements, scientific consultancy, participation in clinical trials, and drafting of publications from: Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, Cantabria Pharma, Chiesi, Esteve, Faes, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, MSD, Novartis, Pfizer, Rovi, Teva, and Takeda.

The other authors state that they have no conflict of interests with regard to this manuscript.

References

1. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018;12, 1753465817750524.
2. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. Eur Respir J. 2016;48:880–8.
3. Lopez-Campos JL, Marquez-Martin E, Casanova C. Beta-blockers COPD: the show must go on. Eur Respir J. 2016;48:600–3.
4. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013;369: 1491–501.
5. Wang MT, Liou JT, Lin CW, Tsai CL, Wang YH, Hsu YJ, et al. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: a nested case–control study. JAMA Intern Med. 2018;178:229–38.
6. O'Donnell DE, Webb KA, Neder JA. Lung hyperinflation in COPD: applying physiology to clinical practice. COPD Res Pract. 2015;1:2–12.
7. Santus P, Radovanovic D, di Marco S, Valenti V, Raccanelli R, Blasi F, et al. Effect of indacaterol on lung deflation improves cardiac performance in hyperinflated COPD patients: an interventional, randomized, double-blind clinical trial. Int J Chron Obstruct Pulmon Dis. 2015;10:1917–23.
8. Kato M, Komamura K, Kitakaze M, Hirayama A. The impact of bronchodilator therapy on systolic heart failure with concomitant mild to moderate COPD. Diseases. 2017;6:pii: E4.
9. Stone IS, Barnes NC, James WY, Midwinter D, Boubertakh R, Follows R, et al. Lung deflation and cardiovascular structure and function in chronic obstructive pulmonary disease. a randomized controlled trial. Am J Respir Crit Care Med. 2016;193:717–26.
10. Hohlfeld JM, Vogel-Claussen J, Biller H, Berliner D, Berschneider K, Tillmann HC, et al. 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. 2018;6:368–78.
11. Kinno M, Nagpal P, Horgan S, Waller AH. Comparison of echocardiography cardiac magnetic resonance, and computed tomographic imaging for the evaluation of left ventricular myocardial function: Part 1 (Global Assessment). Curr Cardiol Rep. 2017;19:9.
12. Kinno M, Nagpal P, Horgan S, Waller AH. Comparison of echocardiography cardiac magnetic resonance, and computed tomographic imaging for the evaluation of left ventricular myocardial function: Part 2 (Diastolic and Regional Assessment). Curr Cardiol Rep. 2017;19:6.
13. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson. 2015;17:29.