International Journal of Cardiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms

Alessandro Matarese [a], Celestino Sardu [b], Jun Shu [c], Gaetano Santulli [c,d,*]

[a] Department of Pneumology and Oncology, AORN "Ospedale dei Colli", Naples, Italy
[b] Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[c] Department of Medicine, Division of Cardiology, Albert Einstein College of Medicine, Montefiore University Hospital, New York, NY, USA
[d] Department of Biomedical Advanced Sciences, "Federico II" University, Naples, Italy

ARTICLE INFO

Article history:
Received 19 October 2018
Accepted 22 October 2018
Available online xxxx

1. Definitions and epidemiology

1.1. Chronic obstructive pulmonary disease (COPD)

COPD is a progressive life-threatening obstructive lung disease, characterized by long-term breathing problems and overall poor airflow. The key symptoms include cough with sputum production and shortness of breath. With its rising incidence and a prevalence of 251 million cases globally, COPD represents a major public health problem. The primary cause of COPD is exposure to tobacco smoke (either active or second-hand!); other risk factors include frequent lower respiratory infections during childhood, indoor and/or outdoor air pollution, and exposure to occupational dusts, fumes, irritants, and vapors. Notably, exposure to indoor air pollution can also affect the unborn child and represents a serious risk factor for developing COPD later in life [1]. Moreover, COPD predisposes to exacerbations and severe illness, including cardiac disorders. In fact, the main cause of death in COPD patients is given by cardiovascular disease rather than respiratory failure.

1.2. Atrial fibrillation (AFib)

AFib is a supraventricular arrhythmia characterized by uncoordinated atrial activity. AFib is the most commonly occurring sustained arrhythmia, and its incidence and prevalence is increasing worldwide [2]: ~9% of people ≥65-year-old and ~2% of people <65-year-old have AFib; AFib is predicted to affect 6–12 million people in the US by 2050 and 17.9 millions in Europe by 2060. AFib is classified into the following three types:

-*Paroxysmal*: recurrent (>1 episode ≥30 s) AFib that terminates spontaneously within 7 days;
-*Persistent*: lasts <7 days but necessitates pharmacologic or electrocardioversion or is sustained >7 days (defined *Longstanding* when>1 year);
-*Permanent*: refractory to cardioversion or accepted as a final rhythm.

2. COPD and AFib: evidence of an intimate association from clinical studies

The main parameters to determine the severity of COPD are the forced expiratory volume in 1 s (FEV1, defined as the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration) and the forced vital capacity (FVC, defined as the maximal volume of air exhaled with maximally forced effort from a maximal inspiration).

Interestingly, both FEV1 and FVC have been shown to be inversely related to the incidence of AFib, in the Copenhagen City Heart Study [3] and in the Multi-Ethnic Study of Atherosclerosis-Lung Study [4], respectively. Furthermore, the risk for AFib hospitalization is higher among patients with low FEV1. A prospective, population-based cohort study (Rotterdam Study) demonstrated that COPD is associated with a 28% increased risk of developing AFib, and that having frequent COPD exacerbations increases the AFib risk approximately 2-fold [5].

3. Clinical scores and scales useful for risk stratification

The following scales are used to quantify the respiratory disability and provide a prognostic evaluation:

-The Medical Research Council (*MRC*) dyspnea scale comprises five statements that describe almost the entire range of respiratory disability from none (Grade 1) to almost complete incapacity (Grade 5).
-The Dyspnea, Eosinopenia, Consolidation, Acidemia and AFib (*DECAF*) score was introduced as a predictor of mortality in

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.09.056.
* Corresponding author
E-mail address: gsantulli001@gmail.com (G. Santulli).

https://doi.org/10.1016/j.ijcard.2018.10.075

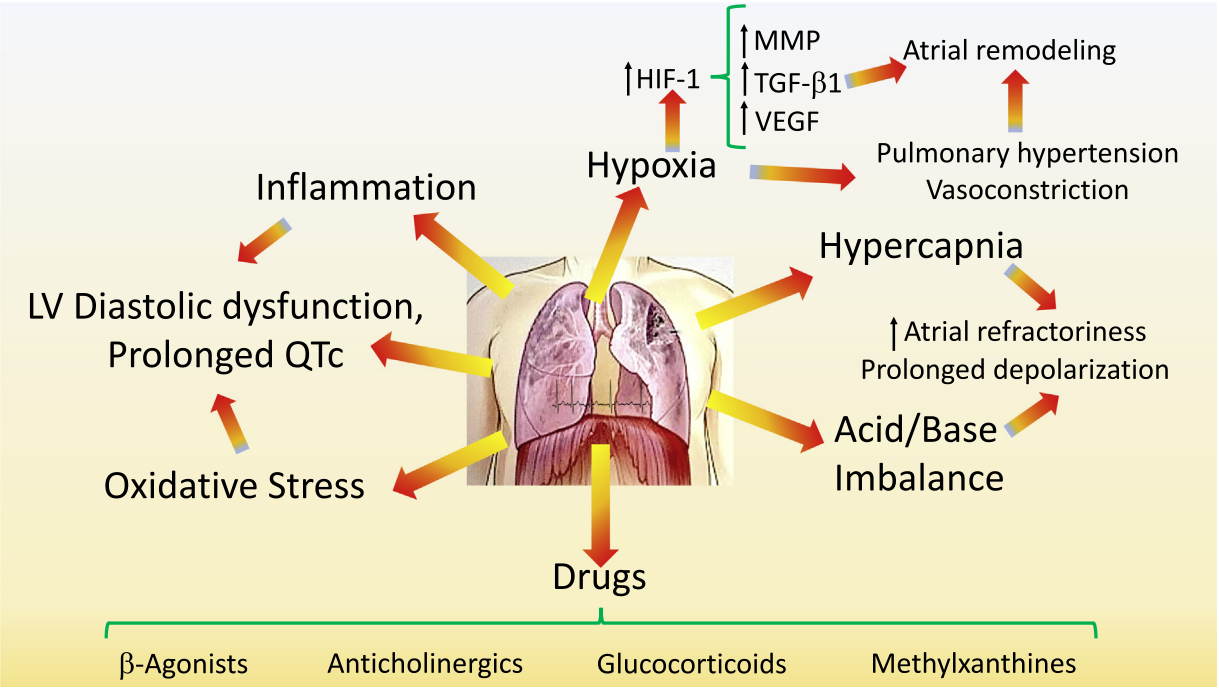

Fig. 1. Potential mechanisms linking COPD and AFib. Several pathogenic mechanisms present in COPD can lead to Afib, including some drugs used to treat COPD. Abbreviations: HIF-1: Hypoxia-inducible factor 1; LV: left ventricle; MMP: Matrix metalloproteinase; QTc: corrected QT interval; TGF-β1: Transforming growth factor β1; VEGF: Vascular endothelial growth factor.

hospitalized patients with COPD exacerbations. The DECAF score includes in its acronym the 5 strongest predictors of mortality.

-The *CURB65* includes the following criteria: Confusion; Blood Urea >19 mg/dL, Respiratory rate ≥ 30 bpm, Blood pressure ≤ 60/90 mm Hg, Age ≥ 65-years-old.

-The *BODE* index is a multidimensional 10-point scale which integrates body mass index, degree of airflow obstruction and dyspnea, and exercise capacity. Patients with higher BODE index scores have a significantly greater prevalence of supraventricular arrhythmias including AFib. The score is also directly proportional with mortality.

-The *HATCH* (Hypertension, Age > 75-year-old, previous Transient Ischemic Attack or stroke, COPD, Heart failure) score was generated performing a subgroup analysis studying AFib progression from paroxysmal to persistent within the European Heart Survey (EHS); remarkably, all the HATCH criteria are independent predictors of AFib progression.

In addition to the above-mentioned scores, a left atrial diameter of >45 mm and heart failure are among the strongest independent predictors of AFib [6].

4. COPD in AFib patients: a two-way relationship?

Alongside the increased risk of developing AFib observed in COPD patients, mounting evidence indicates that also the opposite association occurs. Indeed, the presence of COPD in AFib patients is associated with AFib progression, recurrence of AFib after catheter ablation, augmented risk of stroke, and increased cardiovascular mortality. Additionally, COPD contributes most to the increased all-cause mortality of AFib, whereas the absence of COPD represents also an independent predictor for a successful electro-cardioversion at 1-year follow-up [6].

5. The association of COPD with AFib: the potential underlying mechanisms

The potential mechanisms underlying the ominous association between COPD and AFib are depicted in Fig. 1. Hypoxia is definitely a key tenet of COPD that can lead to atrial remodeling and eventually to AFib via an augmented vascular tone which elicits pulmonary hypertension. Several molecular pathways triggered by COPD-related hypoxia can mediate the pro-fibrotic remodeling of the atrial tissue, including hypoxia-inducible factor 1 (HIF-1), transforming growth factor β1 (TGF-β1); vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMP). Equally important, chronic respiratory acidosis can prolong atrial depolarization and augment its refractoriness. Increased oxidation (including mitochondrial oxidative stress [7]) and inflammation are fundamental features of both COPD and AFib [8], and have been mechanistically linked to ventricular dysfunction, affecting diastolic function and causing ECG abnormalities. Supporting this view, the above-mentioned Rotterdam Study actually indicates that systemic inflammation in COPD seems to be crucial in driving the risk of incident AFib [5]. Some of these mechanisms could also help to enlight the recently reported relation between obstructive sleep apnea syndrome (OSAS) and AFib: in fact, OSAS has been shown not only to promote initiation of AFib but also to have a significant negative impact on its treatment.

Drugs commonly used to treat COPD have been independently associated with phenomena that can initiate AFib, including suppression of the parasympathetic system (anticholinergic drugs), chronotropic effects (β-adrenergic agonists, especially if not-β_2-selective [9]), electrolyte depletion, such as increased excretion of potassium and magnesium (methylxanthines). Moreover, oral glucocorticoids, especially high-dose steroids, are associated with an increased risk of developing AFib. Other potential mechanisms not fully studied include exosomes and microRNAs [10], which can mediate a cross-talk between lungs and atrial cells.

Please cite this article as: A. Matarese, et al., Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.10.075

Acknowledgements

GS is supported by the NIH, US, DK107895.

Conflict of interest

None.

References

[1] N.N. Hansel, M.C. McCormack, V. Kim, The effects of air pollution and temperature on COPD, COPD 13 (2016) 372–379.
[2] M.R. Patel, K.W. Mahaffey, J. Garg, G. Pan, D.E. Singer, W. Hacke, G. Breithardt, J.L. Halperin, G.J. Hankey, J.P. Piccini, R.C. Becker, C.C. Nessel, J.F. Paolini, S.D. Berkowitz, K.A. Fox, R.M. Califf, R.A. Investigators, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N. Engl. J. Med. 365 (2011) 883–891.
[3] P. Buch, J. Friberg, H. Scharling, P. Lange, E. Prescott, Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study, Eur. Respir. J. 21 (2003) 1012–1016.
[4] H. Chahal, S.R. Heckbert, R.G. Barr, D.A. Bluemke, A. Jain, M. Habibi, A. Alonso, R. Kronmal, D.R. Jacobs Jr., J.A. Lima, K.E. Watson, K. Liu, L.J. Smith, P. Greenland, Ability of reduced lung function to predict development of atrial fibrillation in persons aged 45 to 84 years (from the multi-ethnic study of atherosclerosis-lung study), Am. J. Cardiol. 115 (2015) 1700–1704.
[5] M. Grymonprez, V. Vakaet, M. Kavousi, B.H. Stricker, M.A. Ikram, J. Heeringa, O.H. Franco, G.G. Brusselle, L. Lahousse, Chronic obstructive pulmonary disease and the development of atrial fibrillation, Int. J. Cardiol. (2018) In press.
[6] S. Kochhauser, D.G. Dechering, K. Trought, P. Hache, T. Haig-Carter, Y. Khaykin, Z. Wulffhart, A. Pantano, B. Tsang, L. Eckardt, A. Verma, Predictors for progression of atrial fibrillation in patients awaiting atrial fibrillation ablation, Can. J. Cardiol. 32 (2016) 1348–1354.
[7] W. Xie, G. Santulli, S.R. Reiken, Q. Yuan, B.W. Osborne, B.X. Chen, A.R. Marks, Mitochondrial oxidative stress promotes atrial fibrillation, Sci. Rep. 5 (2015), 11427.
[8] A. Matarese, G. Santulli, Angiogenesis in chronic obstructive pulmonary disease: a translational appraisal, Transl. Med. UniSa. 3 (2012) 49–56.
[9] M. Ciccarelli, D. Sorriento, E. Coscioni, G. Iaccarino, G. Santulli, Adrenergic receptors, in: J. Schisler, C. Lang, M. Willis (Eds.), Endocrinology of the Heart in Health and Disease, Academic Press, London, UK 2017, pp. 285–315.
[10] G. Santulli, G. Iaccarino, N. De Luca, B. Trimarco, G. Condorelli, Atrial fibrillation and microRNAs, Front. Physiol. 5 (2014) 15.

Please cite this article as: A. Matarese, et al., Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.10.075