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OPINION

The COPD control panel: towards personalised medicine in COPD

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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease whose assessment and management have traditionally been based on the severity of airflow limitation (forced expiratory volume in 1 s (FEV_1)). Yet, it is now clear that FEV_1 alone cannot describe the complexity of the disease. In fact, the recently released Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2011 revision has proposed a new combined assessment method using three variables (symptoms, airflow limitation and exacerbations).

Methods Here, we go one step further and propose that in the near future physicians will need a 'control panel' for the assessment and optimal management of individual patients with complex diseases, including COPD, that provides a path towards personalised medicine.

Results We propose that such a 'COPD control panel' should include at least three different domains of the disease: severity, activity and impact. Each of these domains presents information on different 'elements' of the disease with potential prognostic value and/or with specific therapeutic requirements. All this information can be easily incorporated into an 'app' for daily use in clinical practice.

Conclusion We recognise that this preliminary proposal needs debate, validation and evolution (eg, including 'omics' and molecular imaging information in the future), but we hope that it may stimulate debate and research in the field.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with pulmonary and extrapulmonary manifestations.[1] Until very recently its diagnosis and assessment was based on the presence and severity of chronic airflow limitation (forced expiratory volume in 1 s (FEV_1)).[2] Yet, the relationship between FEV_1 and clinically relevant domains of the disease, such as symptoms, exercise capacity, frequency of exacerbations or the presence of comorbidity, is poor or non-existent.[1] Importantly, each of these domains is clinically relevant because they can influence outcomes, such as prognosis, significantly and independently[3] and may deserve specific therapeutic interventions. Hence, proper clinical assessment of patients with COPD must include domains other than FEV_1.[4] The recently released Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recognises these limitations and proposes to combine FEV_1, the level of symptoms and the past history of exacerbations to assess and manage patients with COPD more comprehensively.[5] This is an important step forward but it should not be viewed as the final one because it is largely based on expert opinion, and therefore, likely to be modified by future research.

Here, we hypothesise that the future assessment and management of patients with COPD will have to consider other domains of the disease to properly capture its complexity and to provide the best possible care to individual patients, hence moving the field towards personalised medicine in COPD. To do so, we propose that a 'COPD control panel' will have to be designed and validated. In this paper, we present the theoretical basis of this approach; propose an initial version of such a 'control panel' that considers three domains of the disease (severity, activity and impact of the disease); and explore its potential application in two hypothetical individual patients.

COPD AS A COMPLEX SYSTEM

A complex system is a collection of linked individual elements with so-called emerging properties that cannot be attributed to each element considered separately.[6 7] A plane (figure 1A) is a complex system since it is formed by numerous linked elements (engines, wings, fuselage, tires, others) and has one emerging property: flying. Yet, none of the individual elements of a plane can fly it on its own. Life, health and disease are emerging properties of an extremely complex system: the human body. In this context, the emerging discipline of systems/network medicine states that diseases should be viewed (diagnosed and treated) as the consequence of one or more biological networks in the relevant organ that become disease perturbed through genetic and/or environmental pathogenic changes.[8 9]

To fly the plane safely, pilots need a 'control panel' (figure 1B) that allows them to visualise the status of the relevant elements of the plane (instruments) and the environmental conditions that surround it to make the appropriate decisions. We propose that, similarly to pilots, doctors caring for patients with COPD (and likely other complex diseases[9]) should have a 'COPD control panel' that allows them to visualise the status of the relevant domains of the disease (and the environment) to make the appropriate therapeutic decisions. This is exactly what a good clinician does: to integrate information coming from diverse sources (clinical, biological, radiological, etc) to make a proper diagnosis and determine the best therapy in each patient. Thus, medicine has been 'personalised'

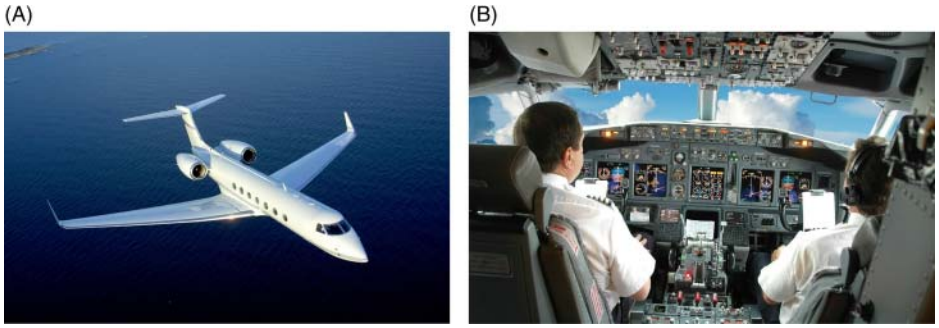

Figure 1 A plane (A) is a complex system and flying is an emerging property of the system. To fly the plane, the pilot in the cockpit (B) uses a control panel formed by different modules that inform them of the functioning of the system and the environment.

since its very beginnings. The challenge today is that the volume and complexity of information that the clinician has to integrate has increased in proportion to the complexity of the disease and will increase exponentially in the future as a result of high throughput technologies that will provide data on proteomics, metabolomics and genomics, and others such as molecular imaging. Thus a 'COPD control panel' is likely to be important in the individualised management of this and other complex diseases.

THE COPD CONTROL PANEL: A THREE-DOMAIN PROPOSAL

We propose that a COPD control panel could be constructed using three disease domains (severity, activity and impact). Each of these domains contains information on a number of elements of the system (COPD) that provide complementary and relevant information for the proper management of the individual patient, either because of its prognostic implications and/or requirement for specific therapeutic intervention (figure 2).

The severity of a given disease (including COPD) is inversely proportional to the functional reserve left in the target organ.[10] In COPD, FEV_1 is a good estimate of that functional reserve, although other physiological measurements such as the inspiratory to total lung capacity ratio (IC/TLC),[11] arterial blood gases[5] and exercise capacity[11] provide complementary information that also reflect the severity of COPD, and importantly, may require specific therapeutic interventions (bronchodilator treatment/lung volume reduction surgery, oxygen therapy or rehabilitation, respectively). Hence, we propose that the 'severity' module of the COPD control panel includes information on FEV_1, IC/TLC, arterial oxygenation and exercise capacity. We also propose to include the number and severity of the comorbidities because of their well known prognostic impact and need for specific therapy.[3] The Charlson index[12] may be a good indicator of comorbidities to be included in the severity domain, but individual comorbidities present in COPD (cardiovascular disease, metabolic syndrome, and depression, etc) would be an alternative.[13]

The activity of a disease reflects the intensity of the biological mechanisms that cause it.[10 14] The concept of 'activity of COPD' has been ignored until now.[15] Importantly activity and severity do not always run in parallel. For instance, activity may be high in the early stages of COPD but severity is mild. By contrast, advanced disease may be severe but may have low disease activity due to the spontaneous and/or therapeutically

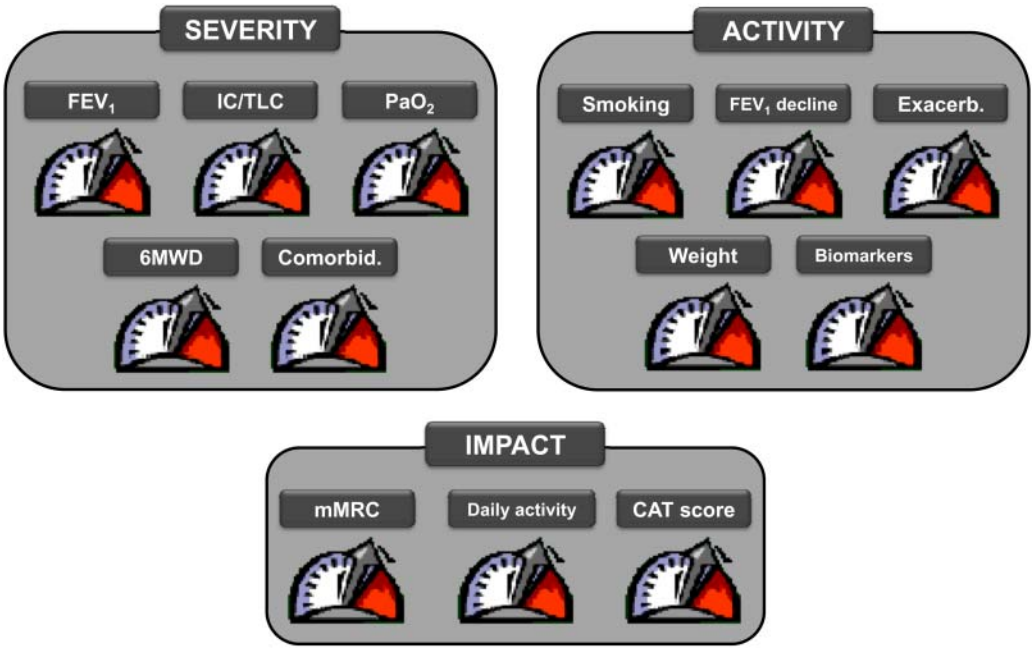

Figure 2 Proposal for a chronic obstructive pulmonary disease control panel. For further explanation, see text. 6MWD, 6 min walk distance; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; FEV_1, forced expiratory volume in 1 s; IC/TLC, inspiratory to total lung capacity ratio; mMRC, modified Medical Research Council Dyspnea Scale; PaO_2, arterial oxygen pressure.

induced downregulation of the biological mechanisms that caused it. The most appropriate marker of activity in COPD is an unresolved issue[15] but several clinical and biological candidates may be considered. Among the former, the rate of decline of FEV_1 is an obvious one since recent research has shown that the rate of change in FEV_1 among patients with COPD is highly variable.[16–18] Given that smoking is the major pathogenic mechanism in the development of COPD, continued smoking may also be considered a marker of disease activity. Another potential clinical marker of disease activity may be the frequency of exacerbations since, although they tend to increase in patients with more severe disease, the frequent exacerbator phenotype can also occur in moderate disease.[19] Among potential biological markers of disease activity, recent research has shown that the persistence of systemic inflammation (as indicated by circulating leukocytes, C-reactive protein, interleukin-6 and/or fibrinogen) is associated with increased mortality and exacerbation rate,[20] and that the addition of similar biomarkers improves the ability of established clinical variables to predict mortality in COPD.[21] Finally, it is well known that unintentional weight loss is also associated with poor prognosis in COPD,[22] although the persistence of systemic inflammation alluded to above appears to be associated with an increased body mass index (BMI).[20] Hence we propose that the activity domain of the COPD control panel includes information on smoking status, FEV_1 decline, annual rate of exacerbation, BMI and selected systemic biomarkers.

The impact of any disease depends on how the patient perceives the disease and modifies his/her activities of daily living. This perception is likely to vary substantially between individuals, as it is well established in asthma.[23] In COPD, we have traditionally assumed that mild disease (as assessed by FEV_1) has a minor impact on the patient, whereas the impact is much greater in severe disease. Yet, instruments that measure such an impact, like the St George's Respiratory Questionnaire[24] and the COPD Assessment Test (CAT),[25] have shown that the relationship between FEV_1 and health status is poor and individual variability is enormous.[1] In fact, as discussed above, the new GOLD 2011 recommendations recognise this variability and propose to determine the level of symptoms as a key component of the assessment of these patients.[5] Similar arguments can be applied to other domains of the disease, such as exacerbations,[19] since a number of patients suffer 'unreported exacerbations'[26] and lung function is severely impaired in a subgroup of patients who had never required hospitalisation because of exacerbation.[27] These observations suggest that, as described in asthma,[23 28] there may be poor symptom perceivers among patients with COPD. Finally, it is of note that daily activities are impaired in some, but not all, patients with COPD,[29] and that objectively measured physical activity is the strongest predictor of all-cause mortality in patients with COPD.[30] Hence, we propose that the impact domain of the COPD control panel includes some symptom measures (modified Medical Research Council Dyspnea Scale (mMRC) and/or CAT) as well as the level of daily activity.

In summary, we propose that such a 'COPD control panel' provides a way to visualise the complexity of COPD, and that the combined assessment of the severity, impact and activity can best inform the physician on the most appropriate management strategies for an individual patient.[5] Yet, we acknowledge that our proposal has limitations. For instance, the type of measures included in each domain needs to be discussed and validated, and how to link this type of holistic information to specific therapeutic interventions needs to be determined.

TOWARDS PERSONALISED MEDICINE IN COPD

The practice of medicine was originally based largely on personal experience. It was only in the late 1980s when evidence-based medicine (EBM) was introduced.[31] EBM has facilitated the development and refinement of clinical practice guidelines[32] but has well recognised limitations. The clearest one is that randomised clinical trials, the cornerstone of EBM, study a subset of the whole population of patients, and as a result, a significant degree of extrapolation is needed. Besides, they do not take into account the individual phenotypic variation that occurs inevitably in any disease. Thus only recommendations for the general population of patients can be formulated. As a result of these limitations, there is increasing interest in studying well identified subgroups, so-called 'clinical phenotypes' of patients who are associated with different outcomes and/or deserve specific therapeutic interventions.[33] This is not yet 'personalised' medicine (perhaps 'stratified' medicine), but it is clearly a step forward in this direction.[34] In this setting, two hypothetical patients may illustrate the potential practical use of the COPD control panel.

Patient A has mild disease (GOLD grade II, no hyperinflation, normal arterial oxygen pressure, normal exercise tolerance and no comorbidities), low impact (normal mMRC and CAT scores, normal daily activity) but a high level of disease activity (current smoker, increased FEV_1 decline with two exacerbations over the past 8 months plus raised levels of a potential biomarker of disease activity). Despite the 'mild' clinical presentation, the evidence of increased disease activity may indicate the need for a therapeutic intervention (anti-inflammatory therapy?) that prevents future progression of the disease. By contrast, patient B is characterised by severe disease (FEV_1<50% predicted, hyperinflation, low exercise capacity, comorbidities (cardiovascular disease and obesity)) and high impact (high mMRC, low CAT, house bound). Yet, there is little evidence of disease activity (ex-smoker, constant FEV_1, no frequent exacerbations, stable BMI and normal levels of potential biomarker(s) of disease activity). In this case, the physician may need to optimise bronchodilator treatment, treat comorbidities, and provide rehabilitation but may question the need for anti-inflammatory therapy.

CONCLUSIONS

We propose an integrated way to address the complexity of COPD: the 'COPD control panel'. This proposal should be considered the starting point of a debate that, we hope, might result in better clinical care of patients with COPD. We predict that, in the near future, the availability of quick and cheap 'omic' analyses will add to the 'control panel', and that new user-friendly bioinformatic technologies (so-called clinical decision support systems, which will be easily downloaded as 'apps')[9] will allow the clinician to integrate this vast amount of information for the benefit of a single patient, hence fulfilling the goal of 'personalised' medicine in COPD.

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