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Should we use gait speed in COPD, FEV1 in frailty and dyspnoea in both?

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Frailty is a progressive physiological decline in multiple organ systems marked by loss of function, loss of physiological reserve and increased vulnerability to disease [1]. Biological (inflammation and loss of hormones), clinical (*e.g.* sarcopenia and osteoporosis) and social factors are involved in frailty onset, evolution and prognosis [2, 3].

Many chronic diseases are associated with frailty and functional decline in older people [4]. Older people suffering from frailty often receive fragmented chronic care from multiple professionals. Coordination of care using a multidimensional approach is needed to develop interventions aimed at reducing frailty. Chronic respiratory diseases (CRD) represent a model of chronic diseases across the life course [5]. As with any noncommunicable disease, they can be associated with frailty [6]. It is possible that markers of frailty (gait speed) or CRD (pulmonary function tests) can be used in both frailty and CRD as independent markers for severity and trajectories. Moreover, they may represent interesting outcome measures adding value in clinical practice but that have been underestimated.

CRD and frailty are key targets of good practices emerging from the European Innovation Partnership on Active and Healthy Ageing (EIP–AHA) [7, 8]. Links between them represent a novel and practical approach between action groups of the EIP–AHA.

Frailty in COPD

Chronic obstructive pulmonary disease can be associated with frailty

Unrecognised chronic obstructive pulmonary disease (COPD) may be detected in community-dwelling frail elderly people using a near-home screening strategy that is simple to implement [9]. Patients with chronic

lung disease frequently meet the criteria of Fried for frailty [10]. Sarcopenia affects up to 15% of patients with stable COPD and impairs function and health status [11]. Many patients with COPD are frail [12] and physical activity level can predict the absence or presence of frailty in subjects with stable and exacerbated COPD [13]. In the Cardiovascular Health Study, frailty and respiratory impairment (airflow limitation or restrictive pattern) are strongly associated with one another and substantially increase the risk of death when both are present [14]. Establishing these associations may inform interventions designed to reverse or prevent the progression of either condition and reduce adverse outcomes.

It remains to be proven, however, whether optimising treatment of frail COPD patients with multimorbidities and polypharmacy improves health outcomes. Integrated care services in frail community-dwelling COPD patients improved clinical outcomes such as survival and decreased the emergency department visits, but it did not reduce hospital admissions [15].

Gait speed is a surrogate marker of COPD management and prognosis

Gait speed, a key marker of frailty, is mainly determined by exercise capacity but also reflects global well-being and may capture many of the multi-systemic effects of disease severity in COPD rather than pulmonary impairment alone. The usual gait speed is correlated with the 6-min walk distance (6MWD) [16]. Gait speed may be used as a functional capacity indicator in COPD patients [17]. The reliability and validity of the 4-m gait speed was demonstrated in patients with COPD. Gait speed slows down with increasing COPD severity. It correlates with age, clinical symptoms, pulmonary functions and quality of life scores. In community-dwelling elderly people, gait speed is a consistent predictor of adverse outcomes in patients with COPD [18]. It independently predicts the risk of readmission in older patients hospitalised for COPD [19]. The changes in usual gait speed and 6MWD are associated with increased mortality in patients with severe COPD [20]. Gait speed is promising as a simple test that can inform the clinician about many important functional aspects of the COPD patient [21] and be used in primary care [22].

Prognostic value of pulmonary function in nonrespiratory chronic diseases and older aged adults

COPD is commonly associated with cardiovascular diseases (CVDs) since they share many common pathogenic mechanisms [23]. CVD is the most common cause of death in COPD. It has long been known that obstructive and restrictive lung diseases are significant predictors of earlier death [24, 25].

Nonrespiratory chronic diseases

Forced expiratory volume in 1 s (FEV_1) is an independent predictor of all-cause and CVD mortality [26–30]. The addition of global CVD risk scores to lung function data significantly improves risk stratification of patients with COPD for CVD and total mortality [31]. Diabetes mellitus is associated with decreased pulmonary function. Reduced lung function is inversely related to blood glucose levels, diabetes duration and severity, and is independent of smoking or obesity [32]. Pulmonary function is a risk factor for other nonrespiratory diseases such as dementia [33]. Thus, FEV_1 appears to be an independent risk factor for nonrespiratory diseases [34, 35] and may be considered as a measure of physiological health that may improve risk stratification of noncommunicable disease patients.

Chronic airflow obstruction results in impaired lung gas exchange and hypoxia [36]. Hypoxia plays a key role in the pathophysiology of CVD, cancer, stroke and other causes of mortality. Hypoxia impedes cellular oxygen consumption and, more importantly, triggers various molecular and cellular responses leading to metabolic reprogramming and inflammatory responses [37]. As a result, the function of many organs or systems, including the kidneys, central nervous system, cardiovascular system, skeletal muscles and even the immune system, are affected by chronic hypoxic insult [38]. This might explain some of the links between impaired lung function and extrathoracic organ disorders [39]. Hypoxia has pervasive effects on the function of adipocytes and appears to be a key factor in adipose tissue dysfunction in obesity [40].

These considerations need to be better understood and confirmed by other trials but they open new fields of interest and research for improved management of all patients.

Older aged adults

There are many age-associated changes in the respiratory system physiology and immunology [41] that impact on pulmonary function [42, 43]. In healthy ageing there is a steady decline of dynamic lung volumes that does not limit oxygen transport and uptake [44]. Expiratory flow is reduced and the flow–volume curve may resemble COPD [45]. Moreover, the criteria used to define the various stages of COPD or restrictive pattern need to be age specific [45, 46]. Alternatives of FEV_1 (*e.g.* FEV_1/FEV_6 or FEV_1 divided by height cubed [3]) have been proposed in this age group [47, 48]. Thus, FEV_1 should not be considered as a diagnostic tool or a measure of severity of CRD with the criteria used in adults.

A few studies in older aged adults have used spirometry-based parameters for prognosis beyond respiratory morbidity and mortality [49]. A low FEV_1 is a significant predictor of all-cause mortality in older people [47]. In very old adults, low FEV_1 divided by height [3] is a predictor of all-cause mortality and hospitalisation independently of age, smoking status, chronic lung disease and other comorbidities [48].

FEV_1 and forced vital capacity are inversely associated with risk of future CVD events in older adults and may add to CVD risk stratification [50]. In the Berlin Aging Study II, type 2 diabetes and metabolic syndrome were associated with decreased lung volumes [51]. Muscle mass and abdominal obesity were the most important factors influencing pulmonary function. Measurement of grip strength for the determination of muscle mass and waist circumference for determining abdominal obesity could contribute to the interpretation of the results of pulmonary function tests. In this group, levels of lipoprotein(a), a lipid parameter independently associated with CVD, are not associated with the increased CVD risk in people with reduced lung function [52],

Due to the strong and consistent association with mortality, pulmonary function has been viewed as a biomarker of ageing [53]. Lung function in individuals with exceptional longevity has been associated with rare genetic variants underlying the linkage peak in chromosome 6 for FEV_1 [54]. However, more data are needed to consider FEV_1 and its alternatives as a measure of physiological health in older adults that may improve prognosis of frail older adults.

However, we need to disconnect pulmonary function from lung diseases in adults and older aged people and use some parameters as indicators of noncommunicable disease prognosis across the life cycle or frailty in older aged adults, irrespective of lung diseases.

Dyspnoea as a common entry point for the clinician

One possible candidate among such parameters is dyspnoea, a ubiquitous and nonspecific symptom. It is a major determinant of poor quality of life in all CRDs, many CVDs, neuromuscular disorders and in severe obesity [55]. Dyspnoea may also relate to ageing and frailty, independently of organ-specific disorders. Muscle deconditioning and sarcopenia, alone or in combination with reduced ventilatory and lung vascular reserves, constitute a mechanism for age-related exertional dyspnoea. In older aged adults, dyspnoea is associated with frailty and reduced proximal muscle function independently of spirometric data [56]. Dyspnoea can contribute to frailty both by accelerating muscle loss (according to the same type of vicious dyspnoea–deconditioning–dyspnoea circle in COPD) and by increasing social isolation through dyspnoea-related reduction in activities and relationships.

Identifying dyspnoea in older aged adults prompts a respiratory and cardiac work-up as a standard medical response. In the future, it might also prompt a wider assessment that would include frailty. In addition, dyspnoea is an independent predictor for mortality in COPD [57] and CVD [58], but also in the general population [59] and for all-cause mortality in older aged adults [60–62].

Thus, dyspnoea appears as an entry point to identify specific physiological disorders and nonspecific conditions, such as frailty in older adults, and could prove a simple tool to prioritise decisions. Of note, dyspnoea spontaneous self-report is reduced and qualitatively modified in older aged [63, 64] in a manner similar to pain [65, 66]. This has two clinical consequences: 1) a spontaneous complaint of dyspnoea in older aged adults should represent as an important alert and be considered carefully; and 2) dyspnoea should probably be sought proactively and in a systematic manner by all caregivers dealing with older aged adults [67]. This could have positive impacts beyond symptom management, by improving the identification of both specific diseases and frailty.

Relevance to the EIP on AHA

As populations continue to age, efforts to support the process of ageing well are important goals. Ageing is intertwined with socioeconomic inequalities, providing an under-appreciated cause of poverty, and hinders economic development, particularly of underserved populations and women. Active and healthy ageing is a major societal challenge that is common in all countries and in all populations [68] Active and healthy ageing allows people to realise their potential for physical, social (economic, cultural, spiritual and civic affairs) and mental wellbeing throughout the life course.

Action Plan A3 of the EIP on AHA is helping to prevent functional decline and frailty whereas Action Plan B3 is promoting integrated care models for chronic diseases The objective of the Integrated Care Pathways for Airway Diseases (AIRWAYS-ICPs) [8] is to launch a collaboration to develop multisector care pathways for CRD in European countries and regions as part of the EIP on AHA (Area 5 of Action Plan B3) and to scale up globally in order to: 1) reduce the burden of the CRD; and 2) promote active healthy ageing using innovative approaches.

Synergies between action plans are needed and the links between COPD and frailty represent one of the first synergies proposed for the renovated action plan of the EIP on AHA.

In order to foster discussion about key determinants of CRD and frailty and to highlight good practices for replicability and scaling-up, an EIP on AHA meeting was organised by the Région Languedoc-Roussillon (Languedoc-Roussillon, France) [69] and Region Centro Portugal (Lisbon, Portugal) on July 1–2, 2015. This was followed by a meeting on December 7–8, 2015 in Montpellier (France) that considered possible synergies between actions groups of the EIP on AHA.

A synergy entitled "*CRDs in old age people: an under-recognized societal problem*" (J. Bousquet, unpublished data) has been approved by a Task Force of the EIP. One of the key actions will be to make practical recommendations and implement the links between COPD and frailty.

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