CHEST

The Impending Epidemic of Chronic Cardiopulmonary Disease and Multimorbidity

The Need for New Research Approaches to Guide Daily Practice

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Mortality caused by acute cardiopulmonary disease is decreasing, and in many countries the population is aging rapidly. Yet, the life-years gained are often spent with multiple chronic and slowly progressive conditions, and this particularly applies to patients with cardiopulmonary disease. Affected individuals often have multiple diagnoses related to the cardiopulmonary-metabolic axis with accelerated aging and gradually progressive failure of organs that provide the body with oxygen and nutrients. This more or less reflects an "engine running out of fuel." This, for instance, is the case with the concurrent presence of COPD and heart failure in one patient that is often combined with other comorbidities such as atrial fibrillation, renal failure, or diabetes. This asks for a paradigm shift: away from single-disease-oriented patient management and toward patient-tailored multimorbidity medicine. Daily clinical practice is already recognizing this on a daily basis, yet clinical research and guidelines are still lagging behind. Thus, novel research approaches are needed to better guide evidence-based clinical practice. These approaches include the construction of diagnostic models to predict the presence of multiple diseases simultaneously, individual patient data meta-analysis as a method to examine variation in the effects of treatments or diagnostic tests depending on comorbidity, and the construction of therapeutic prediction models that predict the therapeutic effect of drugs based on the presence (or absence) of relevant comorbidity. We argue that multimorbidity should be regarded as a "friend" and not as a "foe" in clinical research addressing the current clinical problems in daily practice. CHEST 2015; 148(4):865-869

ABBREVIATIONS: IPD = individual patient data; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist

The impressive decline in mortality caused by acute cardiopulmonary disease over recent decades, notably in developed countries, has contributed to an increase in the prevalence of chronic progressive cardiopulmonary diseases. This increase occurs in an already aging multimorbid population. Physicians in their daily clinics are increasingly confronted with difficulties in managing these patients. Treatment options for one disease can interfere with another disease present in the same patient. For instance, β-blockers are helpful in patients with heart failure, yet their impact

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on the patient's prognosis may be challenged if the same patient has not only heart failure but also atrial fibrillation or COPD.[1,2] Similarly, diagnostic tests may be helpful in younger patients without comorbidity, yet they may be completely uninformative if performed in older patients with much comorbidity. For example, D-dimer testing and clinical prediction rules are helpful to rule out pulmonary embolism in younger patients, yet they are much less informative in older patients with comorbidity.[3] Although clinicians see these problems on a daily basis, guidelines and clinical research (unfortunately) are lagging behind, as they still mainly focus on a single disease. Some authors consider the evidence-based medicine movement in crisis because of the lack of acknowledging the impact of multimorbidity in clinical research.[4] Others comment on the increasing complexity and challenges in coordinating care for aging patients suffering from multimorbidity.[5] All agree that there is a need for new research approaches to really tackle this increasing clinical complexity of multimorbidity and to provide clinicians with useful diagnostic and prognostic algorithms and therapeutic options, notably in the field of cardiopulmonary care. In addition to an improvement in patient care, these approaches may provide more insight in the common pathways shared by chronic progressive diseases and, thus, may also help discover novel biomarkers and treatment targets that have a farther-reaching effect than simply improving the understanding or management of a single disease. Such pathophysiologic evidence is emerging and indeed provides very interesting insights. For instance, it has long been recognized that the incidence of cardiovascular disease is increased after an episode of pneumonia.[6,7] Studies have identified that clotting activation (eg, an upregulation of tissue factor and a downregulation of activated protein C) is observed in patients with a lung infection.[8] Following this laboratory-based evidence, clinical studies are now investigating the effects of antithrombotic drugs in patients with pneumonia. In this context, statin use was shown in a meta-analysis to reduce short-term mortality in patients with a community-acquired pneumonia.[9] Thus, an epidemiologic observation related to comorbidity (more cardiovascular disease after pneumonia) is followed by basic laboratory science, and these findings are subsequently used to develop or test new treatment options. This article explains some novel epidemiologic techniques that we believe can and should be used more often in future clinical research, given that clinicians already see the impending epidemic of multimorbidity in their clinics. With this, we hope to help close the gap between current single-disease-oriented evidence-based medicine and clinical practice that faces the reality of multimorbidity on a daily basis.

Common Pathways and the Link Between Cardiac and Noncardiac Multimorbidity in an Aging Population

More than one-half of the population in developed countries suffers from more than one disease by age 60 years.[10] This commonly includes chronic progressive diseases related to the cardiopulmonary-metabolic axis, involving organs that play a crucial role in providing the body with oxygen and nutrients. As a result, affected patients show accelerated aging of multiple organs, resembling more or less "an engine running out of fuel." Diseases involved include heart failure, atrial fibrillation, and stroke, but also diabetes, renal failure, osteoarthritis, and COPD.[10] Several of these conditions share common risk factors and underlying mechanisms, such as cigarette smoking, low-grade inflammation, and hypercoagulability, and all are characterized by some degree of endothelial dysfunction.[11] This can lead to a mutually reinforcing relationship where the presence of one disease causes progression or development of the other or influences the (early) diagnosis of other diseases or treatment options. The entanglement of both cardiac and noncardiac chronic progressive diseases has clear and easily recognizable implications on patient care and, thus, also for evidence needed to guide clinical practice and for clinical research.

As an example, typically around 25% of patients with heart failure also have COPD, and vice versa. Yet, in many patients, recognizing this concurrent presence is difficult.[12] Reasons for "overlooking" heart failure in the presence of COPD (or vice versa) include overlap in signs and symptoms but also the lack of clear evidence-based guidance on how to recognize this concurrent presence and—importantly—how to treat a patient when in fact both diseases are present. As a consequence, the management of these patients may be suboptimal. As health-care professionals, we recognize this high prevalence of multimorbidity in these patients, yet we do not completely understand the true diagnostic, prognostic, and therapeutic consequences of this concomitant presence of multiple underlying conditions. This knowledge should be provided by clinical research specifically focusing on comorbidity and not by research considering comorbidity as a nuisance, as exemplified by the plethora of therapeutic trials excluding patients with relevant comorbidity. Comorbidity research until now largely focused on the development of comorbidity