International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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REVIEW

Temporal Dynamics of Cardiovascular Risk in Patients with Chronic Obstructive Pulmonary Disease During Stable Disease and Exacerbations: Review of the Mechanisms and Implications

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Introduction: Exacerbations of chronic obstructive pulmonary disease (COPD) are risk factors for severe cardiovascular (CV) events, with the risk remaining significantly elevated long after the symptomatic phase of the exacerbation. The pathophysiology underpinning the relationship between acute events of both COPD and CV diseases has been understudied. Our objectives were to review the mechanisms by which COPD exacerbations increase the risk of CV events and understand the temporality of this risk.

Methods: A pragmatic and targeted literature review was conducted with a focus on identifying recent, high-impact papers up to June 2023, guided by insights from subject matter experts including pulmonologists and cardiologists.

Results: A substantial number of inter-related mechanisms underpin the spiral of anatomical and functional deterioration of lung and heart affecting COPD patients during stable state. In turn, an exacerbation of COPD may trigger a CV event, during and beyond the symptomatic phase, due to ventilation/perfusion mismatch, oxygen supply-demand imbalance, oxidative stress, systemic inflammation, hypercoagulable state, dynamic hyperinflation, pulmonary hypertension, and sympathetic activation. However, no study was identified that explored the mechanisms by which an exacerbation confers a sustained risk of CV event.

Conclusion: While our review identified multiple dynamic and interacting pathophysiological mechanisms during and after an exacerbation of COPD that contribute to increasing the risk of a wide range of cardiac events, little is known regarding the precise long-term mechanisms after acute exacerbation to explain the persistent increased CV event risk beyond the symptomatic phase. The temporal changes in static and dynamic substrates need further characterization to better understand the different risk factors and risk periods for a CV event following the onset of an exacerbation. Moreover, guideline-directed cardiopulmonary therapies should be implemented at every opportunity; preventing exacerbations and intensively treating traditional CV risk factors should be a focus in COPD management.

Keywords: acute events, cardiovascular disease, cardiovascular events, cardiopulmonary

Introduction

Chronic obstructive pulmonary disease (COPD) can be defined as

> a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration) due to persistent abnormalities of the airways (bronchitis, bronchiolitis), alveoli (emphysema), and/or pulmonary vessels, confirmed by spirometrically determined airflow limitation and/or objective evidence of structural or physiological pulmonary dysfunction.[1]

It has been established that observed structural changes are also due to failed regeneration processes.[2]

Received: 29 April 2024
Accepted: 23 August 2024
Published: 10 October 2024

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COPD is strongly associated with cardiovascular disease (CVD, eg, heart failure, coronary artery disease, arrhythmias, peripheral vascular disease and hypertension).[3,4] COPD and CVD have a syndemic relationship, clustering through shared biological, social and environmental risk factors (aging, occupational, smoking, or exposure to air pollution).[5] The interacting mechanistic pathways reflect a matrix of interwoven acute and chronic, pulmonary and cardiovascular (CV), local and systemic, continuous pathophysiological processes.[6–8] Individuals with COPD are two- to five-fold more likely to be diagnosed with CVD compared with those without COPD,[9] and CVDs are among the most common comorbidities seen in COPD.[3] The prevalence of heart failure in COPD patients is 12–23%,[10] while the prevalences of atrial fibrillation and coronary artery disease can be up to 30%[10] and 60%,[9,10] respectively. Coexisting COPD and CVD worsen the burden of disease and prognosis.[11–14] Both have therapies which reduce morbidity and mortality, yet COPD remains the only major non-communicable disease for which the prognosis is not improving.[1]

Exacerbations of COPD are periods of increased risk of severe CV events. Recent advances have extended our knowledge in several key domains (see Supplementary Appendix),[15–21] supported by meta-analyses of observational studies.[22] Firstly, the risk of a severe CV event was found to be markedly increased following both a moderate and a severe exacerbation, its risk being highest after the latter (pooled adjusted hazard ratio [HR] for a severe CV event or all-cause death 1–7 days after an exacerbation; 2.37 [moderate exacerbation] versus 20.57 [severe exacerbation]).[22] Secondly, CV event risk increases exponentially with temporal proximity to the onset of the exacerbation (pooled adjusted HR for a severe CV event or all-cause death after a severe exacerbation; 1.49 [after >365 days], 2.34 [after 31–180 days] and 20.57 [after 1–7 days]).[22] The risk is more than two-fold higher in the first compared with second week following the onset of an exacerbation[16] and remains significantly elevated long after the acute and symptomatic phase of the exacerbation – beyond one year for some CV outcomes.[15–18,23] Thirdly, recent studies indicate that even those individuals with newly diagnosed COPD are at increased risk for severe CV events following a first exacerbation (pooled adjusted HR for a severe CV event of all-cause death 1–7 days after first exacerbation; 9.34).[19–23] Finally, the increase in risk extends across a wide range of cardio- and cerebrovascular outcomes, including acute coronary syndrome, ischemic stroke, arrhythmias, heart failure decompensation,[16] pulmonary embolism,[19] and pulmonary hypertension.[18] An integrated pathophysiologic perspective of the cardiopulmonary continuum has the potential to support a more holistic therapeutic approach, where multidisciplinary teams manage shared risk factors and disease. In particular, the pathophysiology underpinning the relationship between acute events and chronic disease progression of both COPD and CVDs has been understudied but offers an opportunity to intervene and disrupt the cycle of decompensation and longer-term cardiopulmonary remodeling.

The objectives of this literature summary were to (a) review the pathophysiological links between COPD and the development of CVDs; (b) review the mechanisms by which COPD exacerbations increase the risk of acute CV events; and (c) understand the temporality of this risk. With this evidence, we aimed to address the following clinical questions: 1) why is there an association between exacerbations of COPD and increased risks of a wide range of CV events? 2) why do these associations persist beyond the symptomatic phase of an exacerbation?

Methods

A pragmatic, targeted literature review was conducted with a focus on identifying recent, high-impact papers up to June 2023, guided by insights from subject matter experts including pulmonologists and cardiologists. A visualization of the search approach is presented in Figure 1.

A series of focused searches for original studies, systematic reviews, and literature reviews were run in PubMed (NLM) and the Cochrane Library (Wiley), up until June 2023, to identify relevant literature on the relationship between COPD and CVD. The terms COPD, AECOPD, exacerbations, CV, acute myocardial infarction, stroke, heart failure, arrhythmia, pathophysiological, mechanism, and other related keywords and abbreviations were used to search the PubMed database. Identified records were imported into Rayyan and screened by a single reviewer at title and abstract stage, and those studies included at this stage were reviewed at full text stage.

Exploratory internet searches were conducted on Google Scholar. A "snowball" method of iteratively reviewing the bibliographies and citation tracking of the most relevant included studies was also performed.

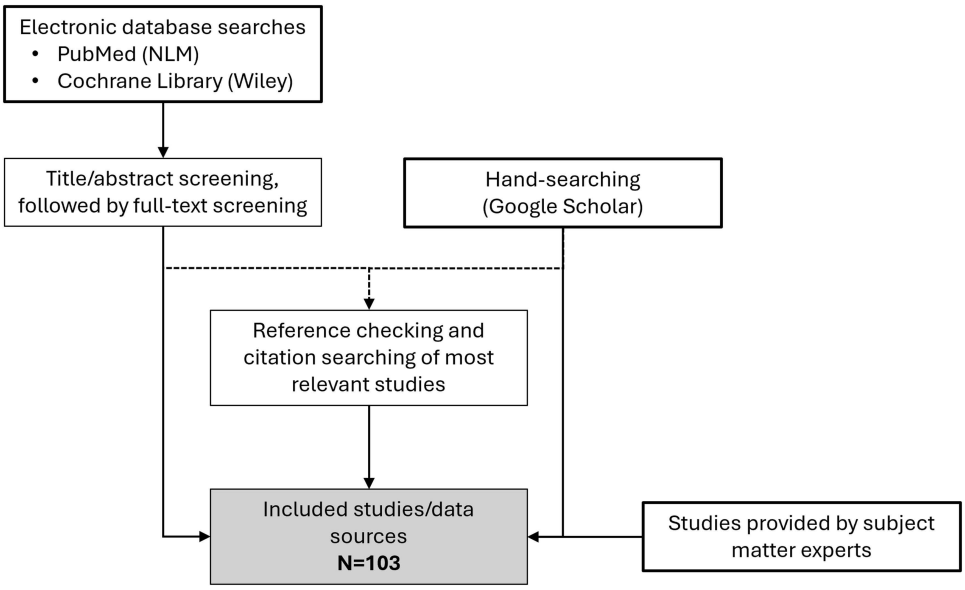

Figure 1 Flow diagram of study identification and inclusion.

Results

Linking COPD to the Development of Cardiovascular Disease

Several factors contribute to the overall increased risk of CVD seen in individuals living with COPD. Shared risk factors for CVD and COPD cluster together including age, cigarette smoking, hypertension, dyslipidemia, diabetes, physical inactivity, and socioeconomic deprivation.[24–26] However, these shared risk factors do not fully explain the association between COPD and CVDs, suggesting the presence of other mechanisms.

Hallmark to the development of COPD is the prolonged toxic exposure to exogenous oxidants (eg, cigarette smoking, noxious gases, airborne pollutants)[12,27] causing oxidative stress which leads to epithelial and endothelial injury and promotes local inflammation.[28] The increase in inflammatory mediators can extend (spillover) from the respiratory system into the systemic circulation[12] and contribute to developing or aggravating CVD.[29] It is unclear if this spillover is the only source of the increased systemic inflammatory response or if it represents a more generalized systemic state of heightened inflammation in COPD.[7]

Chronic hypoxemia is another cause of increased oxidative stress and systemic inflammation.[30] Airway remodeling arises in COPD following repeated cycles of injury and subsequent repair of the extracellular matrix.[31] Progressive airflow limitation and alveoli damage lead to ventilation-perfusion (V/Q) mismatch.[32] The resulting hypoxemia limits oxygen levels in organs and tissues (hypoxia).[33] Chronic hypoxia and inflammation in COPD promote pulmonary vasoconstriction and vascular remodeling, impairing right ventricular function.

Many of the anatomical changes seen in COPD, such as the loss of elastic recoil and the development of emphysema,[31,34] are also seen in the healthy aging lung and, as such, there is increasing evidence that COPD can be considered a disease of accelerated aging. Mechanisms behind accelerated aging include the shortening of telomeres, reducing potential in cell proliferation, and cell senescence. Similar aging pathways have been identified in CVD which suggest common underlying mechanisms of aging in both COPD and CVD.[35]

As the exposure to noxious pollutants persists in individuals "at risk", airflow obstruction becomes clinically evident and the diagnosis of COPD is potentially made. Current treatment guidelines use forced expiratory volume/ forced vital capacity (FEV1/FVC) <0.70 as a cut-off to diagnose COPD.[11] However, decline in FEV1 occurs late in COPD trajectory and the recent Lancet Commission paper on COPD has suggested other tests to capture airflow obstruction, and thus COPD earlier.[36] Such developing airflow obstruction promotes dynamic hyperinflation which is potentially an important stressor to the CV system.[37–40] Dynamic pulmonary hyperinflation is a transient and variable increase in end-expiratory lung volume observed during increased ventilation, particularly during exercise or an exacerbation, among flow-limited

patients.[39,40] This phenomenon persists despite active recruitment of expiratory muscles. In COPD, static hyperinflation may result from parenchymal destruction and loss of elastic recoil. Concurrently, dynamic hyperinflation occurs at any COPD stage, where patients breathe in before fully exhaling, trapping air within the lungs. Exertional dynamic hyperinflation leads to limited tidal volume expansion, placing a substantial burden on inspiratory muscles with notable mechanical and heart rhythm consequences.

Effect of COPD on Vasculature, Heart Function and Rhythm

Atherosclerosis is likely accelerated in COPD due to systemic inflammation, high oxidative stress, and sympathetic overactivity.[7,41,42] Indeed, airflow limitation is an independent predictor of atherosclerosis,[43] and patients with COPD exhibit morphologically worse coronary atherosclerotic plaques than those without COPD.[41] Proposed mechanisms include complex adaptive immune cell responses, increased vascular cell adhesion molecules, altered chemokine signaling, cellular recruitment including macrophage and foam cells, enhanced collagenase expression, endothelial cell injury, and plaque development.[12] Reactive oxygen species (ROS) released from activated inflammatory cells contribute to the development and instability of atherosclerotic plaques[12] via interaction with activated platelets,[8] which are implicated in the development of heart failure and coronary artery disease.[44]

COPD also affects heart function and can lead to both heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), though the latter is predominant in COPD.[45] COPD is associated with myocardial remodeling; specifically, increased left ventricular hypertrophy and increased mass, abnormal myocardial relaxation, and reduced left ventricular end-diastolic volumes. Chronic inflammation with "spillover" through the pulmonary to cardiac circulation is likely a key driver of myocardial remodeling. A systemic proinflammatory state causes coronary microvascular endothelial dysfunction, which reduces nitric oxide bioavailability, cyclic guanosine monophosphate content, and protein kinase G activity in adjacent cardiomyocytes. This in turn induces hypertrophy and increases resting tension due to myocardial titin hypophosphorylation. The resulting hypertrophy, interstitial fibrosis, and cellular stiffness increase left ventricular diastolic rigidity leading to HFpEF.[46] These morphological changes are exacerbated by mechanical and hemodynamic heart-lung interactions.

Increased intrathoracic pressure – as a consequence of lung hyperinflation – increases left ventricular wall stress,[47] compressing the ventricles and impairing cardiac filling and output.[48] Airway obstruction and hyperinflation are significantly associated with echocardiographic diastolic filling parameters of preload.[49] Increased pulmonary vascular resistance causes right heart strain and dilatation, increasing right ventricular end-diastolic volumes and further impairing cardiac output through ventricular interdependence.[50] Finally, in addition to pre-load, right heart, and interventricular mechanisms, afterload is also increased. Systemic arterial stiffness is increased in patients with COPD compared with age- and smoking-matched controls,[51] and in patients with frequent as compared to infrequent exacerbators.[52]

COPD affects heart rhythm through multiple interacting pathways based on substrate modification and autonomic modulation.[53,54] The prevalence of atrial fibrillation is high in patients with COPD, approaching 25%, and increases with disease severity.[9,38,55] New onset of atrial arrhythmia is twice as common in patients with COPD than those without.[56,57] Airflow obstruction defined by FEV1 was an independent predictor of incident atrial fibrillation in the Copenhagen Heart,[57] the Atherosclerosis Risk in Community[58] and the Malmo Prevention studies.[59] The increased risk of atrial fibrillation in COPD relates to substrate in the form of structural and electrical remodeling, combined with more dynamic precipitants.

The structural and functional ventricular myocardial changes create an atrial fibrillation maintaining substrate through chronic biatrial elevated pressures and atrial fibrosis. Oxidative stress and systemic inflammation due to chronic hypoxemia promote pro-fibrotic remodeling of atrial tissue,[30] providing a substrate for maintained atrial fibrillation,[30,38,60] and longstanding advanced COPD is associated with right heart disease.[37] Airflow limitation and low FEV1 lead to increased respiratory effort and large intrathoracic pressure swings, which affect sympathetic tone and increase sympathetic nerve activity and pulmonary vascular constriction.[7,38,48] Sympathetic overactivity is also involved in the progression of atrial fibrillation[61] and has been observed in patients with and without hypoxemia.[62,63] The cardiac autonomic nervous system contributes to the initiation, maintenance, and progression of atrial fibrillation by altering impulse formation (eg, triggers in the pulmonary veins and atria) and impulse propagation (eg, in the left atrial substrate).

Exacerbations of COPD and Cardiovascular Disease: A Perfect Storm

Exacerbations of COPD are a sudden worsening of symptoms over ≤14 days, including increased dyspnea, cough, sputum production or sputum purulence, and are often triggered by infections and environmental factors.[11] Exacerbations are serious events that lead to accelerated lung function decline, decreased health status and increased mortality. There is increasing interest in the CV consequences of those respiratory events. During an exacerbation of COPD, all mechanisms described above cluster together rendering such an event a perfect storm for developing a serious CV event.

Exacerbations of COPD may cause myocardial necrosis through either type 1 myocardial ischemia (coronary plaque rupture or erosion and superimposed thrombosis) or type 2 myocardial ischemia (oxygen supply and demand imbalance).[64] Acute rupture of atherosclerotic plaques (type 1 myocardial ischemia) are likely precipitated by "spillover" of pulmonary inflammation into the systemic circulation.[65] Some infectious agents such as influenza virus promote local and systemic inflammation through direct cardiomyocyte invasion.[66,67]

Regarding coronary plaque rupture, circulatory inflammatory biomarkers and neutrophils are elevated during and immediately after exacerbations.[68] Inflammatory cytokines (eg tumor necrosis factor-α and interleukins 1, 6, and 8) promote vascular endothelial dysfunction, leukocyte and macrophage signaling, C-reactive protein and complement activation, and, in turn, rupture of susceptible plaques.[68]

Regarding superimposed thrombosis, the hypercoagulable state observed during exacerbations is underpinned by systemic inflammation, thus making exacerbations a potent prothrombotic stimuli, pairing clotting cascade activation with impaired fibrinolysis. Inflammatory mediators increase serum fibrinogen levels, stimulate thrombin generation and platelet reactivity.[69–71] Hypoxia, sympathetic activation, and platelet stimulating factors combine to activate platelet cyclooxygenase-1 with thromboxane formation.[72] Thromboxane is a positive feedback platelet activator and potent vasoconstrictor. The resulting hypercoagulability leads to thrombosis at sites of endothelial injury and increased thromboembolic risk, particularly in patients with atrial fibrillation, highlighting the complex interplay between those mechanisms.[73]

Oxygen supply-demand imbalance (type 2 myocardial ischemia) has multiple mechanisms, occurring alone or in combination during COPD exacerbation. Supply may be compromised by a combination of coronary macrovascular hypoperfusion (reduced cardiac output, vasodilatory hypotension/shock), microvascular dysfunction, reduced oxygenation (hypoxia, respiratory failure), or reduced oxygen carrying capacity (hypercapnia, acidosis, anemia as comorbidity). V/Q mismatch occurs at the beginning of a COPD exacerbation, and may lead to the development of hypercapnic respiratory failure.[74] Demand may be increased by increased afterload (hypertension), tachyarrhythmia, left ventricular hypertrophy (secondary to hypertension and comorbidities), systolic and diastolic dysfunction, and volume overload. This multifactorial oxygen supply-demand imbalance may occur in the absence of coronary artery disease or exacerbate existing fixed coronary atherosclerosis. Finally, additional coronary occlusive events may occur, including coronary vasospasm, coronary artery dissection, and coronary embolism.

Besides myocardial ischemia, COPD exacerbations may acutely depress cardiac output through multiple interacting mechanisms. First, inflammation directly inhibits myocardial contractility.[75,76] Systemic inflammatory response syndrome manifests varying phenotypes and severity, including left ventricular systolic dysfunction, left ventricular diastolic dysfunction, and right ventricular dysfunction.[77] The inflammatory response can lead to decompensated heart failure.[66] Concurrently, dynamic hyperinflation induces intrinsic positive end-expiratory pressure.[30] This increased thoracic pressure compromises ventricular filling, exacerbating diastolic dysfunction, reducing preload and sarcomere contraction force, and ultimately reducing stroke volume and cardiac output. Increased airflow limitation, tachypnea and decreased compliance during an exacerbation also lead to increased negative thoracic pressures during respiration[78] then increasing transmural pressures and increased left ventricular afterload.[79] Thirdly, gas exchange abnormalities, notably hypoxemia and hypercapnia, lead to pulmonary vasoconstriction and acute pulmonary hypertension, thus increasing right ventricular afterload.[80] The resulting elevated right ventricular pressure further compromises left ventricular output through ventricular interdependence and septal bowing, while dilating the right ventricle and disrupting valvular function.

Exacerbations of COPD also induce *de novo* rhythm disorders or aggravate existing ones.[81–83] The biventricular impairment of preload, afterload, and contractility not only reduces cardiac output but increases atrial strain. The adverse

atrial pressure loading is exacerbated by hypoxia, hypercapnia, acidosis, and intrathoracic pressure swings, leading to sympathetic activation, increased automaticity, and shortening of the action potential and effective refractory period. Finally, sympathomimetic and parasympatholytic medications trigger further local conduction disturbances.[38] Figure 2 provides an overview of the interconnected mechanisms from exacerbations to CV events.

In the present literature search, we did not identify studies assessing acute changes in cardiac valve structure and function during exacerbations of COPD. Little is known about the possible impact of exacerbations on valve function. In other populations, pulmonary hypertension is associated with functional tricuspid regurgitation due to right ventricular and tricuspid annular dilatation, papillary muscle displacement, and tricuspid valve tethering.[84]

Prolonged CVD Risk After an Exacerbation of COPD

Though acute respiratory deterioration may explain the very short-term incidence of CV events, recent epidemiological studies have shown a persistent increased CV risk lasting for months following the initial insult,[15–19] echoing results seen for other (respiratory) infections.[85] The sustained risk increase was observed for ischemic events, arrhythmias, and decompensated heart failure. Despite the accumulating epidemiological evidence of long-term cardiopulmonary risk, the underlying mechanisms remain under-explored and poorly understood. We did not identify any studies of the long-term mechanisms involved after the onset of an exacerbation to explain the persistence of the increased CV event risk beyond the symptomatic phase.

To bridge the gap, we propose an overarching "temporal dynamics of cardiovascular risk" hypothesis, connecting the aforementioned chronic and acute mechanisms with two additional concepts of prolonged and incomplete cardiopulmonary recovery combined with cascading cardiopulmonary events (Figure 3). The biological and functional mechanisms underpinning the immediate increase in risk of a CV event may persist beyond the symptomatic phase of an exacerbation. First, there could be a prolonged post-exacerbation proinflammatory trajectory, as seen in severe sepsis trajectories,[86] that prolongs and accelerates all of the aforementioned chronic vascular and myocardial processes associated with inflammation. For example, arterial stiffness remains elevated months after an exacerbation.[52] Second, slow recovery of V/Q mismatch may increase pulmonary artery pressure and place persistent strain on the right ventricle. Pulmonary hypertension is also a longer-term complication arising from the acute oxidative stress of inflammation.[87]

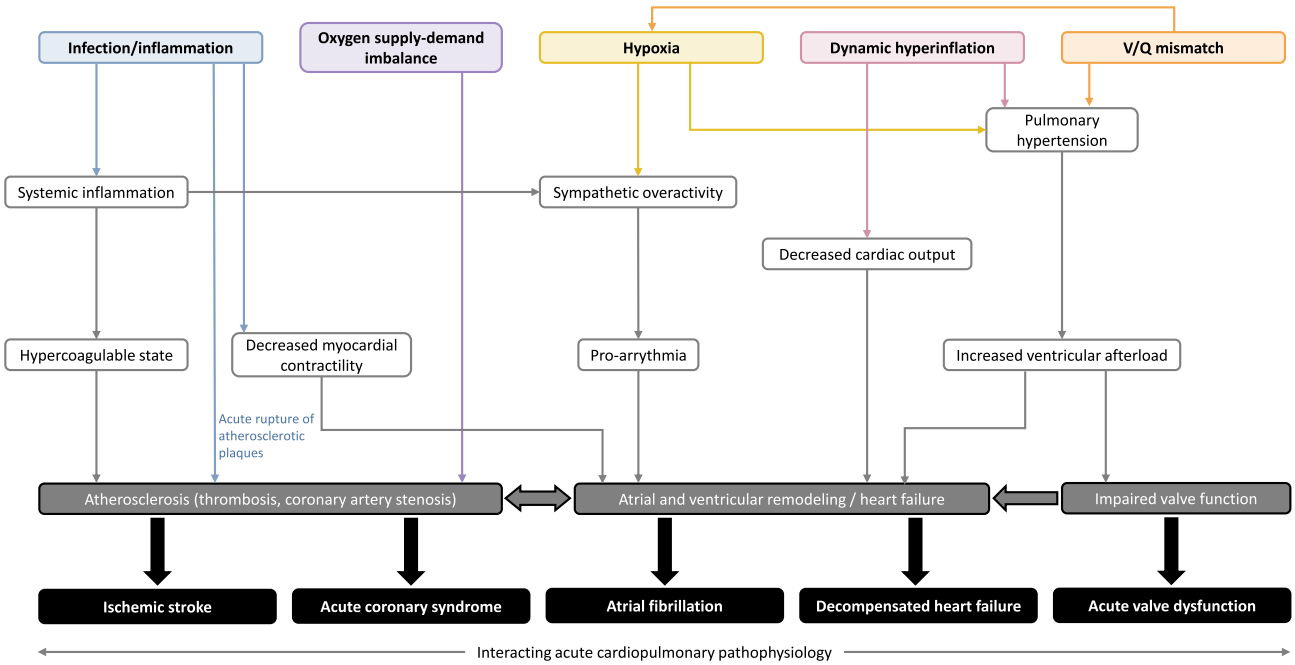

Figure 2 Acute exacerbations of COPD: a perfect storm.

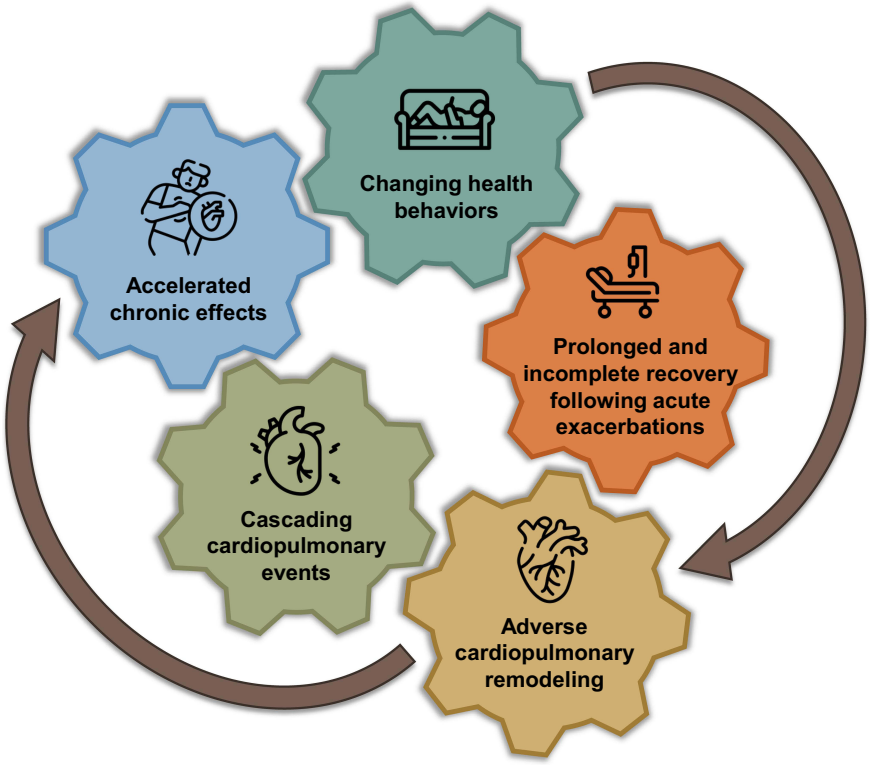

Figure 3 Interacting and overlapping concepts contributing to the extended cardiovascular risk following an exacerbation of COPD.

Finally, exacerbations are associated with accelerated lung function decline, with incomplete recovery 30 days after exacerbation in 14% of patients with COPD.[88]

Besides such biological mechanisms, changing health behavior of individuals following the onset of an exacerbation may contribute to the development of CVD. Patients may reduce physical activities due to breathlessness. Similarly, deterioration of limb muscle function is a possible aftermath of exacerbations of COPD that can decrease activities even further.[89] In turn, decreased physical activity and weight gain may, for example, increase arterial stiffness and blood pressure and contribute to cardiac disease decompensation in the long-term. Another possibility is the risk of CV adverse events – for instance atrial fibrillation[90] or venous thromboembolism[91] – following use of systemic corticosteroids in the context of moderate exacerbations.

Temporal Dynamics of the CV Risk in COPD

The heart and lungs should be considered a unified cardiopulmonary unit rather than simply adjoining organs. This biological system undergoes continuous cellular and structural remodeling with every beat and breath in response to gene-environmental interactions throughout the life course. Exacerbations impact oxygenation, thrombosis, perfusion, myocardial substrate, function, and arrhythmia through dynamic interacting biomechanical networks with acute and chronic pathways. Atherosclerosis, vascular and myocardial remodeling progress over years, underpinned by chronic inflammation and clustering of CV risk factors. Exacerbations augment and accelerate these chronic cellular and tissue changes, superimpose transient CVD promoting factors and acute physiological stress, and accumulate CVD promoting factors through incomplete recovery. The major CVD pathways exhibit different time courses and distinct dynamic components, and as in any complex adaptive system, networks interact, magnify, and exhibit emergent behavior.

Hypothetical Clinical Example – Long-Term Increased Risk of a CV Event

Figure 4 provides an illustrative, hypothetical example of how the CV event risk associated with each promoting factor may change in the short and long term after an exacerbation. As CV event risk increases exponentially with temporal proximity to

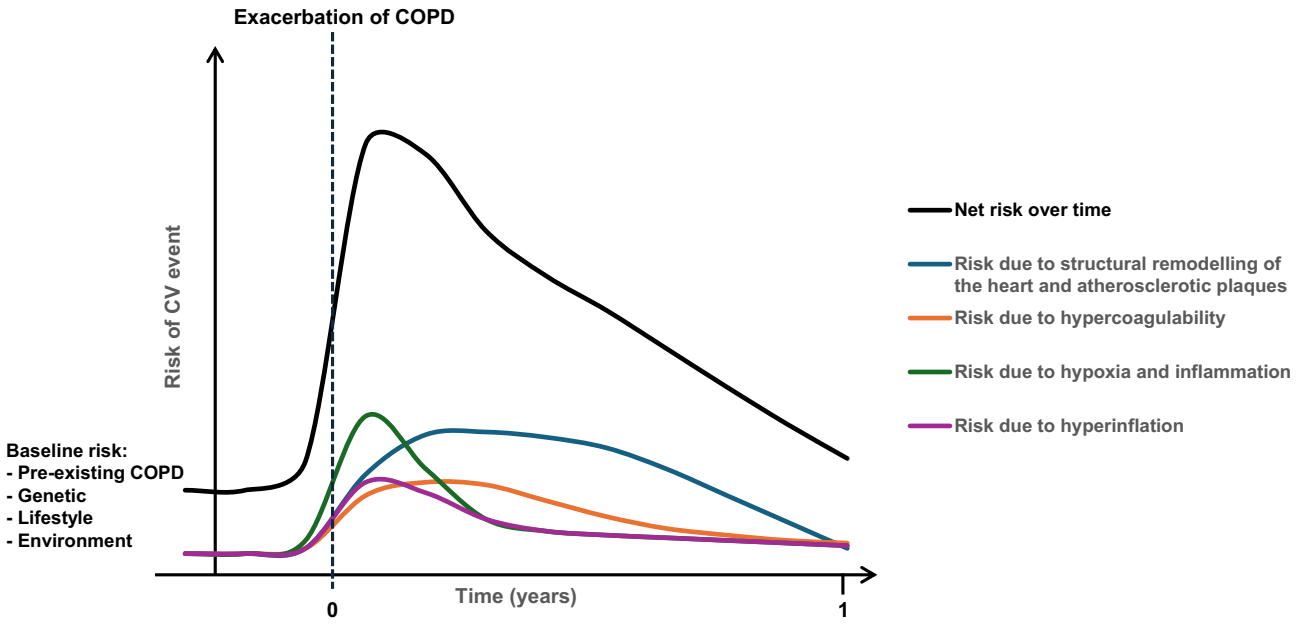

Figure 4 Hypothetical temporal dynamics of CVD risk factors following an exacerbation of COPD.
Notes: Trajectories are hypothetical. Based on previous epidemiological studies, the risk of a CV event increases rapidly following the onset of an exacerbation and remains increased for up to a year.

the onset of the exacerbation,[22] it is assumed that the risk factors are additive. Factors such as hypoxia and inflammation are associated with exacerbations of COPD as well as CV events, correlating with a decreased risk after 90 days,[15] whereas factors such as structural remodeling of the heart occur after the hypoxia and inflammation (see Figure 2), so likely contribute to the CV event risk for longer. Understanding each of these specific and time-dependent components of CVD risk after an exacerbation of COPD would have important implication for the timing of management and prevention of the increased cardiopulmonary risk in COPD.

Consider for example a patient without prior diagnosed CVD, multiple CV risk factors (smoking, poorly controlled hypertension, and dyslipidemia) and an initial hospitalization for a severe exacerbation. This patient has moderate coronary atherosclerosis, diastolic dysfunction, and atrial dilatation. These static substrates for CVD are punctuated by the occurrence of dynamic substrates triggered by the severe exacerbation, each with its specific time window. The initial exacerbation is associated with troponin elevation which is attributed as concurrent type 2 myocardial infarction, but is in fact plaque rupture. The resulting left ventricular impairment, even relatively small, combines with decline in ventilatory function and deconditioning to further impair physical activity, promote weight gain, and worsen CV risk factor control. Inflammatory spillover is heightened, atherosclerosis accelerates, myocardial fibrosis and hypertrophy continues, and autonomic dysregulation worsens. Episodes of atrial fibrillation precipitate further acute care in the early months after exacerbation, treated by ventricular rate control yet further impairing overall cardiac output. The downward spiral continues, with an unreported exacerbation later that year tipping the fragile cardiopulmonary reserve, leading to volume overload and hospitalization for HFpEF.

Discussion

Key Findings

In this comprehensive review, we summarized the contemporary understanding of the strong links between COPD and CVDs, in stable state and during periods of disease decompensation. Our results highlight the spiral of anatomical and functional deterioration of lung and heart affecting COPD patients during stable state, and during and after exacerbations of COPD. A substantial number of inter-related mechanisms are at play during, and potentially beyond, the symptomatic phase of an exacerbation and may trigger a CV event. These include V/Q mismatch, oxygen supply-demand imbalance, oxidative stress,

systemic inflammation, hypercoagulable state, dynamic hyperinflation, pulmonary hypertension, and sympathetic activation. The very wide range of mechanisms echoes the high rate and diversity of CV events, whose incidence was found to increase following an exacerbation in previous population-based observational studies.[15–21] Exacerbations of COPD accelerate and create multiple interwoven static and dynamic substrates across the spectrum of CVD. As such, exacerbations of COPD should not be seen only as an acute clinical event, but also as the exacerbation of the continual biological and mechanical interactions within the cardiopulmonary organ system. The subsequent risk of both respiratory and cardiac events in COPD should be understood as "the cardiopulmonary risk" and treatment for individuals with COPD should be directed to mitigate this risk within the cardiopulmonary organ system.[92]

Surprisingly, we did not identify any studies of the long-term mechanisms involved after the onset of an exacerbation to explain the persistence of the increased CV event risk beyond the symptomatic phase consistently reported in observational research. We thus proposed various hypotheses which will need to be supported by clinical research exploring, eg, the temporality of inflammation biomarkers increase, or evolution of cardiac rhythm and heart function in time periods following an exacerbation of COPD.

Study Limitations

Our review was not systematic, and thus, relevant publications may have been overlooked. However, the risk of not identifying important information was minimized by the prioritization of recent articles published in high-impact journals and the use of an iterative snowball method. Moreover, three international experts in COPD-CVD interactions (NH, SS and PR) contributed to the study.

Clinical Implication

The body of evidence on the pathophysiological link between exacerbations of COPD and decompensated CVDs, detailed in the present study, suggests that the associations observed between COPD exacerbations and subsequent CV events likely are of causal nature. The consistency between epidemiological and pathophysiological data has important therapeutic implications. Firstly, the management of cardiac and respiratory risk factors is key to slow down or stop the spiral of deterioration and decrease cardiopulmonary risk in people living with COPD. Secondly, we should focus our attention on implementing guideline-directed cardiopulmonary therapies at every opportunity, focusing on preventing exacerbations in the first place and intensively treating traditional CV risk factors. The prevention of COPD exacerbations, including moderate ones, is a fundamental goal of disease management. This should focus on COPD management optimization with single inhaled therapies as well as eg, smoking cessation support, increasing physical activity and vaccination.[11,93,94] Once exacerbations occur, our review underscores an extended vulnerable post-exacerbation period, during which appropriate cardiopulmonary therapies should be confirmed and intensified. In addition to preventive measures, the efficacy of active cardiac monitoring (cardiac rhythm, heart function) and of cardiac medications (such as antiplatelet drugs or renin-angiotensin-aldosterone inhibitors) following the onset of a COPD exacerbation should be explored. Finally, it can be hypothesized that therapeutic measures known to improve pulmonary state following an exacerbation could also benefit the cardiovascular system, such as early initiation of pulmonary rehabilitation,[95] long-term oxygen therapy[96] or inhaled maintenance therapy adaptation.[11]

Conclusion

The pathophysiological mechanisms during and after an exacerbation of COPD are multiple, dynamic, interacting, and all contribute to increasing the risk of a very wide range of cardiac events (ischemic events, arrhythmias and heart failure decompensation). However, little is known regarding the precise long-term mechanisms after acute exacerbation to explain the persistent increased CV event risk beyond the symptomatic phase. The identification of specific cardiac biomarkers present during and after a COPD exacerbation would improve understanding of the mechanisms and drivers of CV events. The temporal changes in static and dynamic substrates need further characterization to understand the different risk factors and risk periods for a CV event following the onset of an exacerbation. Future work should also investigate post-exacerbation interventions which could reduce the risk of CV events.

Disclosure

Sami O. Simons has received, as payment to his institution: grants or contracts from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and Roche; consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici and GlaxoSmithKline; and payment or honoraria for events from AstraZeneca and Chiesi Farmaceutici. Paola Rogliani has participated as a faculty member and advisor in scientific meetings and courses under the sponsorship of AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, Novartis, Recipharm, Sanofi and Zambon, and her department was funded by Arcede Pharma, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, Verona Pharma and Zambon. Nathaniel M. Hawkins participated on advisory boards for Bayer, Boehringer Ingelheim, and Servier. He also received honoraria for speakers bureau from AstraZeneca, Novartis, and Servier and grants/research support from AstraZeneca and Novartis and consulting fees from AstraZeneca. Amy Heptinstall and Zoe Marjenberg received consulting fees from AstraZeneca. Jonathan Marshall, Hana Mullerova and Clementine Nordon are employees of AstraZeneca and shareholders of the company. The authors report no other conflicts of interest in this work.

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