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Chronic obstructive pulmonary disease and sudden cardiac death: A systematic review

Marten E. van den Berg, MD[a], *Bruno H. Stricker, PhD*[b,c,d], *Guy G. Brusselle, MD, PhD*[b,e,f], *and Lies Lahousse, PhD*[b,e,*]

[a]*Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands*
[b]*Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands*
[c]*Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands*
[d]*Inspectorate of Healthcare, The Hague, The Netherlands*
[e]*Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium*
[f]*Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands*

A B S T R A C T

Both chronic obstructive pulmonary disease (COPD) and sudden cardiac death (SCD) are major health burdens. A number of studies have addressed their interrelationship, but currently no systematic review has been published. Our objective is to give an overview of the literature of the association between COPD and SCD. A search on PubMed with both MeSH headings and free-text keywords was performed. We selected all original articles of studies in humans that assessed COPD on the one hand and SCD, electrocardiographic markers for SCD, ventricular arrhythmias, or asystole on the other. The electronic search yielded 251 articles, from which 27 full publications were selected after careful evaluation of the full-text articles. In these studies, COPD was associated with a prolonged and shortened QT interval. In patients with a myocardial infarction (MI), COPD was associated with an increased risk of ventricular arrhythmias and decreased survival. COPD was a risk factor for SCD both in cardiovascular patient groups and in community-based studies, independent from cardiovascular risk profile. Studies of the potential impact of respiratory treatment on the occurrence of SCD showed conflicting results. In conclusion, cumulating evidence associates COPD with an increased risk of SCD. Asystole and pulseless electric activity could be more common than VT/VF in deaths associated with COPD. Underlying mechanisms explaining this association require further investigation.

Key words: COPD, Sudden cardiac death, Ventricular arrhythmia, Cardiac arrest.

Introduction

Cardiovascular disease is the leading cause of death and imposes a large global burden of morbidity and mortality [1–4]. About half of all cardiovascular deaths are sudden cardiac deaths (SCDs). SCDs occur suddenly and unexpectedly, often as a first sign of cardiac disease [5,6]. SCD remains a major cause of death, even though the incidence seems to be decreasing in Western Europe [2,7]. The majority of SCDs is thought to result from ventricular arrhythmias [8]. However, in recent years the proportion of SCDs resulting from pulseless electrical activity (PEA) and

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*Corresponding author at: Department of Epidemiology, Erasmus Medical Center, Rotterdam, PO Box 2040, 3000 CA, Rotterdam, The Netherlands. Tel.: +31 10 70 44292; fax: +31 10 70 44657.

E-mail address: l.lahousse@erasmusmc.nl (L. Lahousse).

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asystole is increasing [9], possibly due to advances in treatment of coronary heart disease (CHD) and increased use of an implantable cardioverter defibrillators (ICDs) [10]. SCD can be the result of a variety of underlying causes, such as CHD [11], cardiomyopathies [12], or use of QT-prolonging drugs [13]. However, many possible etiologies have not been established [6].

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally [4]. Progressive airflow limitation is the hallmark of COPD. Progressive airflow limitation is associated with a local chronic inflammatory response in the airways and lungs [14], but in a subgroup of patients with COPD biomarkers of systemic inflammation (e.g., fibrinogen and C-reactive protein) are also increased [15–17]. COPD and cardiovascular disease are notably linked. For example, ECG abnormalities such as bundle branch blocks and axis deviations are common in COPD patients [18]. COPD patients also have a higher rate of cardiovascular morbidity and mortality than the general population [19]. Moreover, half of the deaths of COPD patients are attributable to cardiovascular disease [19]. The association of COPD with cardiovascular disease in general suggests that there could also be an association between COPD and SCD. Indeed, COPD can cause respiratory arrest, which can lead to PEA and asystole, and ultimately SCD. Accurate prediction of SCD in the general population is still a challenge because most cases of SCD occur in people with seemingly low cardiovascular risk [6]. Thus, risk assessment of SCD might be improved by studying the link between COPD and SCD. Studying the association of COPD with SCD includes assessing possible common risk factors (e.g., ageing or smoking) and the effect of respiratory drugs on SCD risk. To date, there has not yet been a systematic review of the literature that has studied the association of COPD with SCD. The objective of this article is to provide an overview of the published literature on this association.

Methods

We searched PubMed from inception until December 10, 2015 using a combination of MeSH terms and free-text keywords. For COPD we used the MeSH term “Pulmonary Disease, Chronic Obstructive.” The free-text keywords were all terms derived from COPD and pulmonary emphysema, including the terms “obstructive pulmonary disease” and “COPD.” For SCD we used the MeSH terms “Death, Sudden, Cardiac,” “Heart Arrest,” “Tachycardia, Ventricular,” “Ventricular Fibrillation,” “Ventricular Flutter,” and “torsades de pointes.” Free-text keywords for SCD were all derived from these MeSH terms. In order to retrieve unindexed articles we searched without additional filters for the publication dates after 2014. After that, we filtered our search results on articles written in English and on human participants aged older than 18 years. The online supplement contains the complete search strategy, including all MeSH terms and free-text keywords. Citation lists of the publications found by the electronic search were handsearched for additional relevant publications.

Articles were deemed relevant for this review if they contained original research, included COPD patients or lung function measurements and the outcome SCD, ventricular arrhythmias, or electrocardiographic (ECG) markers for SCD. We extracted relevant articles from the list of the initial search in a two-step process. In the first step, two reviewers (M.v.d.B. and L.L.) independently screened the abstracts of the list of articles. Disagreements in abstract selection were resolved with consensus meetings. In the second step, the full-text articles were retrieved and all relevant information was extracted and tabulated. Based on this, a final selection was made.

Results

General findings

The electronic search on PubMed yielded 251 publications. An additional five publications were found by hand-searching citation lists. After screening the abstracts, we included 27 publications for reviewing. The selection process and its results are shown in more detail in Fig. 1. The selected articles included 26 observational studies (10 cohort studies, 9 cross-sectional studies, and 7 case–control studies) and one randomized controlled clinical trial (RCT). A list with summaries of all included articles is provided in Supplementary Table 1.

The results section consists of two parts. Part one addresses the association of COPD with SCD, ventricular arrhythmias, and ECG markers for SCD. First, we review COPD and electrocardiographic markers associated with SCD. Then, we review publications addressing COPD, ventricular arrhythmias, and cardiac arrest; and provide an overview of studies addressing COPD and SCD in patient cohorts and community-based studies. In part two, we

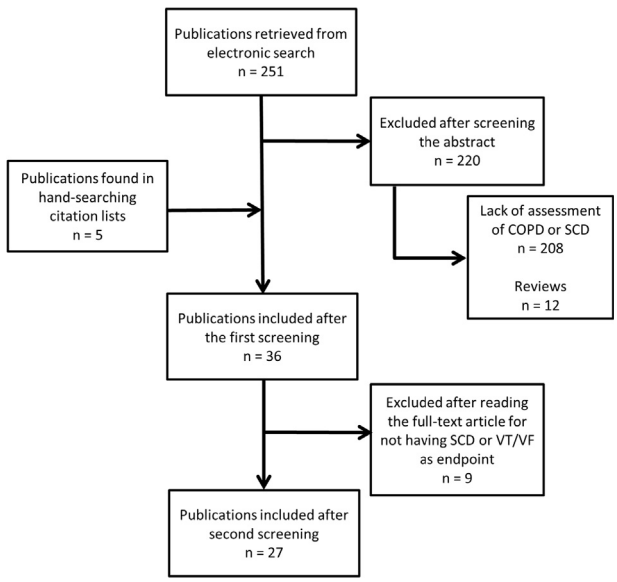

Fig. 1 – An overview of the electronic search and selection process. Abbreviations—COPD: chronic obstructive pulmonary disease, SCD: sudden cardiac death, VT/VF: ventricular tachycardia/ventricular fibrillation.

discuss potential sex differences in the association between COPD and SCD. Finally, we focus on possible mechanisms underlying the association of SCD and COPD, including smoking, hypertension, respiratory drugs, and the role of COPD exacerbations.

Part one: Association of COPD with SCD, ventricular arrhythmias, and ECG markers for SCD

COPD and electrocardiographic markers of SCD

The heart rate corrected QT (QTc) interval is a known risk factor for SCD [20], and it was the most commonly used ECG marker in the studies we found. In the study by Zulli et al. [21], QTc prolongation was associated with an increased mortality risk in a cohort of 246 COPD patients [21]. The association of COPD with the QTc interval was addressed in four studies, with mixed results—Tukek et al. [22] (total $n = 73$) and Sievi et al. [23] ($n = 164$) found that QTc was significantly higher in COPD cases compared with controls [22,23], but the study by Lahousse et al. [24], which compared 1615 COPD patients with all other participants ($n = 11,856$) at baseline, and Zupanic et al. ($n = 62$) [25] did not find a significant difference. However, Lahousse et al. [24] only compared the median QTc of COPD patients to participants without COPD at baseline and the study by Zupanic et al. [25] was possibly underpowered. A fifth study by Yildiz et al. [26], measured the maximum QT interval without heart rate correction on 24-h Holter recordings. This study found that the uncorrected maximum 24-h QT interval was significantly higher in COPD patients [26].

An abnormally short QT interval ($\leq$300 ms) has also been associated with SCD [27]. A large cross-sectional population-based study found that although QT shortening was rare (incidence of 2.7 per 100,000 persons), it was significantly associated with COPD with an odds ratio (OR) of 2.4 (95% CI: 1.3–3.5) [28]. This study included 6,547,785 ECGs of which 660,534 were recorded in COPD patients [28].

In addition to the QTc interval, heart rate variability has also been associated with SCD [29]. Heart rate variability was assessed next to the QTc interval by Tukek et al. [22], Yildiz et al. [26], and Zupanic et al. [25] These studies found that heart rate variability was significantly decreased in COPD patients [20,21,23]. A reduced heart rate variability is indicative of an increased sympathetic tone and a reduced vagal tone, which might be pathways from COPD to an increased SCD risk [30].

QT dispersion (QTD) is the difference between the longest and shortest QT interval in any lead for a given set of ECG leads [31]. QTD has been challenged on the ground that it is only a derivative attribute of T-loop morphology and not indicative of repolarization instability, and therefore an unsound marker for the prediction of ventricular arrhythmias [31,32]. Nevertheless, four studies addressed this marker [21–23,26]. In the study by Sievi et al. [23], QTD was not significantly increased in COPD patients compared with controls matched for age, cardiovascular risk, and medication use, but it was increased in COPD patients in Tukek et al. [22] and Yildiz et al. [26] Finally, in the cohort study of Zulli et al. [21], an increased QTD was associated with higher mortality risk [21].

COPD, ventricular arrhythmias, and cardiac arrest

Between 30% and 70% of SCD cases result from ventricular tachycardia and ventricular fibrillation (VT/VF) [9,10]. For this reason, the association of COPD with ventricular arrhythmias can be relevant for the association of COPD with SCD. Two studies addressed the underlying rhythm of COPD patients with a cardiac or a respiratory arrest. First, a study [33] in 70 patients with chronic airway obstruction admitted for acute respiratory failure noted that 15 patients (21.4%) developed cardiac arrest (which included VF and asystole), and four patients (5.7%) developed VT [33]. In a cross-sectional study ($n = 5415$) [34] of people who were resuscitated for out-of-hospital cardiac arrests (OHCAs), 20% of OHCAs were judged to be caused by COPD based on case history. The initial rhythm of resuscitation differed between the causes of the OHCAs—for the OHCAs with a cardiac cause, the initial rhythm was VT/VF in 48% of the cases, and PEA or asystole in 50% of the cases. For the OHCAs caused by COPD, the initial rhythm was VT/VF in 8% of the cases, and PEA or asystole in 88% of the cases [34]. These studies indicate that the occurrence of VT/VF in COPD patients is relatively low and PEA might be more frequently associated with SCD in COPD [33,34]. Furthermore, there was no significant increase of sustained VTs on a 24-h ECG in stable COPD patients after adjustment for cardiovascular risk factors [35]. In patients with a non–ST-segment elevation myocardial infarction (non-STEMI), the association of COPD with VT/VF seems to be stronger—in 26,416 patients with a non-STEMI, a history of COPD was associated with a significantly increased risk of VT (HR = 1.9, 95% CI: 1.1–3.1) and VF (HR = 2.5, 95% CI: 1.6–4.1) [36]. In addition to this, one study found that after an OHCA with VT/VF, 30-day survival was significantly lower in COPD patients [37].

COPD and SCD in cohorts of patient populations

Almost all studies defined SCD first as a witnessed unexpected death within 1 h of onset of abrupt change in symptoms and second as an unwitnessed death within 24 h of the last observation as medically stable. Supplementary Table 1 shows the definitions of SCD for all included studies.

A study in 5992 COPD patients reported that 7.7% of all deaths were SCDs [38], while a study of non-traumatic prehospital SCDs (defined as death within 1 h post-ER arrival, $n = 905$) found that COPD was relatively common in those SCD cases (11% had COPD) [39]. However, neither study had a control group (non-COPD patients and non-SCD deaths, respectively).

Studies in patient groups with cardiac diseases found that COPD as comorbidity is a risk factor for SCD. These clinic-based cohorts included patients who survived percutaneous coronary interventions (PCIs, $n = 6846$) [40] and coronary artery bypass graft (CABG, $n = 2910$) [40] and patients with atrial fibrillation (AF, $n = 334$) who underwent atrioventricular node ablation [41]. However, COPD was not a significant risk factor for SCD in a study in elderly patients ($n = 3726$, mean

age = 81 years) who underwent transcatheter aortic valve replacement (TAVR) [42].

Patients with an ICD are a special patient group for the study of ventricular arrhythmias and SCD. COPD was a risk factor for appropriate ICD shocks, which indicate the occurrence of ventricular arrhythmias in a cohort study of patients with an ICD ($n = 628$) [43]. A second cohort study ($n = 202$) found that COPD was also associated with ICD shocks, but this study did not differentiate appropriate from inappropriate ICD shocks (due to non-ventricular arrhythmias) [44].

COPD and SCD in community-based studies

Three community-based studies investigated the association of SCD or SCA with COPD. First, SCA risk was increased in COPD patients (OR = 1.4, 95% CI: 1.2–1.6), in a case–control study that compared SCA patients with VT/VF ($n = 1310$) to controls matched for age, sex, and index date ($n = 5793$). This study adjusted for cardiovascular risk factors, which were estimated by the use of cardiovascular drugs [45]. Second, COPD was a risk factor for SCD in a population-based cohort of middle-aged and elderly participants (HR = 1.4, 95% CI: 1.0–1.5). This study additionally created competing risk models, which showed that COPD is a risk factor for SCD beyond the generalized increased risk of death in COPD patients [24]. Third, a higher frequency of respiratory diseases (international classification of diseases 10—group J which includes COPD) was observed in SCA patients. However, this was not statistically significant ($p = 0.184$). In this study, a large cross-sectional study of emergency medical service interventions, the medical records on comorbid conditions of patients with out-of-hospital sudden cardiac arrest (SCA, $n = 245$) were examined retrospectively and compared with patients that underwent interventions for other reasons ($n = 26{,}398$) [46]. The fact that the higher frequency of respiratory diseases was not significant could be explained by the lack of specific COPD phenotyping or by the underdiagnosis of COPD in the medical records of emergency operations.

Part two: Sex differences and mechanisms of the association of SCD and COPD

Sex differences in the association of COPD with SCD

Three studies analyzed sex differences as possible effect modifiers of the association between COPD and VT/VF or SCD. First, men were more prone to VT than women in a cross-sectional study of ambulatory ECGs of 69 COPD patients [47]. In contrast, there was no sex difference in the risk of SCA between participants with COPD or asthma and participants without COPD or asthma in a study of SCA cases ($n = 1568$) [48]. Third, SCD occurred more frequently in men with COPD in the population-based study of Lahousse et al. [24] with 13,471 community-dwelling participants. However, this study found that frequent COPD exacerbations carried a slightly higher risk for women (HR = 3.5, 95% CI: 1.8–6.8) than for men (HR = 3.1, 95% CI: 1.7–5.5) [24]. Since the risk increased further when restricted to post-menopausal women, a role of stress-induced cardiomyopathy during COPD exacerbations was suggested [24].

Smoking

The association of COPD with SCD was adjusted for smoking in two cohort studies. The first cohort study (total $n = 7441$) found that low FEV_1 and FVC were associated with SCD both in smokers and non-smokers [15], and the study by Lahousse et al. [24] reported that the association between COPD and SCD was independent of smoking behavior. Moreover, smoking was not a significant predictor for ICD shocks in a study in a cohort of patients with ICDs [44]. These studies suggest that the association of COPD and SCD is independent of smoking.

Hypertension and timing of SCA/SCD

Two studies assessed factors associated with both COPD and cardiac endpoints [myocardial infarction (MI) or OHCA]. First, hypertension—acute MI patients admitted to the ICU with hypertension more often had COPD than normotensive MI patients, but they presented less often with VF [49]. Second, the time of incidence—nighttime admissions for OHCAs more often had COPD as comorbidity, and lower 1-year survival [49]. Furthermore, in the study by Lahousse et al. [24], SCDs in COPD patients occurred more often at night than SCDs in non-COPD patients (53% vs. 36%) [24]. The increased number of ventricular ectopic episodes during sleep could be the result of reduced ventilation and a blunted response to hypercapnia [50,51].

Respiratory drugs

The study by Warnier et al. [45] reported that use of inhaled short-acting beta-agonists (SABAs) and use of inhaled muscarinic antagonists (the study did not specify if these were long-acting or short-acting anticholinergics) were associated with sudden cardiac arrest (SCA) due to VT/VF. The OR for SABAs was 3.9 (95% CI: 1.7–8.8) and for anticholinergics 2.7 (95% CI: 1.5–4.8), after adjustment for concomitant cardiovascular disease. Use of inhaled corticosteroids was not associated with SCA in this study [45]. However, increased drug use during exacerbations or increased drug use due to more severe COPD might be plausible confounders for the increased risk of SCA in users of SABAs and anticholinergics [52]. In contrast, two studies found no effect of respiratory drugs on the risk of SCD in COPD. First, use of the long-acting anticholinergic tiotropium did not increase the risk of VT/VF in a meta-analysis combining 30 clinical trials and including 19,545 COPD patients [53]. However, because there were only five fatal VT/VF cases, this meta-analysis was underpowered for this endpoint [53]. Clinical trials of COPD patients possibly have a low incidence of VT/VF due to the selection of relatively stable patients without significant cardiovascular comorbidities [54]. Second, use of sympathomimetic respiratory drugs did not significantly interact with COPD on the risk of SCD in the study by Lahousse et al. [24], but this study did not take duration of drug use or dosage into account.

COPD exacerbations

In the study by Lahousse et al. [24], long-term COPD patients with frequent exacerbations had a higher risk of SCD (HR = 3.2, 95% CI: 2.1–5.0) than long-term COPD patients without frequent exacerbations (HR = 1.52, 95% CI: 1.1–2.2). Exacerbations only increased the risk of SCD in those participants with elevated systemic inflammation at cohort entry, indicating that the association of COPD exacerbations with SCD is at least partially mediated by systemic inflammation. Thus, severity and duration of COPD are of importance for the risk of SCD [24].

Discussion

The majority of the studies support the hypothesis that COPD is associated with SCD. COPD was a risk factor for SCD independent of cardiovascular risk profile, both in cohorts of cardiovascular patients and in community-based studies. Evidence for the association of COPD with VT/VF is much weaker, and the evidence for the potential impact of respiratory treatment on the onset of SCD is inconclusive. COPD was also associated with reduced heart rate variability, while the studies for QTc prolongation were inconclusive.

There are several theoretical explanations for an association between COPD and SCD, which are illustrated in Fig. 2. We will review each of these mechanisms and note what has been studied, and identify gaps needing further research. First, COPD might cause pathophysiological changes that directly increase the risk of SCD. Examples of previously studied pathological changes in COPD are changes in cardiac repolarization, represented by QT or QTc interval abnormalities [22–26,28], and increased sympathetic tone or reduced vagal tone indicated by a reduced heart rate variability [22,25,26]. Other studies have also found that COPD is associated with baroreceptor sensitivity abnormalities [55], heart rate variability abnormalities [56], and a direct increase in muscle sympathetic nerve activity [57]. Further research might focus on the interaction of COPD and autonomic neuropathy for the risk of SCD. The evidence for the association of COPD with QTc interval prolongation was inconclusive, and QT interval variability, a promising ECG marker of ventricular arrhythmias and SCD [58], has not yet been studied in COPD. Therefore, QT variability might be an avenue for future research. Besides ECG markers, the effect of systemic inflammation in COPD on the risk of SCD has been assessed [24]. However, there are also a number of pathophysiological changes associated with COPD that have not yet been studied in relation to SCD risk, including hypoxia and hypoxemia [14], cardiac ischemia [8,19], heart failure [59], and possibly pulmonary hyperinflation and pulmonary hypertension [24].

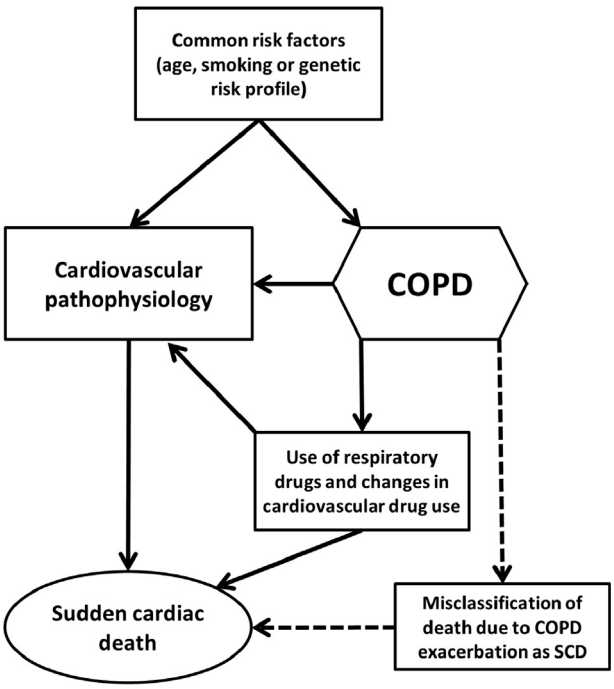

Fig. 2 – Possible mechanisms of the association between COPD and SCD. *Note*: Besides potential misclassification, COPD exacerbations are known to amplify both cardiovascular pathophysiology and the use of respiratory drugs. Abbreviations—COPD: chronic obstructive pulmonary disease, SCD: sudden cardiac death.

Second, there may be common risk factors acting as confounders. The association of COPD with SCD was independent of smoking, which was addressed in two studies [15,24]. The role of common genetic risk factors needs to be elucidated, since these studies will provide more insights into common pathogenic pathways that lead to increased SCD risk in COPD (e.g., systemic inflammation or tissue remodeling). No study to date has assessed common genetic risk factors between COPD and SCD.

Third, use of respiratory drugs could be associated with SCD. The studies included in this review give contradictory results and no study assessed the dose–response relationship of respiratory drugs and SCD [24,45,53]. The TIOSPIR [60] and SUMMIT [61] randomized controlled trials were not included in our review because they have not (or not yet) reported on the endpoint SCD. Because the association of respiratory drugs with SCD risk is probably dose dependent, future studies should address the dose effect. In addition to inhaled COPD drugs, none of the included studies have addressed the oral macrolide antibiotics, which are often prescribed for COPD exacerbations. These antibiotics are known QT-prolonging drugs, and suspected of increasing the risk of ventricular arrhythmias and SCD [20,62].

Fourth, the diagnosis of COPD could change the prescription pattern of cardiovascular drugs. On the one hand, contra-indications for drugs like beta-blockers might lead to inadequate cardiovascular prevention, which might increase the risk of SCD. On the other hand, the medical attention that is sought for COPD may also lead to improved cardiovascular prognosis by active prevention of cardiovascular risks (such as smoking and hypertension). Warnier et al. [45] studied the prevalence of use of cardiovascular drugs in SCD cases and controls, but did not assess the interaction with COPD. Therefore, a time-dependent and dose-dependent assessment of individual cardiovascular drugs in COPD patients and non-COPD patients, and the associated SCD risk, is needed.

Fifth, the association of COPD with SCD could be caused by misclassification of acute respiratory deaths as sudden cardiac deaths especially when non-witnessed. However, the ratio of witnessed to non-witnessed SCD was not different for participants with COPD compared with participants without COPD in the largest study of the association between COPD and SCD [24].

Lastly, the occurrence of a higher rate of exacerbations has also been reported to increase the risk of SCD in COPD patients [24]. Among explanatory mechanisms recently reviewed [52], this association can be caused by a direct increase in systemic inflammation associated with frequent exacerbations [63], or indirectly by use (and abuse) of SABAs and LABAs. Excessive use of SABAs and LABAs may lead to hypomagnesemia [64], which has also been associated with an increased risk of SCD [65].

A strength of the studies addressing SCD is the uniform definition of SCD as a witnessed unexpected death within 1 h of onset of abrupt change in symptoms or an unwitnessed death within 24 h of the last observation as medically stable. However, none of the studies with the endpoint SCD reported the preceding cardiac arrhythmia. Therefore, we were unable to distinguish between SCD caused by VT/VF and SCDs resulting from PEA and asystole. One study indicates that PEA and asystole are more common than VT/VF in COPD patients with cardiac arrest [34]. As these different direct causes of SCD are possibly the results of different pathologies and associated with different risk factors, this is a limitation of the studies included in this review.

In conclusion, accumulating evidence associates COPD with an increased risk of SCD. Asystole and PEA could be more common than VT/VF in COPD-associated deaths. Underlying mechanisms explaining this association require further investigation. Promising avenues of further research include studies of QT variability and hypoxia, genetic studies and pharmaco-epidemiological studies.

Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tcm.2016.04.001.

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