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Review Article

Nocturnal oxygen therapy in patients with chronic heart failure and sleep apnea: a systematic review

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ABSTRACT

Chronic heart failure (CHF) is a public health problem which affects >2% of the adult population, with high morbidity, mortality, and financial cost. Sleep apnea, prevalent in >50% of patients with CHF, can aggravate vital prognosis due to worsening of heart failure. It is considered that a decrease in the apnea–hypopnea load may improve outcomes for those patients. Nocturnal non invasive ventilation can be proposed to treat sleep apnea in this situation, there being few alternatives. The present review concerns the use of nocturnal oxygen therapy (NOT) in patients suffering from both CHF and sleep apnea. The interest of NOT in this situation lies in its ability to reduce the central apnea–hypopnea index and to improve nocturnal oximetry disorders related to sleep apnea. Impact on cardiac contractility, patient tolerance, side effects, and costs of NOT are also approached as well as the underlying mechanisms of NOT. In addition, the results of the SERVE-HF trial have shown an increased death rate in patients with CHF and central sleep apnea and who were treated with adaptive servo-ventilation versus control patients. This may lead to renewed interest in NOT in those patients.

1. Introduction

Chronic heart failure (CHF) is a public health problem. It affects more than 2% of the adult population, with a 50% death rate at five years and with a high financial cost partly because of repeated and prolonged hospitalizations for hemodynamic decompensation [1–3]. It is established that the sleep apnea prevalence is more than 50% in patients with CHF and reduced left ventricular ejection fraction (LVEF) [4–9]. In those patients, it is possible to observe both obstructive sleep apnea (OSA) and central sleep apnea, which is often Cheyne–Stokes respiration (CSA/CSR), or mixed sleep apnea [7,10–13]. It has been reported that both OSA and CSA/CSR can increase morbidity and mortality in patients with CHF, principally by the aggravation of heart failure [7–9]. Noninvasive ventilation systems can be proposed to treat OSA or CSA/CSR in patients with CHF [7,10–12]. Although the effects of these ventilation systems on morbidity and mortality are not entirely clear, several studies have shown that positive airway pressure ventilation could improve the prognosis in patients with CHF and sleep apnea [8–12]. However, this is now in contrast to the results of the SERVE-HF trial [14]. Concerning CSA/CSR in particular, beneficial effects have also been reported, for example with medication recommended in CHF [11,15], cardiac resynchronization therapy [16], and nocturnal oxygen therapy (NOT) [17,18]. Nevertheless, with regard to this latter option, the impact of long-term oxygen therapy on the prognosis in patients with CHF remains unknown [19,20].

The present review of the literature concerns the use of NOT in patients with both CHF and sleep apnea. The interest in NOT for this indication can be justified by the following: the search for alternatives to nocturnal ventilation, not always accepted or tolerated by patients and are also capable of causing premature death [11,14]; the fact that sleep apnea is accompanied by intermittent and repetitive nocturnal hypoxia episodes, which might further worsen cardiac performance in patients with CHF [8,9,21,22]; and the fact that the role of NOT can be considered even when there are no effects on respiratory events. From a pathophysiological point of view, the alleviation of CSA/CSR with NOT is of interest. In a section on the underlying mechanisms of NOT, this review also considers the relationship between myocardial function, central respiratory drive, and blood gasometry. In addition to the above points concerning interest in NOT, the objective of the present review is to determine whether NOT can be recommended as a valid therapy for patients with CHF and sleep apnea, notably as a replacement for nocturnal positive airway pressure ventilation.

2. Methods

In January 2015, an all-field and no-date-limit PubMed search associating the terms *heart failure*, *sleep apnea*, and *oxygen therapy* displayed 184 referenced publications. These included 156

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references in English, of which 44 were reviews. Because our interest was only in original intervention-based studies, and so as not to be influenced by previous reviews on the topic, the 44 review articles were excluded. Nevertheless, it can be noted that, among the review references, 22 were on either sleep-disordered breathing or CSA/CSR and heart failure but none were dedicated to NOT in patients with sleep apnea. Upon analysis of the 22 reviews, some statements or short paragraphs were found on NOT in patients with CHF and sleep apnea but rarely in the form of fully developed sections [17]. While scrutinizing the reference lists of those review articles, no extra references were found on NOT in patients with CHF and sleep apnea in addition to those included further to our literature database search. Among the 112 remaining original intervention-based studies, 15 related specifically to the use of NOT in patients with CHF and sleep apnea [23–37]. Each of the 15 references consisted of a full paper reporting detailed results concerning the effects of NOT on nocturnal respiratory events. Two further references appeared when *sleep apnea* was replaced by *Cheyne–Stokes respiration* [38,39]. No other references were found using the key words *chronic* or *congestive* heart failure and *nocturnal* oxygen therapy. The effects of NOT on sleep apnea in patients with CHF were therefore analyzed in 17 studies. The structure of the review follows most of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, taking into account its 2009 checklist and providing a PRISMA-compatible flow diagram (Fig. 1). The *systematic* nature of the manuscript was in the PubMed search criteria and the reading of the 112 selected papers in English. We intentionally chose to use this single publications database, which generally contains most of the relevant and peer-reviewed references in medical journals. The fact that we did not use any other publications database may confer a restrictive sense to the word *systematic* in the present review that may be considered as a study limitation. No meta-analysis was carried out for reasons detailed below.

3. Results

3.1. Study features and design

Study populations were always of limited size and situated in a single study center, with the exception of the two principal studies concerning the HOT-CHF study group [31,35]. Three principal study designs were found: basic, control, and crossover. *Basic* design refers to comparison in the study population of baseline versus NOT data observed during a diagnostic nocturnal recording in room air versus a second nocturnal recording with NOT [24,25,27,30,32,33]. In a *control* design, the study population is split into a control group, with two nocturnal recordings in room air, and a NOT group, with baseline and NOT nocturnal recordings [31,35,37]. A *crossover* design compares either compressed room air with NOT or a ventilation system with NOT [23,26,28,36,38,39]. Compressed room air is provided by a concentrator that delivers pressurized air instead of oxygen. Baseline data were not always available in these crossover studies, comparison being directly proposed between the two interventions [23,38].

The majority of the study populations comprised patients characterized by systolic CHF with LVEF often below 45% and with New York Heart Association functional class II–IV heart failure. No study was available regarding the use of NOT in patients with CHF with preserved LVEF and sleep apnea [5,40].

It was not always clear whether the study populations really experienced sleep apnea. For instance, the impact of NOT on CSA/CSR times was studied in patients showing 6–217 or 6–474 minutes of CSR time at night-time for baseline readings [23,38]. This resulted in a high degree of heterogeneity in the study populations. In addition, when a diagnosis cut-off value was proposed to include

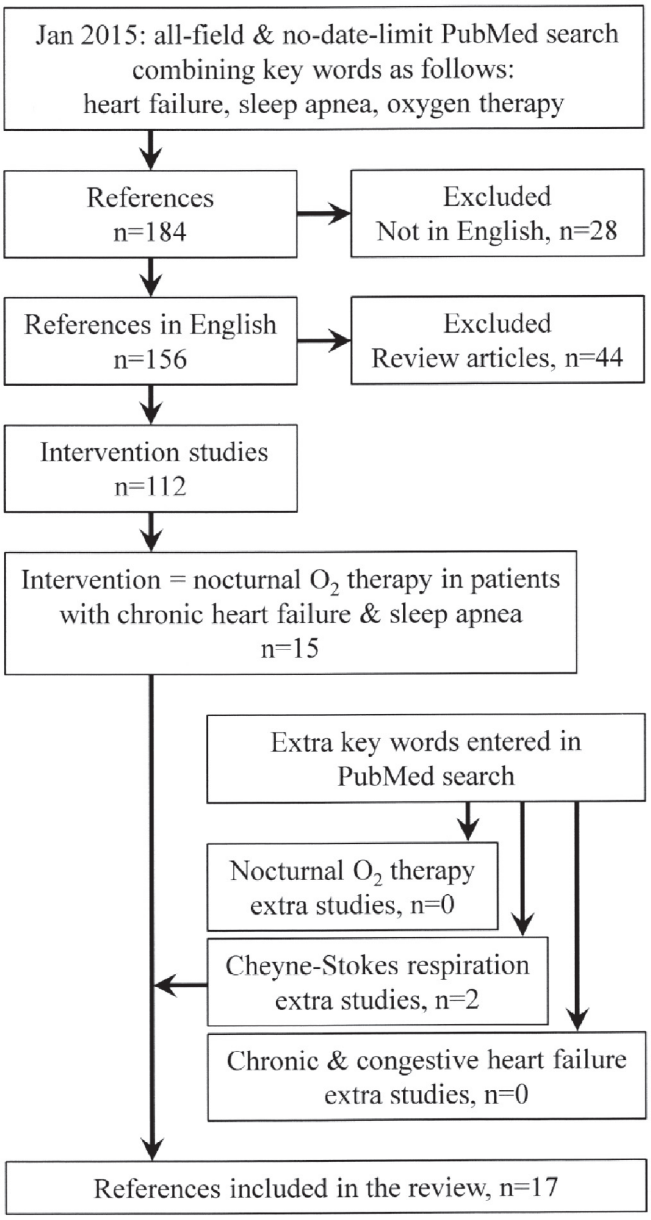

Fig. 1. Flow diagram of the study.

or exclude patients, disparate values were used, eg, an apnea–hypopnea index (AHI) of more than 5 or more than 15 events per hour. CSA/CSR was predominant in the study populations, but some studies also included patients with obstructive or mixed respiratory events.

A particular aspect of the studies analyzed was to highlight the duration of NOT use. Short-term meant one night or one week with NOT [23–28,30,32,37,38]. Staniforth et al. were the first to study NOT for one month, and called it long-term therapy [39]. Subsequent studies proposed NOT use for between 1–12 months [29–31,33–37]. Long-term studies were carried out to determine whether the acute effects of NOT on CSA/CSR would be sustained over time, or whether patients would show progressively positive NOT effects. Two studies reported short- and long-term effects of NOT: Krachman et al., with one night and one month of NOT, and Bordier et al., with one night and six months of NOT [30,37]. No study was designed to determine the impact of long-term use of NOT on survival.