International Journal of Cardiology 206 (2016) S16–S21

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Measuring therapeutic efficacy in the treatment of central sleep apnoea in patients with heart failure

Andrew J. Stewart Coats *, Louise G. Shewan

[a] Monash University, Australia
[b] University of Warwick, Coventry, UK

ARTICLE INFO

Article history:
Received 18 December 2015
Accepted 21 February 2016
Available online 24 February 2016

Keywords:
Central sleep apnoea
Cheyne Stokes respiration
Chronic heart failure
Therapy

ABSTRACT

The goal of treating sleep disordered breathing (SDB) has traditionally focused on improving daytime sleepiness and fatigue. In heart failure (HF) patients with SDB, this is not as easy to ascertain as their symptoms overlap with HF. Thus, improvement in treating SDB in HF patients must focus more on overall quality of life. Over the past 5 years, there has been a shift in sleep medicine from only improving symptoms in SDB, to preventing the long term consequences. The specialist Heart Failure community is, however, desirous of also seeing benefit in reduction of major clinical events for their patients with interventions, such as effects on mortality or re-hospitalisation rates and so may wish to see other benefits beyond a reduction in sleep apnea events before either commencing therapy or referring their patients for sleep study evaluation and further management. To expect lower mortality as well may be asking for too much. Consequently, success in the treatment in SDB should focus on three items: 1) proof that the underlying disease is treated, 2) symptomatic benefit and 3) demonstration that the pathological consequences are prevented. These benefits must then be balanced with a strong safety profile.
Here we evaluate a variety of end-points of value to our CSA patients, in an effort to see what may reasonably be required for treating physicians to recommend an intervention for their CHF patients with CSA by looking at candidate measures of treatment success in CSA within a heart failure population.

Contents

1. Introduction

Approximately 50% of heart failure patients have sleeping disorders and recognition of the importance of these co-morbidities has led to

* Corresponding author.
E-mail address: ajscoats@aol.com (A.J.S. Coats).

http://dx.doi.org/10.1016/j.ijcard.2016.02.123
0167-5273/

inclusion of sleep in cardiology guidelines worldwide [1,2]. Understanding which patients are at risk and how to identify them is of growing concern in the care of these patients. Sleep medicine has developed into a distinct specialty with specialist physicians, dedicated clinics and specialist societies publishing guidelines related to the diagnosis, assessment and management of affected patients [3,4]. The spectrum of sleep disordered breathing (SDB) includes two major subtypes, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA); many patients have some component of each disorder. With 10% of the adult male population diagnosed with OSA, this form of SDB alone makes up the majority of patients seen in sleep clinics [4]. Thus, only a small proportion of patients seen within the sleep clinic are diagnosed with CSA [3]. In contrast, approximately 1/3 of patients with heart failure have CSA [5]. These patients have higher morbidity and mortality than their counterparts without SDB [6]. As most of these patients are often seen within the cardiology practice identification and treatment of these patients should be a focus of cardiologists. In addition, a focus on developing relationships between sleep and HF specialists is important to improve the care of these patients. Cardiologists therefore are presented with the problem of how to manage a condition (CSA) which is epidemiologically largely secondary to CHF whose patients attend specialist heart failure services, but which is usually identified and treated by a separate specialist community (Respiratory Sleep Physicians) whose more usual patient has the OSA type of SDB. It is therefore crucial to do two things: to differentiate between OSA and CSA and to educate CHF specialists in how to identify, assess and manage CSA as they have the patients who are more likely to have the CSA pattern of disorder.

It may seem surprising that so few patients with CSA are typically identified in sleep clinics. However, the typical presentation of sleep apnea is absent in patients with heart failure. Patients with heart failure typically deny daytime sleepiness and questionnaires typically used with healthy patients are not predictive in patients with HF. Recently a sleep apnea "score" was developed to identify heart failure patients at high risk for sleep apnea. This test uses information commonly found in a patient's chart such as NYHA class, age and gender to identify risk and trigger testing for the patients [7].

Since 1985 when a very small study first suggested a high prevalence of CSA in CHF patients and a heightened risk of death associated with CSA, multiple studies have confirmed the importance of CSA on prognosis in CHF [8–11]. An AHI above a critical value of >30 episodes per hour has been repeatedly shown to be a powerful marker of adverse outcome in SDB. A recent meta-analysis has confirmed that CSA confers an increased mortality outcome on CHF patients (comparing an AHI of less than compared to more than 30/h) whereas no significant effects were seen for OSA in the CHF population [12]. Eleven studies were identified recruiting 1944 patients (1399 in the SDB group and 545 in the no-SDB group). Patients with SDB showed significantly increased all-cause mortality compared to controls [RR 1.66 (1.19–2.31). This was driven almost entirely by an increased risk associated with CSA [RR 1.48 (1.15–1.91) with no significant effect of OSA being seen.

We need to evaluate treatment aims for CSA both because it is a high-risk co-morbidity of CHF but also because of the added symptom burden of sleep-disorder in CHF. To do so we need to evaluate markers of treatment efficacy short of requiring large scale mortality trials for every new treatment modality and variant. This article will review the efficacy metrics we should utilise in measuring "success" in treating CSA in HF patients as it is clearly not feasible to evaluate mortality effects for every co-morbidity affecting HF patients.

2. Differentiating CSA and OSA

There are many detailed reviews of the differing underlying pathophysiology of OSA and CSA; to briefly summarise, OSA is caused by upper airway obstruction, usually associated with upper airway collapse and CSA by fluctuating central respiratory drive [13–15]. OSA manifests as intermittent airway occlusions, accompanied by consequent loss of airflow, arterial deoxygenation and arousal due to the stimulatory effects of chemoreflex firing secondary to the disturbed arterial blood gases. These obstructive apnoeas or hypopnoeas can occur throughout sleep and are somewhat irregular. CSA in contrast, is a fluctuation in the neural drive to breathe that causes classically an oscillatory pattern with more regular periods of apnoea (occasioned by absent drive to breathe as opposed to obstructed breathing), and followed smoothly by over-compensatory hyperventilation. It is at times indistinguishable from Cheyne–Stokes respiration (CSR) and is usually associated with exaggerated chemoreflex sensitivity and reduced arterial carbon dioxide levels and periodic sympathetic stimulation, arterial desaturations and semi-arousals. These distinctions between CSA and OSA can be blurred as either type can, when present, generate aspects of the other; such as the arousal from an obstructive episode causing hyperventilation which then blows off CO_2 and initiates cycles of CSA, and conversely a central episode can reduce arterial oxygenation that can lead to loss of upper airway tone which can lead to an increased risk of obstructive episodes. This overlap and mutual entrainment mean that it is at times a complex matter to completely separate the two major types of SDB in patients. Yet it is important to attempt to do so because their pathophysiological antecedents are quite different and hence treatments for one type may not work or may be detrimental if applied to the other type inappropriately. The overlap is worsened by the fact both types of SDB share common risk factors especially those of chronic heart disease (obesity, hypertension, male gender). Chronic heart failure (CHF) is a common end stage of many heart diseases and hence the prevalence of OSA is expected to be high. Independently CHF is the condition more than any other that predisposes to CSA (or CSR), because it is associated with heightened chemoreflex sensitivity, reduced arterial CO_2 levels, reduced buffering capacity of the lungs to absorb fluctuations in CO_2 levels and an increased circulation time, all of which make oscillatory breathing more likely to develop [15].

3. What efficacy metric should be used to measure "success" in treating CSA in HF patients?

The goal of treating SDB has traditionally focused on improving daytime sleepiness and fatigue [4]. In HF patients with SDB, this is not as easy to ascertain as their symptoms overlap with HF [7]. Thus, improvement in treating SDB in HF patients must focus more on overall quality of life. Over the past 5 years, there has been a shift in sleep medicine from only improving symptoms in SDB, to preventing the long term consequences [16]. Much of the harm associated with SDB (increased CV risk, accelerated CV disease progression, increased risk of sudden death and ventricular arrhythmias) is thought to be related to repetitive and marked episodes of arterial deoxygenation and hyperoxia [15]. Thus, a second goal of therapy therefore is to decrease these episodes and their associated CV risk. The specialist Heart Failure community is, however, desirous of also seeing benefit in reduction of major clinical events for their patients with interventions, such as effects on mortality or re-hospitalisation rates and so may wish to see other benefits beyond a reduction in sleep apnea events before either commencing therapy or referring their patients for sleep study evaluation and further management. To expect lower mortality as well may be asking for too much. Consequently, success in the treatment in SDB should focus on three items: 1) proof that the underlying disease is treated, 2) symptomatic benefit and 3) demonstration that the pathological consequences are prevented. These benefits must then be balanced with a strong safety profile.

We must therefore look at a variety of end-points of value to our CSA patients, to find what would be required for treating physicians to recommend an intervention for their CHF patients with CSA. Some experts may be seeking any effective therapies that reduce the apnea-hypoxia index (AHI), apnea burden or some other measure that better encapsulates the burden of CSA. Others may wish also to see different benefits,