Canadian Journal of Cardiology 31 (2015) 898–908

Review

Heart Failure and Sleep Apnea

Owen D. Lyons, MBBCh,[a,b] and T. Douglas Bradley, MD[a,b,c]

[a] Sleep Research Laboratory of the University Health Network Toronto Rehabilitation Institute, Toronto, Ontario, Canada

[b] Centre for Sleep Medicine and Circadian Biology of the University of Toronto, Toronto, Ontario, Canada

[c] Department of Medicine of the University Health Network Toronto General Hospital, Toronto, Ontario, Canada

ABSTRACT

Obstructive and central sleep apnea are far more common in heart failure patients than in the general population and their presence might contribute to the progression of heart failure by exposing the heart to intermittent hypoxia, increased preload and afterload, sympathetic nervous system activation, and vascular endothelial dysfunction. There is now substantial evidence that supports a role for fluid overload and nocturnal rostral fluid shift from the legs as unifying mechanisms in the pathogenesis of obstructive and central sleep apnea in heart failure patients, such that the predominant type of sleep apnea is related to the relative distribution of fluid from the leg to the neck and chest. Despite advances in therapies for heart failure, mortality rates remain high. Accordingly, the identification and treatment of sleep apnea in patients with heart failure might offer a novel therapeutic target to modulate this increased risk. In heart failure patients

RÉSUMÉ

L'apnée obstructive et l'apnée centrale du sommeil sont beaucoup plus fréquentes chez les patients souffrant d'insuffisance cardiaque que dans la population générale. Par conséquent, leur présence contribuerait à la progression de l'insuffisance cardiaque en exposant le cœur à une hypoxie intermittente, à une augmentation de la précharge et de la postcharge, à l'activation du système nerveux sympathique et á la dysfonction endothéliale vasculaire. Il existe désormais des preuves solides qui appuient le rôle de la surcharge liquidienne et du déplacement rostral des fluides des jambes pendant la nuit puisqu'il unifie les mécanismes de la pathogenèse de l'apnée obstructive et de l'apnée centrale du sommeil chez les patients souffrant d'insuffisance cardiaque de façon que le type prédominant d'apnée du sommeil soit lié à la distribution relative des fluides des jambes vers le cou et la poitrine. En dépit des avancées dans les traitements de l'insuffisance

It is estimated that heart failure (HF) affects > 260,000 Canadians.[1] These patients have a poor prognosis with average 1-year mortality of 33%.[2] Furthermore, HF accounts for approximately 30,000 hospital admissions in Canada each year, with readmission rates within 1 year as high as 24%.[2] Until the last decade of the 20th century, 5-year mortality rates for HF were as high as 70%.[3] However, over the past 20 years, improvements in the treatment of HF with angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, β-blockers, implantable cardioverter defibrillators, and cardiac resynchronization therapy have led to improved survival and reduced hospitalizations.[3-6] Despite these advances in HF therapy, mortality remains high.[3-6]

Obstructive and central sleep apnea (OSA and CSA, respectively) are common in HF patients with either reduced[7-9] or preserved left ventricular (LV) ejection fraction (LVEF).[10-12] OSA and CSA might participate in the progression of HF by exposing the heart to intermittent hypoxia, increased preload, afterload,[13,14] and sympathetic nervous system activity (SNA),[15] and vascular endothelial dysfunction.[16] However, although there is substantial evidence that the presence of sleep apnea in HF patients contributes to disease progression and that treatment of OSA and CSA improves cardiovascular function in patients with HF, large long-term randomized trials of different interventions are required to determine whether treatment of OSA and CSA can improve morbidity and mortality.

The high prevalence of OSA and CSA in HF is similar to that in end-stage renal disease,[17] another condition characterized by fluid overload. This observation suggests that fluid overload might contribute to the pathogenesis of OSA and CSA in these conditions. Overnight rostral fluid shift from the legs to the neck and lungs has been shown to contribute to the pathogenesis of OSA and CSA, respectively, in various patient populations, including HF, and treatment that reduces total body fluid or overnight fluid shift can attenuate sleep apnea.

The aims of this article are to: review the clinical features and epidemiology of OSA and CSA in HF patients; discuss the pathophysiology of OSA and CSA including the role of fluid retention and displacement; consider the effect of OSA

Received for publication February 2, 2015. Accepted April 12, 2015.

Corresponding author: Dr T. Douglas Bradley, University Health Network Toronto General Hospital, 9N-943, 200 Elizabeth St, Toronto, Ontario M5G 2C4, Canada. Tel.: +1-416-340-4719; fax: +1-416-340-4197.

E-mail: douglas.bradley@utoronto.ca

See page 905 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.04.017

with obstructive or central sleep apnea, continuous positive airway pressure has been shown to improve cardiovascular function in short-term trials but this has not translated to improved mortality or reduced hospital admissions in long-term randomized trials. Other forms of positive airway pressure such as adaptive servoventilation have shown promising results in terms of attenuation of sleep apnea and improvement in cardiovascular function in short-term trials. Large scale, randomized trials are required to determine whether treating sleep apnea with various interventions can reduce morbidity and mortality.

cardiaque, les taux de mortalité restent élevés. Par conséquent, l'identification et le traitement de l'apnée du sommeil chez les patients souffrant d'insuffisance cardiaque offriraient une nouvelle cible thérapeutique pour moduler cette augmentation du risque. Chez les patients souffrant d'apnée obstructive ou d'apnée centrale du sommeil, il a été démontré au cours d'essais de courte durée que la pression positive expiratoire continue améliore la fonction cardiovasculaire, mais cela ne s'est pas traduit par l'amélioration de la mortalité ou la réduction des admissions à l'hôpital au cours d'essais à répartition aléatoire de longue durée. D'autres types de pression positive expiratoire comme la servoventilation adaptée a montré des résultats prometteurs en matière d'atténuation de l'apnée du sommeil et d'amélioration de la fonction cardiovasculaire au cours d'essais de courte durée. Des essais à répartition aléatoire de grande échelle sont nécessaires pour déterminer si le traitement de l'apnée du sommeil selon diverses interventions peut réduire la morbidité et la mortalité.

and CSA on cardiac function and clinical outcomes in HF; discuss treatment; and finally, consider gaps in knowledge in need of resolution. Because of the relative paucity of literature concerning sleep apnea in HF with preserved LVEF, the main focus of this article is on sleep apnea in HF with reduced LVEF.

Definitions and Diagnosis

Obstructive apneas and hypopneas are caused by complete or partial upper airway (UA) collapse during sleep, respectively. Central apneas and hypopneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep. OSA and CSA are usually diagnosed using overnight polysomnography (PSG). Apneas are defined as the absence of tidal volume for at least 10 seconds and hypopnea is defined as a decrease in the tidal volume of $\geq$ 30% for at least 10 seconds that is accompanied by at least a 3% decrease in oxygen saturation or terminated by an arousal from sleep.[18] Apneas are classified as obstructive if they are accompanied by inspiratory effort against the occluded pharynx and central if they are not. Hypopneas are classified as obstructive if there are signs of UA flow limitation, or central if there are not.[18] The apnea-hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep. Sleep apnea severity can be classified according to the AHI; no sleep apnea is defined as an AHI of $<$ 5, mild sleep apnea as an AHI of 5-15, moderate as an AHI of 15-30, and severe as an AHI $>$ 30.[19]

Epidemiology

OSA

In a recent study, the prevalence of OSA in the general population aged 30-70 years, using an AHI cutoff $\geq$ 5 were 34% among men and 17% among women, and using an AHI cutoff $\geq$ 15, 13% among men and 6% among women.[20] In a cross-sectional analysis of the Sleep Heart Health Study, comprised of $>$ 6000 men and women, the presence of OSA, with an AHI $\geq$ 11, conferred a 2.38 relative increase in the likelihood of having HF independent of other risk factors.[21] A subsequent prospective analysis of the same study involving 1927 men and 2495 women $\geq$ 40 years of age, free of heart disease at the time of PSG, and who were followed for 8 years, found that after adjusting for confounders, OSA increased the risk of new-onset HF in men (hazard ratio [HR], 1.13 [95% confidence interval (CI), 1.02-1.26] per 10-unit increase in AHI) but not in women. Men with an AHI $>$ 30 events per hour are 58% more likely to develop HF than those with an AHI $<$ 5.[22] Among HF patients, reported prevalence of OSA varies widely; using an AHI cutoff of $\geq$ 15, prevalence was 12%, 15%, 26%, and 32%.[7,8,23,24] Some of these differences could be because of differing populations in which men and women,[8,23] or only men were included,[7,24] or to differing medical therapy that has changed over time. Nevertheless, in general, these rates are higher than in the general population. Risk factors for OSA in the general population, such as older age, male sex, and higher body mass index (BMI) are also risk factors for OSA in HF.[23] However, HF patients have a lower BMI for any given AHI than the general population and the correlation between BMI and AHI is weak.[25]

CSA

The prevalence of CSA in the general population is very low at $<$ 1%.[26] In contrast, among HF patients, prevalence of CSA, using an AHI cutoff of $\geq$ 15 were 21%, 29%, and 37%.[7,8,23] Risk factors for CSA in HF patients include male sex, hypocapnia, atrial fibrillation, and increasing age.[8]

Pathogenesis of Sleep Apnea in HF

OSA

Obstructive apneas and hypopneas are caused by complete or partial UA collapse, which occurs when sleep-related loss in UA dilator muscle tone is superimposed on a narrow and/or collapsible UA.[27,28] Compared with subjects without OSA, patients with OSA have a smaller UA cross-sectional area, and higher UA resistance and compliance.[29,30] The UA of patients with OSA is more collapsible when exposed to negative pressure during wakefulness or under passive conditions during sleep than in healthy subjects.[31,32] UA narrowing is