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**Clinical Research** 

# Prevalence of Sleep-Disordered Breathing-Related Symptoms in Patients with Chronic Heart Failure and Reduced Ejection Fraction

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#### ABSTRACT

Background: Sleep-disordered breathing (SDB) is highly prevalent in patients with chronic heart failure (CHF) and is associated with a poor prognosis. Data on SDB-related symptoms and vigilance impairment in patients with CHF and SDB are rare. Thus, the objective of the present study was to assess a wide spectrum of SDB-related symptoms and objective vigilance testing in patients with CHF with and without SDB. Methods: Patients with CHF (n = 222; average age, 62 years; left ventricular ejection fraction [LVEF], 34%) underwent polysomnography regardless of the presence or absence of SDB-related symptoms. Patients were stratified into those with no SDB (apnea-hypopnea index [AHI] < 15 episodes/h), moderate SDB (AHI  $\geq$  15 to < 30 episodes/h), and severe SDB (AHI  $\geq$  30 episodes/h). A standardized institutional questionnaire assessing a wide spectrum of SDB-related symptoms was applied. A subset of patients underwent objective vigilance testing (Quatember Maly, 100 stimuli within 25 minutes).

**Results:** Daytime fatigue (no SDB, moderate SDB, and severe SDB: 53%, 69%, and 80%, respectively; P = 0.005), unintentional sleep (9%, 15%, and 32%, respectively; P = 0.004), and xerostomia (52%, 49%, and 70%, respectively; P = 0.018), as well as an impaired objective vigilance test result (mean reaction time, 0.516, 0.497, and 0.579 ms, respectively; P < 0.001) occurred more frequently with

Sleep-disordered breathing (SDB) is characterized by repetitive cessation of airflow, caused either by a collapse of the upper airway in obstructive sleep apnea (OSA) or by the absence of respiratory effort in central sleep apnea (CSA).<sup>1,2</sup> SDB exposes the cardiovascular system to intermittent hypoxia, surges of sympathetic drive and blood pressure,<sup>3,4</sup>

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See page 844 for disclosure information.

#### RÉSUMÉ

Introduction : Les troubles respiratoires du sommeil (TRS) qui sont très fréquents chez les patients souffrant d'insuffisance cardiaque chronique (ICC) sont associés à un mauvais pronostic. Les données sur les symptômes liés aux TRS et la diminution de la vigilance chez les patients ayant une ICC et des TRS sont rares. Par conséquent, l'objectif de la présente étude était d'évaluer un large éventail de symptômes liés aux TRS et de tests objectifs de vigilance chez les patients souffrant d'ICC qui n'ont pas de TRS.

**Méthodes :** Les patients souffrant d'ICC (n = 222; âge moyen, 62 ans; fraction d'éjection ventriculaire gauche [FEVG], 34 %) ont subi une polysomnographie indépendamment de la présence ou de l'absence de symptômes liés aux TRS. Les patients ont été stratifiés comme ce qui suit : ceux n'ayant pas de TRS (index d'apnées-hypopnées [IAH] < 15 épisodes/h), ceux ayant des TRS modérés (IAH  $\geq$  15 à < 30 épisodes/h) et ceux ayant des TRS graves (IAH  $\geq$  30 épisodes/h). Un questionnaire institutionnel standardisé évaluant un large éventail de symptômes liés aux TRS a été appliqué. Un sous-ensemble de patients a subi le test objectif de vigilance (Quatember Maly, 100 stimuli en 25 minutes).

**Résultats :** La fatigue diurne (des patients sans TRS, ayant des TRS modérés et des TRS graves : 53 %, 69 % et 80 %, respectivement; P = 0,005), le sommeil involontaire (9 %, 15 % et 32 %, respectivement;

enhanced negative intrathoracic pressure,<sup>5</sup> and thus increased cardiac workload. The long-term effects include the development of hypertension,<sup>6</sup> myocardial hypertrophy, atherosclerosis, and coronary artery disease,<sup>7,8</sup> contributing to the progression of heart failure and increased mortality rates.<sup>9-11</sup> Despite advances in medical and device therapy for CHF within the past 2 decades, SDB remains highly prevalent in patients with CHF.<sup>12-15</sup> Observational studies suggest that treatment of severe SDB with positive airway pressure (PAP) improves survival of patients with CHF.<sup>10,11</sup> In addition, PAP therapy improves quality of life and sleepiness, especially in those patients with CHF who present with SDB-related symptoms.<sup>16-18</sup>

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increasing severity of SDB. Seventy-eight percent of patients with CHF and SDB had at least 3 SDB-related symptoms. In a linear multivariable regression model, the frequency of daytime fatigue (P = 0.014), unintentional sleep (P = 0.001), xerostomia (P = 0.016), and mean reaction time (P = 0.001) were independently associated with increasing AHI independent of age, body mass index, New York Heart Association functional class, and LVEF.

**Conclusions:** The majority of patients with CHF and SDB have several potential SDB-related symptoms and objective impairment of vigilance as potential treatment targets.

The proportion of patients with CHF and SDB-related symptoms is a matter of debate: patients with CHF and SDB have been reported to present with less daytime sleepiness compared with patients with a similar degree of OSA and normal cardiac function.<sup>19</sup> However, previous evaluations of potential SDB-related symptoms in heart failure were either limited to increased daytime sleepiness, usually assessed by the Epworth Sleepiness Scale (ESS),<sup>19-24</sup> or did not relate the occurrence of symptoms to the severity of SDB in general.<sup>25</sup>

We therefore evaluated the following hypotheses in a sample of patients with CHF receiving contemporary medical therapy who underwent full in-laboratory polysomnography (PSG). The first hypothesis was that patients with CHF and SDB present with a wide spectrum of symptoms that may indicate the occurrence of SDB. The second hypothesis was that the occurrence of symptoms, as well as objectively impaired vigilance, is related to the severity of SDB.

# Methods

# Patients

We examined 477 patients with CHF who were referred to the sleep laboratory of the University Hospital Regensburg for PSG between January 2002 and October 2011. The clinical decision of referral for PSG was usually based on the result of an SDB screening by polygraphy regardless of the presence or absence of symptoms. Inclusion criteria for this analysis were CHF caused by ischemic or nonischemic cardiomyopathy with objective evidence of systolic dysfunction (left ventricular ejection fraction [LVEF] < 50%) measured by echocardiography within 3 months before enrollment, stable clinical status, and stable optimal medical therapy for at least 4 weeks. Patients were included regardless of the presence or absence of symptoms of SDB. Exclusion criteria were CHF caused by valvular heart disease, listing for heart transplantation, known life-threatening illnesses (eg, severe pulmonary disease or cancer), current treatment with oxygen or PAP, unstable clinical status, noncompletion of health questionnaires, and current alcohol abuse or insufficient language skills. This retrospective analysis was approved by the local ethics committee.

P = 0,004) et la xérostomie (52 %, 49 % et 70 %, respectivement; P = 0,018), ainsi qu'une diminution des résultats au test objectif de vigilance (temps de réaction moyen, 0,516, 0,497 et 0,579 ms, respectivement; P < 0,001) étaient plus fréquents lorsque la gravité des TRS augmentait. Soixante-dix-huit pour cent des patients souffrant d'ICC et de TRS avaient au moins 3 symptômes liés aux TRS. Dans un modèle de régression linéaire multiple, la fréquence de la fatigue diurne (P = 0,014), du sommeil involontaire (P = 0,001), de la xérostomie (P = 0,016) et du temps de réaction moyen (P = 0,001) était indépendamment associée à l'augmentation de l'IAH, et ce, indépendamment de l'âge, de l'indice de masse corporelle, de la classification fonctionnelle de la New York Heart Association et de la FEVG.

**Conclusions :** La majorité des patients souffrant d'ICC et de TRS ont potentiellement plusieurs symptômes liés aux TRS et une diminution objective de la vigilance comme cibles de traitement potentielles.

## Polysomnography

PSG was performed in all patients using standard polysomnographic techniques as previously described.<sup>10,26</sup> During PSG, body position, eye and leg movements, electrocardiography, nasobuccal airflow, chest and abdominal effort, electroencephalographic monitoring, and arterial oxyhemoglobin saturation (SaO2) assessed by pulse oximetry were recorded (Alice 3.5; Respironics, Pittsburgh, PA). Apnea was defined as a cessation of inspiratory airflow (> 10 seconds), and hypopnea was defined as a reduction of airflow (> 50%)or thoracoabdominal effort lasting  $\geq 10$  seconds resulting in a  $\geq$  4% drop in SaO<sub>2</sub>. The apnea-hypopnea index (AHI) was defined as the number of apneic or hypopneic episodes per hours of sleep. The oxygen desaturation index was defined as the number of oxygen desaturations  $\geq 4\%$  per hour of sleep. Patients were stratified into those without SDB (AHI < 15/h), those with moderate SDB (AHI  $\geq$  15 to < 30/h), and those with severe SDB (AHI  $\geq$  30/h), respectively. For additional comparative analysis, the patients were stratified as having OSA or CSA on the basis of the predominant type of apneic episodes.

# **Epworth Sleepiness Scale**

The ESS is a self-administered questionnaire used as a measurement of the patient's general level of daytime sleepiness. Patients are asked to rate their probability of falling asleep in 8 different common situations of daily life. A cutoff value > 10 of 24 points in total indicates increased daytime sleepiness.<sup>27,28</sup> The validated German version of the ESS questionnaire was used.<sup>28</sup>

## Institutional questionnaire

In our institutional questionnaire (Supplemental Table S1), we asked questions about potential SDB-related symptoms. The questions involved increased daytime sleepiness, unintentional sleep, impaired concentration, snoring, witnessed apneic episodes, xerostomia, nocturnal dyspnea, and nocturia. The questions offered a 5-step response format, in which possible responses ranged from never or rarely, occasionally, and frequently to very

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