Heart, Lung and Circulation (2016) **25,** 435–441
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.09.011

ORIGINAL ARTICLE

Impact of Obstructive Sleep Apnoea on Heart Failure with Preserved Ejection Fraction

Takuo Arikawa, MD [a*], Shigeru Toyoda, MD [a], Akiko Haruyama, MD [a], Hirohisa Amano, MD [a], Shu Inami, MD [a], Naoyuki Otani, MD [a], Masashi Sakuma, MD [a], Isao Taguchi, MD [b], Shichiro Abe, MD [a], Koichi Node, MD [c], Teruo Inoue, MD [a]

[a]Department of Cardiovascular Medicine, Dokkyo Medical University, 321-0293 Mibu, Japan
[b]Department of Cardiology, Koshigaya Hospital, Dokkyo Medical University, 343-8555 Koshigaya, Japan
[c]Department of Cardiovascular Medicine, Saga University Faculty of Medicine, 849-8501 Saga, Japan

Received 6 June 2015; received in revised form 17 August 2015; accepted 14 September 2015; online published-ahead-of-print 18 October 2015

Background The impact of obstructive sleep apnoea on heart failure with preserved ejection fraction is unknown.

Methods Fifty-eight patients who had heart failure with a left ventricular ejection fraction; ≥50% underwent a sleep study. Brain natriuretic peptide (BNP) levels were determined at enrolment and at one, six, 12 and 36 months after enrolment.

Results Obstructive sleep apnoea was found in 39 patients (67%), and they were all subsequently treated with continuous positive airway pressure. Echocardiography at admission showed that E/E′ tended to be higher in the 39 patients with, than in the 19 patients without, obstructive sleep apnoea (15.0±3.6 vs 12.1±1.9, respectively, P=0.05). The median BNP levels at enrolment were similar in patients with and without obstructive sleep apnoea [median (interquartile range): 444 (233-752) vs 316 (218-703) pg/ml]. Although BNP levels decreased over time in both groups, the reduction was less pronounced in patients with obstructive sleep apnoea (P<0.05). Consequently, BNP levels were higher in patients with sleep apnoea at six months, [221 (137-324) vs 76 (38-96) pg/ml, P<0.05], 12 months [123 (98-197) vs 52 (38-76) pg/ml, P<0.05] and 36 months [115 (64-174) vs 56 (25-74) pg/ml, P<0.05].

Conclusion Obstructive sleep apnoea, even when treated appropriately, may worsen long-term cardiac function and outcomes in patients who have heart failure with preserved ejection fraction.

Keywords Obstructive sleep apnoea • Heart failure with preserved ejection fraction • Left ventricular diastolic function • Brain natriuretic peptide • Long-term prognosis

Introduction

Recent evidence suggests that sleep-related breathing disorders including sleep apnoea syndrome are often present in patients with cardiovascular diseases [1–3], and sleep-related breathing disorders are observed in about 50% of chronic heart failure patients [4]. Central sleep apnoea (i.e., Cheyne-Stokes respiration) is a poor outcome sign in heart failure patients [5]. In addition, obstructive sleep apnoea is also thought to be related to heart failure [6] as well as

*Corresponding author at: Department of Cardiovascular Medicine, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan.
Tel.: +81 282 87 2146; fax: +81 282 86 5633, Email: takuoari@dokkyomed.ac.jp

hypertension [7,8], ischaemic heart disease [9], arrhythmia [10] and sudden death [11]. In patients with heart failure, improvements of cardiovascular function and long-term outcome have been reported with therapy for sleep-related breathing disorders such as oxygen inhalation for central sleep apnoea [12] or continuous positive airway pressure for obstructive sleep apnoea [13,14].

Heart failure with preserved left ventricular ejection fraction (HFPEF), or diastolic heart failure, is commonly found in older and female patients with hypertension. This form of heart failure accounts for approximately 50% of all heart failure cases and has an outcome similar to that of systolic heart failure [15]. Nevertheless, the cause of HFPEF is not well known, and effective treatment has not yet been established [16]. In addition, an association between HFPEF and obstructive sleep apnoea is controversial [17–19].

We hypothesised that the presence of obstructive sleep apnoea in HFPEF may worsen long-term outcomes. To test our hypothesis, we evaluated sleep-related breathing disorders using polysomnography in patients with HFPEF and performed serial measurements of plasma brain natriuretic peptide (BNP) levels during 36 months of follow-up.

Methods

Study Design

The subjects included patients with new-onset heart failure, who were admitted to our hospital with New York Heart Association (NYHA) class III or IV symptoms. Heart failure was determined based on the Framingham Criteria for Congestive Heart Failure [20]. None of these patients were receiving any heart failure therapy prior to admission. After patients were treated with standard heart failure medications as well as oxygen inhalation to improve symptoms to NYHA class I or II, the patients underwent echocardiography, and we selected those with HFPEF, defined as a left ventricular ejection fraction ≥50%. Among the HFPEF patients, those who could undergo a sleep study as well as echocardiographic evaluation of left ventricular diastolic function were enrolled, and then all patients were followed-up for 36 months. Since these patients were followed-up by local medical doctors, most of whom were not cardiovascular specialists, no additional echocardiographic examinations were performed. However, plasma BNP levels were measured serially during the 36-month observation period. Patients with acute myocardial infarction, severe valvular heart disease or a serum creatinine level >1.2 mg/ml were excluded from the study. Informed consent was obtained from each patient in accordance with the requirements of the local ethical committee.

Echocardiography

Transthoracic echocardiography was performed with the patients in the left lateral decubitus position. Two dimensional mode (2D-mode) and M-mode echocardiography, and colour- and tissue-Doppler imaging were conducted using a SONOS 7500 (Philips Ultrasound, Bothell, Washington, WS, USA) or Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) system. Image acquisition was performed by two cardiologists who were unaware of the study design. Wall and valve motion were observed in the 2D-mode, and valvular regurgitation was evaluated by colour-flow imaging. The left atrial diameter was measured in the cross-section of the parasternal long axis, and left ventricular fractional shortening was measured in M-mode in the same cross-section. Left ventricular end-diastolic and end-systolic volumes were determined in the four- and two-chamber apical views using the Simpson's method, and left ventricular ejection fraction was estimated from these results. Left ventricular diastolic transmitral flow was recorded at the mitral valve leaflet in the pulsed-Doppler apical view. The peak early diastolic flow velocity (E), E-wave deceleration time and peak atrial systolic flow velocity (A) were determined based on the blood flow patterns, and the ratio of the E-wave to the A-wave (E/A) was calculated. The early diastolic mitral annular velocity (E′) and atrial systolic mitral annular velocity (A′) were determined at the mitral annular septum in the pulsed-Doppler, four-chamber apical view, and the E to E′ ratio (E/E′) was calculated. These parameters were determined by recording three cardiac cycles under stable conditions, and the mean of the measurements was used for analysis.

Sleep Study

Overnight pulse oximetry was performed while the patients were breathing room air under stable conditions as a screening test for sleep-related breathing disorders. An oxygen saturation monitor (Pulsox-M24®, Konica Minolta Sensing Inc., Osaka, Japan) was attached to the left fourth finger to determine oxygen saturation (SpO_2) and pulse rate from 10 pm to 6 am. The frequency of reduction of SpO_2 by ≥3% per hour (oxygen desaturation index) and the lowest SpO_2 were used as parameters for sleep-related breathing disorders. For the patients who had ≥5 oxygen desaturation index events, portable polysomnography with electroencephalography (Sleep Watcher®, Compumedics Ltd, Abbotsford, Australia) was performed to assess obstructive sleep apnoea. The parameters were analysed by two experienced technicians who were unaware of the study design. A respiratory amplitude reduction ≥50% was defined as hypopnoea and ≥80% as apnoea, and the number of apnoea or hypopnoea events/hour was determined as the apnoea-hypopnoea index. Obstructive sleep apnoea was defined as an apnoea-hypopnoea index ≥5, based on the recommendation of the American Academy of Sleep Medicine Task Force [21].

Determination of Plasma BNP Levels

Blood samples were collected at admission and one, six, 12 and 36 months thereafter. The blood was immediately collected in a test tube containing aprotinin and stored on ice or at 4 °C. After centrifugation on the same day, plasma BNP was determined using a specific immunoradiometric assay kit (Shionoria BNP kit, Shionogi, Osaka, Japan). The assay uses two monoclonal antibodies, which recognise the