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Originals

Influence of Obstructive Sleep Apnea on Diastolic Heart Failure

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SUMMARY

Heart failure is frequently complicated by obstructive sleep apnea, which raises blood pressure and arrhythmia and worsens prognosis. However, the incidence and influence of obstructive sleep apnea in patients with diastolic heart failure is unknown. We hypothesized that patients with diastolic heart failure complicated by obstructive sleep apnea may have a worse outcome compared to those without obstructive sleep apnea. The study included 49 patients with an ejection fraction ≥50 %, of whom 34 had diastolic heart failure and 15 did not have diastolic heart failure. The patients were examined in a sleep study and by echocardiography. Brain natriuretic peptide (BNP) levels were determined at admission and 1, 6 and 12 months thereafter. The prevalence of obstructive sleep apnea in patients with diastolic heart failure (18/34, 53 %) was significantly higher than that in those without diastolic heart failure (3/15, 20 %) ($p=0.032$). BNP levels were high at admission in patients with diastolic heart failure, but then decreased gradually in those without obstructive sleep apnea. However, BNP in patients with diastolic heart failure and obstructive sleep apnea remained high and was significantly elevated compared to the level in patients without obstructive sleep apnea at 6 and 12 months after admission. Patients with diastolic heart failure and obstructive sleep apnea showed prolongation of elevated BNP, indicating that complication of diastolic heart failure by obstructive sleep apnea may aggravate cardiac function.

Key Words : diastolic heart failure, obstructive sleep apnea, brain natriuretic peptide

INTRODUCTION

Diastolic heart failure with a preserved left ventricular ejection fraction is most commonly found in older and female patients with hypertension, and this condition accounts for approximately one-half of all heart failure cases and has an outcome similar to that of systolic heart failure [1,2]. However, the cause of diastolic heart failure is unknown and no effective therapy has been established [3].

Several recent cardiovascular studies have focused on complications of sleep-disordered breathing, including obstructive sleep apnea syndrome [4～6], since sleep-disordered breathing has been observed in 50 % of patients with stable heart failure [7] and the outcome of patients with heart failure accompanied by Cheyne-Stokes respiration is poor [8]. Furthermore, obstructive sleep apnea syndrome has been related to hypertension, ischemic cardiac disease, arrhythmia and sudden death [9～13]. However, there is no consensus regarding the occurrence of diastolic heart failure in patients with obstructive sleep apnea syndrome [14～16] and the

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outcome of diastolic dysfunction complicated by sleep-disordered breathing has not been studied.

In this study, diastolic function was examined by echocardiography in patients with a left ventricular ejection fraction of ≥50 %. The patients also underwent a sleep study and the blood concentration of brain natriuretic peptide (BNP) was measured to assess the effect of respiratory disorders in patients with diastolic heart failure.

METHODS

1. Patients

The subjects were patients with heart failure and a left ventricular ejection fraction of ≥50 % at screening who were admitted to our hospital between January, 2004 and December, 2007. Heart failure was also determined based on a physical examination of clinical symptoms such as dyspnea, moist rale and abnormal heart sounds, and on chest X-rays. Patients were diagnosed with heart failure of New York Heart Association class II, III or IV. The patients were treated for heart failure after admission, and underwent a sleep study and echocardiography when heart failure had improved. Informed consent was obtained from all patients in accordance with the ethical code of Dokkyo University School of Medicine. Patients with acute myocardial infarction, severe valvular heart disease, a serum creatinine level ＞1.2 mg/ml, or body mass index ＞30 were excluded from the study.

Forty-nine patients (36 males and 13 females, mean age : 65 ± 10 years old) were enrolled in the study, comprising 34 with diastolic heart failure and 12 without diastolic heart failure. Blood samples were collected at admission, 1 and 6 and 12 months thereafter. The blood was immediately transferred to a test tube containing aprotinin and stored in ice or at 4°C. After centrifugation on the same day, blood BNP was determined using an enzyme-linked immunoassay kit. The normal level of BNP is＜18.4 pg/ml.

2. Sleep Study

At admission, all patients underwent screening by overnight pulse oximetry while breathing room air under stable conditions. An oxygen saturation monitor (Pulsox-M24® ; Konica Minolta Sensing Inc., JAPAN) was attached to the left fourth finger to determine oxygen saturation (SpO_2) and pulse rate from 10 p.m. to 6 a.m. Data was analyzed with the PULSOX analysis program. The frequency of reduction of SpO_2 by ≥4 % and ≥3 % per hour (oxygen desaturation index) and the lowest SpO_2 were used as parameters for sleep-disordered breathing. Patients with 5 or more occurrences of oxygen desaturation of ≥4 % were examined by portable polysomnography including electroencephalography, electro-oculogram, submental electromyogram, airflow at nose and mouth, and respiratory effort (Sleep Watcher® ; Compumedics Ltd, Abbotsford, Australia) to assess obstructive sleep apnea. The parameters were analyzed by experienced technicians. The diagnosis of obstructive sleep apnea was based on the patients history and data of sleep study, and the apnea-hypopnea index was used as the measure of sleep-apnea severity [17]. In this study, obstructive sleep apnea was diagnosed based on a value of the apnea-hypopnea index ≥5. Patients with an apnea-hypopnea index ≥5 were instructed regarding lifestyle changes, including weight loss. Patients with an apnea-hypopnea index ≥20 were treated with appropriate therapy ; continuous positive airway pressure after giving informed consent, that was maintained during the observation period.

3. Echocardiography

Transthoracic echocardiography was performed with the patients in the left lateral decubitus position. 2D- and M-mode echocardiography and color- and tissue-Doppler imaging were conducted using SONOS 7500 (Philips Ultrasound, Bothell, Washington) and Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) systems. Imaging was performed by at least two cardiologists. Wall motion and valves were observed in 2D-mode and valvular regurgitation was evaluated by color-flow imaging. The left atrial distance 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. The left ventricular end-diastolic volume and left ventricular end-systolic volume were determined in four- and two-chamber apical views and the left ventricular ejection fraction was estimated from these results. Left ventricular diastolic transmitral flow was recorded at the mitral valve leaflet in the pulse-Doppler apical

Table 1 Characteristics of patients with and without diastolic heart failure

	with HF (n=34)	without HF (n=15)	p-value
Age (years)	66 ± 9	63 ± 11	0.21
Male, n (%)	26 (77)	10 (67)	0.48
Heart rate (beats/min)	73 ± 14	76 ± 12	0.42
Systolic blood pressure (mmHg)	138 ± 27	136 ± 16	0.67
Diastolic blood pressure (mmHg)	80 ± 15	78 ± 15	0.6
Body mass index (kg/m^2)	25 ± 3.0	26 ± 2.2	0.42
History of illness, n (%)			
Hypertension	21 (62)	10 (67)	0.34
Ischemic heart disease	16 (47)	3 (20)	0.19
Atrial fibrillation	7 (21)	4 (27)	0.56
Diabetes mellitus	10 (29)	3 (20)	0.89
Hyperlipidemia	9 (26)	4 (27)	0.54
Hyperuricemia	1 (3)	0	0.58
Obstructive sleep apnea	18 (53)	3 (20)	0.032
Medication, n (%)			
Calcium antagonists	13 (38)	7 (47)	0.59
Beta-blockers	11 (32)	1 (7)	0.01
ACE inhibitors	8 (24)	0	0.04
Angiotensin II receptor blockers	24 (71)	9 (60)	0.48
Diuretics	17 (50)	3 (20)	0.05
Aspirin	24 (71)	10 (67)	0.79

HF ; heart failure, ACE, Angiotensin-converting enzyme

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. A wave and E/A could not obtain in the patient of atrial fibrillation (n=7). The early diastolic mitral annular velocity (E') and atrial systolic mitral annular velocity (A') were determined at the mitral annular septum in the pulse-Doppler four-chamber apical view, and the E to E' ratio (E/E') was calculated. In this study, diastolic dysfunction was diagnosed based on a value of E/E' ≥12 to make reference to [18,19]. These parameters were determined by recording at least 3 cardiac cycles under stable conditions and the mean of the measurements was used for analysis.

4. Statistical Analysis

Data are presented as means ± standard deviation. Statistical analysis was conducted using analysis of variance (ANOVA) followed by an unpaired Student *t*-test and chi-squared test using SPSS statistical software, version 14.0. A p-value < 0.05 was considered to be significant.

RESULTS

There were no significant differences in age, heart rate and blood pressure among patients with and without diastolic heart failure at admission, but treatment with β-blockers and diuretics was significantly more frequent in patients with diastolic heart failure (Table 1). The prevalence of obstructive sleep apnea in patients with diastolic heart failure (18/34, 53%) was significantly higher than that in patients without diastolic heart failure (3/15, 20%) (p=0.032), and in the sleep study, these group had a higher apnea-hypopnea index, lowest saturation and higher 3% and 4% oxygen desaturation indices (Table 2). Among the patients with diastolic heart failure, there were no significant differences in clinical characteristics, heart rate, and blood pressure between those with and without obstructive sleep apnea (Table 3).

In echocardiography, the E/E' ratio was higher in patients with diastolic heart failure compared to those

Table 2 Data of sleep study

	OSA with HF (n=18)	OSA without HF (n=3)	p-value
Obstructive apnea index (events/hour)	16.9 ± 16.0	14.7 ± 5.8	0.82
Central apnea index (events/hour)	4.2 ± 6.4	6.6 ± 7.8	0.57
Mixed apnea index (events/hour)	2.7 ± 2.1	9.9 ± 7.7	0.003
Apnea-hypopnea index (events/hour)	36.2 ± 17.1	44.4 ± 5.4	0.45
Lowest O_2 saturation (%)	77.8 ± 10.9	60.4 ± 12.1	0.021
3% oxygen desaturation index*	29.5 ± 15.3	36.0 ± 9.5	0.48
4% oxygen desaturation index**	25.4 ± 15.4	35.3 ± 21.1	0.29

* ; The frequency of reduction of oxygen saturation by 3% per hour. ** ; The frequency of reduction of oxygen saturation by 4% per hour.

Table 3 Characteristics of heart failure patients with and without obstructive sleep apnea

	OSA (+) (n=18)	OSA (−) (n=16)	p-value
Age (years)	67 ± 7	66 ± 11	0.79
Male, n (%)	14 (78)	12 (75)	0.86
Heart rate (beats/min)	77 ± 17	68 ± 9	0.07
Systolic blood pressure (mmHg)	140 ± 30	136 ± 21	0.75
Diastolic blood pressure (mmHg)	82 ± 14	77 ± 16	0.40
Body mass index (kg/m^2)	25 ± 2.5	24 ± 3.5	0.14
History of illness, n (%)			
Hypertension	6 (33)	1 (6)	0.05
Ischemic heart disease	6 (33)	10 (63)	0.09
Atrial fibrillation	11 (61)	10 (63)	0.94
Diabetes mellitus	3 (17)	7 (44)	0.09
Hyperlipidemia	4 (22)	5 (31)	0.57
Hyperuricemia	1 (6)	1 (6)	0.93
Medication, n (%)			
Calcium antagonists	6 (33)	7 (44)	0.55
Beta-blockers	10 (56)	7 (44)	0.51
ACE inhibitors	3 (24)	5 (31)	0.33
Angiotensin II receptor blockers	12 (71)	12 (60)	0.61
Diuretics	10 (50)	7 (10)	0.51
Aspirin	12 (71)	12 (60)	0.61

ACE, Angiotensin-converting enzyme

without diastolic heart failure, but the difference was not significant (Table 4). There were no differences in ejection fraction, fractional shortening, E- and A-waves, E/A ratio, the E-wave deceleration time, and E/E' ratio in patients with diastolic heart failure with and without obstructive sleep apnea (Table 5).

At admission, the concentration of BNP was elevated in patients with diastolic heart failure with and without obstructive sleep apnea (609.8 ± 395.6 and 494.8 ± 628.5 pg/ml, respectively) (Figure 1). In patients with diastolic heart failure without obstructive sleep apnea, the BNP level decreased to 88.8 ± 65.3 pg/ml at 1 month after admission, to 65.4 ± 31.8 pg/ml after 6 months, and to 62.6 ± 48.6 pg/ml after 12 months. In contrast, in patients with diastolic heart failure with obstructive sleep apnea the BNP level remained high at 1279.5 ± 206.2 pg/ml at 1 month after admission, at 224.9 ± 175.7 pg/ml after 6 months, and at 225.1 ± 188.6 pg/ml after 12 months. The BNP levels in heart failure patients with obstructive sleep apnea at 1, 6

Table 4 Echocardiographic findings in patients with and without heart failure

	with HF (n=34)	without HF (n=15)	p-value
Heart rate (beats/min)	66 ± 12	58 ± 15	0.48
Left atrial dimension (mm)	40 ± 7	38 ± 5	0.38
End-diastolic volume (ml)	106 ± 36	95 ± 24	0.40
End-systolic volume (ml)	45 ± 21	36 ± 21	0.19
Ejection fraction (%)	61 ± 8	66 ± 10	0.06
Fractional shortening (%)	33 ± 10	37 ± 9	0.34
E wave (m/s)	0.73 ± 0.26	0.64 ± 0.17	0.25
A wave (m/s)	0.79 ± 0.18 [1)]	0.73 ± 0.17 [2)]	0.26
E/A ratio	0.90 ± 0.41 [1)]	0.88 ± 0.24 [2)]	0.90
E wave deceleration time (ms)	201 ± 50	206 ± 38	0.75
E/E' ratio	15.7 ± 4.9	12.5 ± 0.5	0.05
Valvular regurgitation, n (%)			
Mitral	8 (24)	3 (20)	0.89
Aortic	6 (18)	1 (7)	0.51
Tricuspid	8 (24)	6 (40)	0.14
Pulmonary	6 (18)	2 (13)	1

[1)] ; excluded 6 cases of atrial fibrillation. [2)] ; excluded 1 case of atrial fibrillation. E wave ; mitral valve early diastolic velocity, A wave ; mitral valve late diastolic velocity, E/E' ratio ; ratio of mitral valve velocity to mitral annular early diastolic velocity.

Table 5 Echocardiographic findings in heart failure patients with and without obstructive sleep apnea

	OSA (+) (n=18)	OSA (−) (n=16)	p-value
Heart rate (beats/min)	67 ± 15	64 ± 8	0.46
Left atrial dimension (mm)	41 ± 7	39 ± 7	0.39
End-diastolic volume (ml)	107 ± 37	103 ± 36	0.75
End-systolic volume (ml)	45 ± 19	46 ± 23	0.95
Ejection fractoin (%)	62 ± 8	59 ± 8	0.3
Fractional shortening (%)	34 ± 11	32 ± 9	0.5
E wave (m/s)	0.77 ± 0.25	0.68 ± 0.27	0.32
A wave (m/s)	0.79 ± 0.18 [1)]	0.80 ± 0.18 [2)]	0.84
E/A ratio	0.92 ± 0.43 [1)]	0.88 ± 0.41 [2)]	0.78
E wave deceleration time (ms)	202 ± 52	201 ± 48	0.95
E/E' ratio	15.4 ± 4.5	16.1 ± 5.5	0.72
Valvular regurgitation, n (%)			
Mitral	3 (17)	5 (31)	0.32
Aortic	5 (28)	1 (6)	0.11
Tricuspid	5 (28)	3 (19)	0.55
Pulmonary	3 (17)	3 (19)	0.94

[1)] ; excluded 5 cases of atrial fibrillation. [2)] ; excluded 1 case of atrial fibrillation. E wave ; mitral valve early diastolic velocity, A wave ; mitral valve late diastolic velocity, E/E' ratio ; ratio of mitral valve velocity to mitral annular early diastolic velocity.

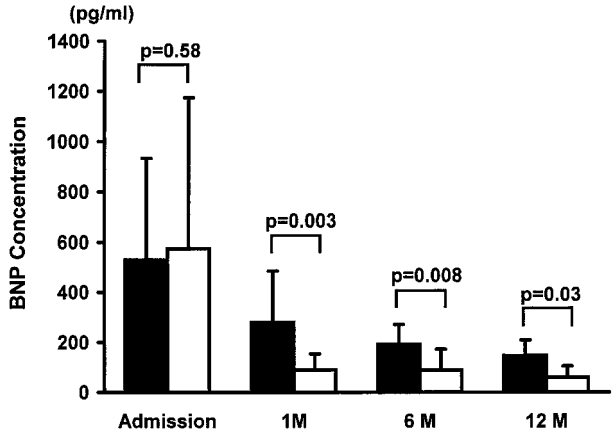

Figure 1 Brain natriuretic peptide concentration of heart failure patients with and without obstructive sleep apnea.

The brain natriuretic peptide (BNP) concentration in heart failure patients with obstructive sleep apnea (■) was significantly higher at 1, 6 and 12 months compared to the respective levels in heart failure patients without obstructive sleep apnea (□). M ; month.

and 12 months after admission were significantly higher than the respective levels in patients without obstructive sleep apnea. In patients without heart failure and obstructive sleep apnea, the BNP level was not significantly elevated and changed during the observation period ; 25.3 ± 13.4 pg/ml at admission, 13.8 ± 13.1 pg/ml at 1 month after admission, 45.0 ± 60.7 pg/ml after 6 months, and 39.0 ± 31.4 pg/ml after 12 months.

DISCUSSION

The results of the study showed that the incidence of obstructive sleep apnea was significantly higher in patients with diastolic heart failure compared with those without diastolic heart failure. Left ventricular diastolic heart failure is observed when left ventricular systolic function is normal, and heart failure guidelines now define diastolic heart failure as "heart failure with a preserved ejection fraction"[20]. Senni et al. reported that 43 % of heart failure patients had diastolic heart failure and that their outcome did not differ from that of patients with systolic heart failure[3]. However, the mortality of diastolic heart failure has gradually increased[1]. The conventional assessment method for evaluation of clinical diastolic function is recording of left ventricular diastolic transmitral flow patterns (E- and A-waves) by pulse-Doppler echocardiography[21], whereas the newest approach uses a combination of this method and recording of the early diastolic mitral annular velocity (E') and atrial systolic mitral annular velocity (A') by tissue-Doppler imaging[18,19].

Sleep apnea syndrome is a common complication in patients with heart failure, and leads to a poor prognosis through elevation of blood pressure and induction of myocardial ischemia and arrhythmia due to increased sympathetic nervous system activity[22]. Obstructive sleep apnea severely influence prognosis and mortality in patients with systolic heart failure[22], and Fung et al. reported that severe obstructive sleep apnea with an apnea-hypoxia index of 40 or higher is related to left ventricular diastolic relaxation[15].

BNP is secreted mainly from the ventricular wall following overload of pressure and volume in the ventricle and extension of the ventricular wall[23]. The BNP level is useful for diagnosis of acute heart failure[24] and diastolic dysfunction[25]. Bursi et al. classified diastolic function into four levels using a combination of pulse- and tissue-Doppler imaging and showed that higher levels of BNP are associated with more severe diastolic dysfunction[26].

In the current study, 39 patients with a mean E/E' ratio of 15.7 and a mean BNP level of 550 pg/ml at admission were diagnosed with diastolic heart failure. Among these patients, the BNP level was significantly higher in those with obstructive sleep apnea at 1, 6 and 12 months after admission for treatment of heart failure. In obstructive sleep apnea, intrathoracic pressure during inspiration is rapidly reduced at night and it is assumed that the increase of venous return and left ventricular afterload may result in overload of pressure and volume in the left ventricle. BNP secretion from the left ventricular wall may be induced by diastolic dysfunction and further increased every night by obstructive sleep-induced increases in venous return and left ventricular afterload mismatching of increased myocardial oxygen demand and decreased oxygen supply caused by apnea. Futher studies are required to elucidate the details of this mechanism.

The study has several limitations. First, patients were treated for obstructive sleep apnea with the therapy of the continuous positive airway pressure during the observation period, but the effect of treat-

ment for obstructive sleep apnea was not assessed in this study. Second, a prospective study would be useful for understanding the influence of obstructive sleep apnea in patients with diastolic heart failure, because the current study was a retrospective investigation. Further studies are required to elucidate the details of the relationship between diastolic heart failure and obstructive sleep apnea, but our results indicate that patients with diastolic heat failure complicated with obstructive sleep apnea may have aggravation of cardiac dysfunction.

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REFERENCES

1) Owan TE, Hodge DO, Herges RM, et al : Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med **355** : 251-259, 2006.
2) Abhayaratna WP, Marwick TH, Smith WT, et al : Characteristics of left ventricular diastolic dysfunction in the community : an echocardiographic study. Heart **92** : 1259-1264, 2006.
3) Senni M, Tribouilloy CM, Rodeheffer RJ, et al : Congestive heart failure in the community. A study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation **98** : 2282-2289, 1998.
4) Wolk R, Kara T, Somers VK : Sleep-disordered breathing and cardiovascular disease. Circulation **108** : 9-12, 2003.
5) Shamsuzzaman ASE, Gersh BJ, Somers VK : Obstructive sleep apnea. Implications for cardiac and vascular disease. JAMA **290** : 1906-1914, 2003.
6) Pack AI : Advances in sleep-disordered breathing. Am J Respir Crit Care Med **173** : 7-15, 2006.
7) Javaheri S, Parker TJ, Liming JD, et al : Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalence, consequence, and presentation. Circulation **97** : 2154-2159, 1998.
8) Hanly PJ, Zuberi-Khokhar NS : Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Respir Care Med **153** : 272-276, 1996.
9) Peppard PE, Young T, Palta M, et al : Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med **342** : 1378-1384, 2000.
10) Nieto FJ, Young TB, Lind BK, et al : Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA **283** : 1829-1836, 2000.
11) Peker Y, Hedner J, Kraiczi H, et al : Respiratory disturbance index. An independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med **162** : 81-6, 2000.
12) Gami AS, Pressman G, Caples SM, et al : Association of atrial fibrillation and obstructive sleep apnea. Circulation **110** : 364-367, 2004.
13) Gami AS, Howard DE, Olson EJ, et al : Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med **352** : 1206-14, 2005.
14) Niroumand M, Kuperstein R, Sasson Z, et al : Impact of obstructive sleep apnea on left ventricular mass and diastolic function. Am J Respir Care Med **163** : 1632-1636, 2001.
15) Fung JWH, Li TST, Choy DKL, et al : Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. Chest **121** : 422-429, 2002.
16) Alchanatis M, Tourkohoriti G, Kosmas EN, et al : Evidence for left ventricular dysfunction in patients with obstructive sleep apnoea syndrome. Eur Respir J **20** : 1239-1245, 2002.
17) Sleep-related breathing disorders in adults : recommendations for syndrome definition and measurement technique in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep **22** : 667-689, 1999.
18) Arques S, Roux E, Luccioni R : Current clinical applications of spectral tissue Doppler echocardiography (E/E' ratio) as a noninvasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. Cariovasc Ultrasound **5** : 16, 2007.
19) Paulus WJ, Tschöpe C, Sanderson JE, et al : How to diagnose diastolic heart failure : a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J **28** : 2539-2550, 2007.

20) ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article. A report of the American College of Cardiology/American Heart Association Task Force on practice guideline (Writing Committee to update the 2001 guidelines for the evaluation and management of heart Failure) Circulation **112** : 1825-52, 2005.
21) Redfield MM, Jacobsen SJ, Burnett JC, et al : Burden of systolic and diastolic ventricular dysfunction in the community. JAMA **289** : 294-202, 2003.
22) Wang H, Parker JD, Newton GE, et al : Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol **49** : 1625-1631, 2007.
23) Kinnunen P, Vuolteenaho O, Ruskoaho H : Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium : effects of stretching. Endocrinology **132** : 1961-1970, 1993.
24) Maisel AS, Krishnaswamy P, Nowak RM, et al : Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med **347** : 161-167, 2002.
25) Lubien E, DeMaria A, Krishnaswamy P, et al : Utility of B-natriuretic peptide in detecting diastolic dysfunction. Comparison with Doppler velocity recordings. Circulation **105** : 595-601, 2002.
26) Bursi F, Weston SA, Redfield MM, et al : Systolic and diastolic heart failure in the community. JAMA **296** : 2209-2216, 2006.