

[ CASE REPORT ]

## A Patient with Heart Failure and Sleep-disordered Breathing Who Presented with Marked Reverse Remodeling by Continuous Positive Airway Pressure Therapy

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### Abstract:

A 49-year-old Japanese man with worsening dyspnea was admitted with the diagnosis of new-onset heart failure (HF). His HF symptoms improved with standard treatment, but his left ventricular ejection fraction (LVEF) 21% remained unchanged. After he was discharged, he was diagnosed with severe sleep-disordered breathing (SDB). Continuous positive airway pressure (CPAP) therapy was introduced. Seven months later, his cardiac function had greatly improved (LVEF 50%). We report this case of a HF patient with SDB whose cardiac function greatly improved by CPAP therapy, and we discuss the pathophysiologic mechanisms of successful cardiac “reverse remodeling” in this case.

**Key words:** heart failure, sleep-disordered breathing, positive airway pressure, reverse remodeling

(Intern Med 56: 2289-2294, 2017)

(DOI: 10.2169/internalmedicine.8525-16)

### Introduction

Sleep-disordered breathing (SDB) including obstructive and central sleep apnea (OSA and CSA) has been observed in from 24-61% of patients with heart failure (1-3). The use of continuous positive airway pressure (CPAP) therapy has been reported to reduce the risk of death and hospitalization in heart failure patients with OSA (4). Moreover, CPAP use ameliorates the cardiac function through mainly decreasing afterload in heart failure patients with OSA (5, 6). However, there are considerable variations among the heart failure patients with OSA regarding the degree of improvement in cardiac function as represented by the left ventricular ejection fraction (LVEF), from only a few percent to more than 20% after CPAP use (7-9). It is not yet known which types of heart failure patients respond well to CPAP (10-12). We herein present the case of a patient with heart failure and SDB whose cardiac function dramatically improved after CPAP therapy was initiated.

### Case Report

A 49-year-old Japanese man with heart failure was referred to our hospital in April 2015. He had been complaining of exertional dyspnea for 1 month and resting dyspnea for 1 week. He had experienced a substantial weight gain over the past 5 years. He was diagnosed to have hypertension 4 years earlier, but had not been treated for it. He had smoked a half-a-pack of cigarettes daily starting 20 years earlier, and drank alcohol occasionally. He had no known family history of heart failure.

On admission, the patient's body height and weight were 170 cm and 94 kg, and his body mass index was 32.5 kg/m<sup>2</sup>. His blood pressure was 142/99 mmHg; pulse rate, 115 bpm; and the oxygen saturation, 99% with 2 L/min via nasal cannula. Auscultation revealed no S3, S4, or audible murmur, and minimal bibasilar coarse crackles were heard. Jugular venous distension and pitting edema in both lower extremities were observed. Blood tests showed a white blood cell count of 10,700/ $\mu$ L, serum creatinine of 1.21 mg/

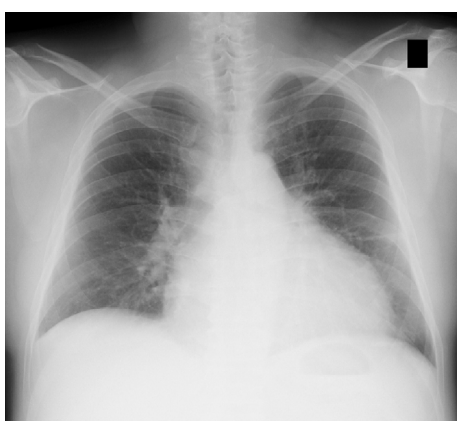
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Received: November 9, 2016; Accepted: January 11, 2017; Advance Publication by J-STAGE: August 10, 2017

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**Table 1. Laboratory Findings on Admission for the Heart Failure Patient.**

WBC	10,700 / $\mu$ L	BNP	599 pg/mL	Plasma epinephrine	32 pg/mL	(<100)*
Neut	82.5 %	CRP	0.52 mg/dL	Plasma norepinephrine	1,441 pg/mL	(100-450)*
Lymph	10.9 %	TP	5.7 g/dL	urinary normetanephrine/creatinine	0.46 $\mu$ g/mgCre	
Mon	5.4 %	Alb	3.3 g/dL	urinary metanephrine/creatinine	0.1 $\mu$ g/mgCre	
Eos	0.8 %	T-Bil	1.1 mg/dL	Plasma renin activity	0.7 ng/mL/hr	(0.2-3.9)*
RBC	520 $\times 10^4$ / $\mu$ L	AST	32 U/L	Plasma aldosterone concentration	120 pg/mL	(30-159)*
Ht	45 %	ALT	42 U/L	Cortisol	12.2 $\mu$ g/dL	(4.0-19.3)*
Hb	14.7 g/dL	CK	176 U/L	TSH	2.051 $\mu$ U/mL	(0.35-4.94)*
Plt	23.7 $\times 10^4$ / $\mu$ L	BUN	22 mg/dL	free T3	2.8 pg/mL	(1.71-3.71)*
		Cre	1.21 mg/dL	free T4	1.18 ng/dL	(0.70-1.48)*
		Na	140 mEq/L			
		K	4.4 mEq/L			

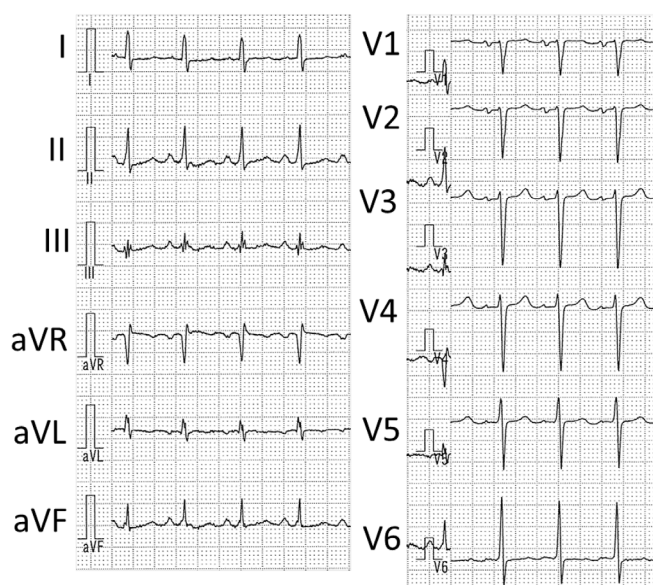
\* represent normal ranges

**Figure 1. Chest radiograph on admission showed cardiomegaly (CTR 65%).**

dL, and brain natriuretic peptide of 599 pg/mL (Table 1). The serum norepinephrine concentration was 1,441 pg/mL (normal range: 100-450 pg/mL), but the results of other endocrine tests were normal. A chest radiograph showed cardiomegaly (cardiothoracic ratio [CTR] 65%; Fig. 1) with congestion. A 12-lead electrocardiogram demonstrated sinus tachycardia, left atrial overload, and clockwise rotation (Fig. 2). Echocardiography on admission showed diffusely reduced left ventricular (LV) contraction: LVEF with modified Simpson's method, 21%; left ventricular end-diastolic diameter (LVDd), 62 mm; left ventricular end-systolic diameter (LVDs), 56 mm; left atrial diameter, 51 mm (Fig. 3). Moderate tricuspid valve regurgitation and mild mitral valve regurgitation were observed.

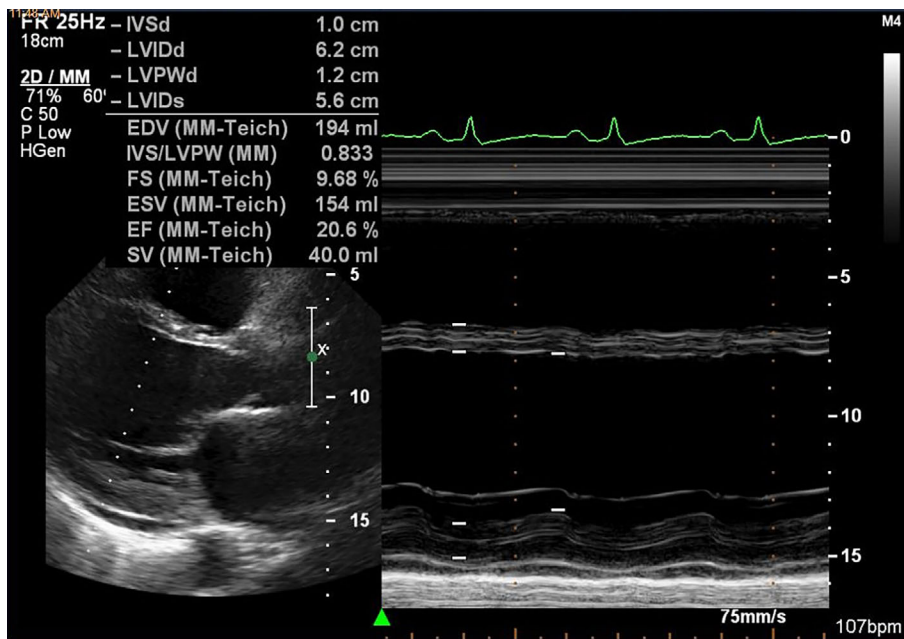
After the patient was hospitalized, he was treated with oxygen inhalation and intravenous (i.v.) furosemide (40 mg). On the 3rd day of admission, i.v. furosemide was changed to an oral dose 40 mg, and enalapril 1.25 mg was started. On the 5th day of admission, bisoprolol 0.625 mg was added and titrated to 1.875 mg. The echocardiography performed on the 14th day demonstrated a still-low LVEF at 25%, LVDd at 66 mm, and LVDs at 58 mm.

Coronary angiography performed on the 17th day revealed no significant coronary stenosis. The right heart

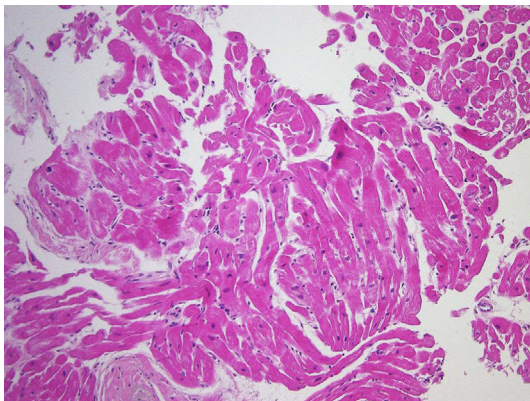
**Figure 2. Twelve-lead electrocardiogram on admission demonstrated sinus tachycardia with a heart rate of 112 bpm, left atrial overload, and clockwise rotation. No ST-T wave abnormality was observed.**

catheterization showed pulmonary capillary wedge pressure (PCWP), 23 mmHg; pulmonary artery systolic/diastolic/mean pressure, 57/23/39 mmHg; right ventricular systolic/diastolic/mean pressure, 54/13/20 mmHg; right atrial systolic/diastolic/mean pressure, 22/19/17 mmHg; and cardiac index, 1.68 L/min/m<sup>2</sup>. An endomyocardial biopsy was performed from the right ventricle, and a histological examination showed mild myocyte hypertrophy, but no particular findings including inflammatory cell infiltration were observed (Fig. 4). According to these findings, it was considered that underlying cause of heart failure had been due to the progression of hypertensive heart disease.

On the 26th day of admission, the patient was discharged from the hospital. Because SDB was strongly suspected based on the patient's wife's report, we administered an overnight apnea test using an unattended portable sleep monitor (SAS-2100; Nihon Kohden, Tokyo, Japan). The re-



**Figure 3.** Echocardiography on admission showed left atrial and LV enlargement with diffuse severe hypokinesis. Moderate tricuspid valve regurgitation and mild mitral valve regurgitation were observed.



**Figure 4.** A histological examination showed mild myocyte hypertrophy, but there was no myocardial disorganization, fibrosis, degeneration, or inflammatory cell infiltration [Hematoxylin and Eosin staining,  $\times 100$ ].

sult of the test was the apnea-hypopnea index (AHI) of 41.2 per hr, 3% oxygen desaturation index of 43.5 per hr, and the lowest oxygen saturation of 64%.

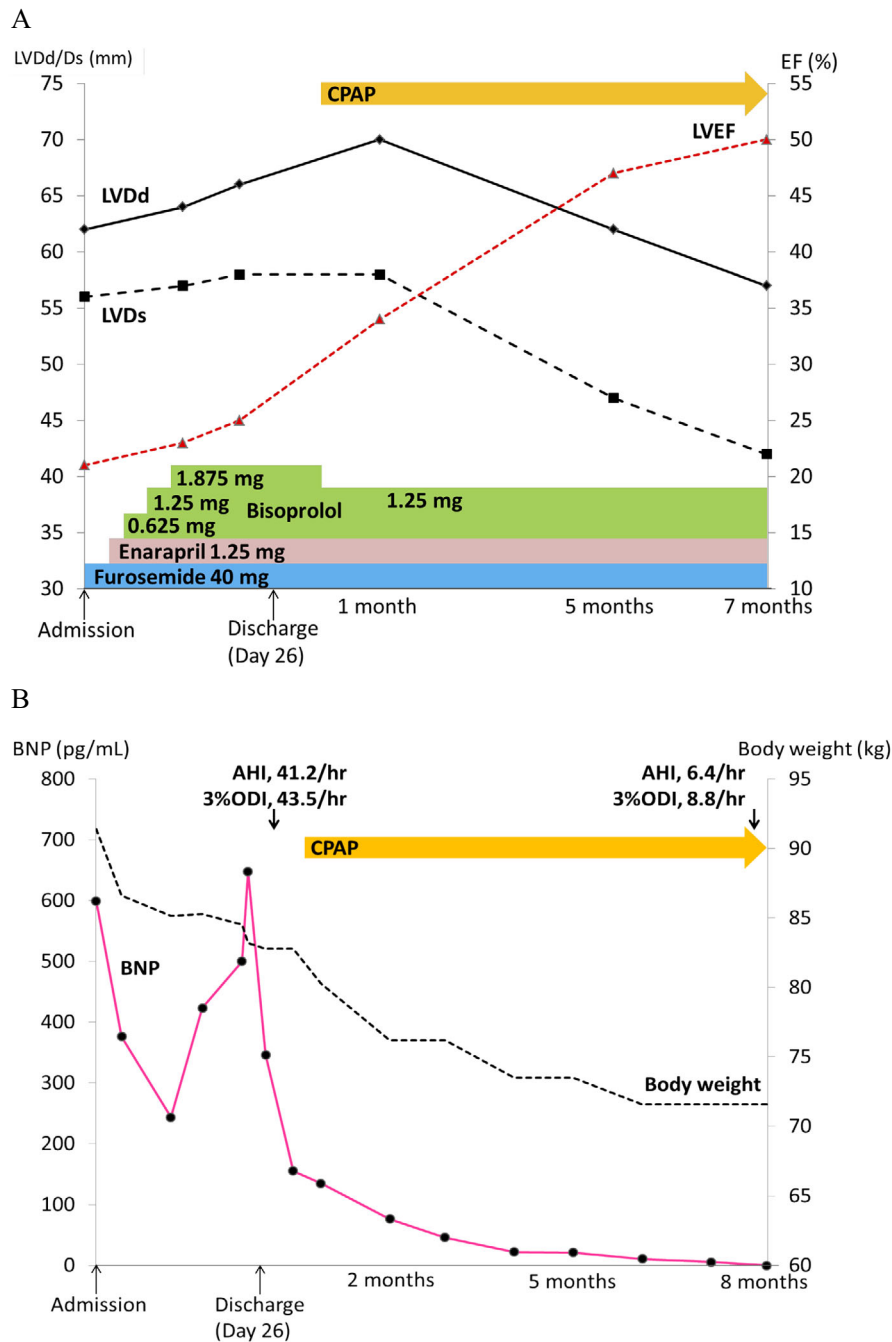
At 3 weeks after the patient's discharge, auto-titrating CPAP (Sleepmate S9 Auto, ResMed, San Diego, CA) was started on an outpatient basis. One month after the introduction of CPAP, the patient's LVEF had increased to 34%. Seven months after the initiation of CPAP, the LVEF had increased to 50%, and the LVDD and LVDs had decreased to 57 mm and 42 mm, respectively (Fig. 5A). In parallel with these parameters, the brain-type natriuretic peptide (BNP) level had dropped to a normal level ( $<10$  pg/mL) (Fig. 5B). In addition, eight months after the start of CPAP, the AHI and 3% oxygen desaturation index without using CPAP had

respectively improved to 6.4 and 8.8 per hr, and the patient's body weight had fallen to 71.6 kg.

## Discussion

We treated a new-onset heart failure patient whose cardiac function dramatically improved after auto-titrating CPAP was initiated for his concurrent severe SDB. Although the standard medications for heart failure ameliorated the patient's subjective symptoms and objective congestive findings, his cardiac function had not improved until CPAP was initiated. Accordingly, we speculate that severe SDB could have had a major pathophysiological influence on the patient's heart failure and that the dramatic improvement in his cardiac function was due to the amelioration of the SDB. Because we performed the sleep apnea test using the unattended portable sleep monitor without polysomnography, the precise classification of SDB in this case is not clear, which is a major limitation associated with this case report. However, his obesity and history of snoring and apnea imply that OSA was the main pathophysiology of his SDB. In fact, the central apnea index analyzing by auto-titrating CPAP device, which was validated previously, during the beginning of treatment was very small number of 1.1 per hr (13). In addition, the restoration of upper airway obstruction through the loss of body weight may also have contributed to the improvement in our patient's cardiac function (14).

When SDB is clinically suspected in patients with heart failure, screening for SDB should be performed. In the following paragraph, we will discuss the effects of CPAP on the cardiac function by focusing on cardiac reverse remodeling and individual differences in the response to CPAP ther-



**Figure 5.** A: The time course of the patient's treatment and echocardiographic parameters during his admission and after discharge. After the introduction of auto-titrating CPAP, the LVDD and LVDs values markedly decreased and the EF value markedly increased. B: The time course of the BNP value and body weight during the patient's admission and after his discharge. After auto-titrating CPAP was initiated, the BNP value and body weight gradually decreased. AHI: apnea-hypopnea index, BNP: brain natriuretic peptide, CPAP: continuous positive airway pressure, EF: ejection fraction, LVDD: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, ODI: oxygen desaturation index

apy.

### The effects of CPAP on cardiac function in OSA patients

In the present case, dramatic reverse remodeling was observed following the introduction of CPAP therapy; the use of auto-titrating CPAP for 6 months increased the LVEF

from 25% to 50% and decreased the LVDD/LVDs from 66/58 mm to 57/42 mm. In previous reports, the extent of LVEF improvement by CPAP was an average of 1% to 12% in heart failure patients with OSA (7-9, 15-18) (Table 2). In addition, CPAP has been reported to reduce the risk of death and hospitalization in patients with heart failure and OSA (4, 19-21).



**Table 2. Changes in LVEF and AHI after CPAP Use in Patients with Heart Failure and Mainly OSA.**

Trial	n	Treatment duration	Mean age	Baseline characteristics			Changes after CPAP use	
				BMI (kg/m <sup>2</sup> )	LVEF (%)	AHI (per hr)	LVEF (%)	AHI (per hr)
15	8	4 wks.	46.9	34.1	37	54.1	12	-53.1
7	12	1 mo.	55.9	30.4	25.0	37.1	8.8	-28.8
8	19	3 mos.	57.2	33.6	37.6	25.0	5.0	-21.1
16	26	6 wks.	61	31	29	36	1	N/A
9	19	6 mos.	58.5	30.2	35.9	30.7	4.7	-17.7
17	28	3 mos.	64	31.7	28.0	43	2.5	-32.9
18	12	1 mo.	56.7	30.3	26.4	30	8.4	-23

AHI: apnea-hypopnea index, BMI: body mass index, CPAP: continuous positive airway pressure, CSA: central sleep apnea, LVEF: left ventricular ejection fraction, OSA: obstructive sleep apnea, SDB: sleep-disordered breathing

Cardiac reverse remodeling, an increase in LVEF and a decrease in the heart chamber size occur in diverse clinical settings, such as the use of beta blockers, an LV assist device, revascularization, and cardiac resynchronization therapy (22). However, the exact mechanism of reverse remodeling is not clear, particularly with regard to the specific molecular pathways. In patients with OSA, CPAP reduces the preload and afterload via an increase in the intrathoracic pressure (12). This leads to a decreased sympathetic nerve activity and a reduction of the myocardial oxygen demand in both the short and long term (5, 6). In the present case, these mechanical, neural and hemodynamic factors in addition to the administration of a beta blocker, which is the standard therapy for heart failure, may be associated with the reverse remodeling.

### Who benefits from CPAP therapy?

In our patient's case, the LVEF increased from 25% to 50% after the introduction of CPAP, which is larger increase than that in previous reports (7-9, 15-18). However, the extent of the change in LVEF after CPAP has been reported to range from only a few percent to more than 20% among patients with heart failure and OSA (7-9).

The exact mechanism underlying the responsiveness to CPAP is not clear. Yamada et al. showed that the PCWP, pulmonary artery systolic pressure, and right atrial pressure values were significantly higher in responders than in non-responders to positive airway pressure devices (10). It was also reported that CPAP increased the cardiac output in heart failure patients with high PCWP, and cardiac output was decreased in those with low PCWP (11, 12). Thus, heart failure patients with high preload and low cardiac function obtained more benefits from CPAP than those with a low preload. Because our patient had a low LVEF with a high PCWP of 23 mmHg, he could be classified as a 'CPAP responder' based on the above-mentioned studies (11, 12).

When standard medications do not sufficiently improve a heart failure patient's cardiac function, screening for SDB should be performed. Concurrent SDB identified in heart

failure patients should be treated using CPAP as recommended in the recent guidelines of the European Society of Cardiology (23). Particularly in heart failure patients with high PCWP, we strongly recommend the use of CPAP therapy.

### Conclusion

We treated a patient with new-onset heart failure with SDB who achieved a dramatic improvement in his cardiac function and showed cardiac reverse remodeling by CPAP therapy in addition to standard medications. In patients with heart failure, especially in those with a high preload, CPAP therapy can be a powerful strategy to improve both cardiac function and morphology. Because patient adherence to CPAP therapy is relatively low, further investigations are needed to clarify the characteristics of heart failure patients with SDB who respond well to CPAP therapy.

**The authors state that they have no Conflict of Interest (COI).**

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