Is Mixed Apnea Associated with Non-Rapid Eye Movement Sleep a Reversible Compensatory Sign of Heart Failure?

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Patient: Male, 24
Final Diagnosis: Dilated cardiomyopathy
Symptoms: Biventricular heart failure • sleep apnea
Medication: —
Clinical Procedure: Heart transplantation
Specialty: Cardiology

Objective: Unusual or unexpected effect of treatment

Background: Sleep-disordered breathing is common in heart failure (HF), and prolonged circulation time and diminished pulmonary volume are considered the main possible causes of sleep apnea in these patients. However, the impact and interrelation between sleep apnea and HF development are unclear. We report the case of a patient with complete elimination of non-rapid-eye-movement (NREM) sleep-associated mixed apnea in HF after heart transplantation.

Case Report: After unsuccessful 12-month conventional treatment with abrupt exacerbation of biventricular HF IV class (according to New York Heart Association Functional Classification), a 26-year-old man was admitted to the hospital. Based on a comprehensive examination including endomyocardial biopsy, dilated cardiomyopathy was diagnosed. Heart transplantation was considered the only possible treatment strategy. Polysomnography showed severe NREM sleep-associated mixed sleep apnea [apnea-hypopnea index 43/h, in rapid eye movement (REM) sleep 3.7/h, in NREM sleep 56.4/h, mean SatO2 93.9%], and periodic breathing. One-month post-transplantation polysomnography did not show sleep-disordered breathing (apnea-hypopnea index 1.0/h; in REM sleep – 2.8/h, in NREM sleep 0.5/h, mean SatO2 97.5%). The patient was discharged from the hospital in improved condition.

Conclusions: NREM sleep-associated mixed apnea occurring in severe systolic HF due to dilated cardiomyopathy might be reversible in case of successful HF treatment. We suggest that mixed sleep apnea strongly associated with NREM sleep occurs in HF, when the brain centers regulating ventilation are intact, and successful HF compensation might be highly effective regarding sleep-breathing disorders without non-invasive ventilation. This is important to know, especially with regard to the recently published data of potentially unfavorable effects of adaptive servoventilation in systolic HF, and the lack of other treatment options.

MeSH Keywords: Cardiomyopathy, Dilated • Heart Failure • Heart Transplantation • Sleep Apnea Syndromes • Noninvasive Ventilation

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Sleep-disordered breathing is known to be associated with cardiovascular diseases and complications: it is an independent risk factor for hypertension, and it also increases risk of coronary heart disease, heart rhythm disorders, and cerebrovascular events [1–5]. However, the data regarding a relation between sleep-disordered breathing and heart failure (HF) are more disputable. On the one hand, there is an evident association between HF and abnormal breathing patterns, and in particular, with Cheyne-Stokes and periodic breathing, which are considered central types of apnea. These central breathing patterns are assumed to be linked to poor prognosis, as well as more severe and terminal states [6–9]. Recent evidence has shown a beneficial effect of the successful treatment of sleep-disordered breathing on cardiac function. On the other hand, there are singular observations of sleep apnea attenuation in patients with improved HF [6–8]. Recently preliminary results of a randomized, controlled trial warn about possible unfavorable prognostic effects of sleep apnea treatment in HF. Thus, the association of sleep-disordered breathing with prognosis and HF treatment remains controversial. We present a case of complete elimination of non-rapid eye movement (NREM) sleep-associated mixed sleep apnea after heart transplantation, with discussion of possible mechanisms and treatment options.

### Case Report

A male 26-year-old man was admitted to the hospital with progressive worsening of biventricular HF IV class (according to New York Heart Association Functional Classification). In the past, at age 24 years, dilated cardiomyopathy was diagnosed after acute viral myocarditis. A year later the patient had a respiratory infection, leading to HF worsening. Despite the multicomponent conventional treatment (Table 1), at 1-year follow-up biventricular dysfunction had progressed significantly.

On admission the physical examination demonstrated the following: weight – 68.7 kg, height – 177 cm; body mass index – 21.93 kg/m² (normal), skin was normal in appearance, texture and temperature, and mucous membranes were moist and pale-pink, and icteric sclera. No lymphadenopathy or thyromegaly were found. There was lower-limb edema up to the proximal part of the shins. Cardiac system: sinus rhythm, 97 beats per minute, blood pressure – 90/60 mmHg in sitting position, 80/50 mmHg while standing. At auscultation S1, S2 were muffled, and systolic murmur was auscultated on the apex. Chest was symmetric, moderate both-sided bubbling rales were auscultated, and there was a right-sided dullness of the sound. The abdomen was symmetrical without distention, soft and non-tender; bowel sounds were normal in quality and intensity in all areas. Hepatomegaly (+2 cm) was found, but there was no splenomegaly. Other vital signs were normal.

#### Table 1. Medication treatment at different time points.

| Type of medication | Before admission to the hospital | At the hospital and intensive care unit | At discharge (after heart transplantation) |
|--------------------|----------------------------------|----------------------------------------|-------------------------------------------|
| Diuretics          | Loop diuretics                  | Combined diuretic therapy:             |                                           |
|                    | Spironolactone                  | Loop diuretics                         |                                           |
|                    |                                 | Aldosterone antagonists                |                                           |
|                    |                                 | Acetazolamide intermitently            |                                           |
| Inotropics         | –                                | Combination of dobutamine              | –                                         |
|                    |                                  | and adrenaline                         |                                           |
| Anticoagulants     | –                                | Anticoagulants (enoxaparin),           | Warfarin was discontinued                 |
|                    |                                  | later changed to warfarin              | 1 year after pulmonary thromboembolism   |
| Other cardiovascular medications | Angiotensin converting enzyme inhibitors | Beta-blockers                         |                                           |
|                    | Beta-blockers                   | Angiotensin converting enzyme inhibitors |                                           |
|                    |                                  | Amiodarone                             |                                           |
| Other              | Immune globulin                 | –                                      | Tacrolimus                                |
|                    |                                  |                                        | Methylprednisolone                        |
|                    |                                  |                                        | Gastroproctor                             |
|                    |                                  |                                        | Valganciclovir                            |
|                    |                                  |                                        | Calcium-vitamin D                         |

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Blood tests are summarized in Table 2, revealing moderate normochromal anemia and mild hypoproteinemia; N-terminal pro-brain natriuretic peptide was significantly elevated.

During hospitalization, based on a comprehensive examination, familial (genetic), endocrine, ischemic, and other potential causes of dilated cardiomyopathy were excluded. The patient had no history of smoking, alcohol and/or drug abuse, confirmed by negative test results.

Electrocardiography showed sinus rhythm, 99 beat per minute, and complete right-bundle branch block. Baseline echocardiography (on admission) showed extremely low ejection fraction, significant enlargement of all cardiac chambers, eccentric left ventricular hypertrophy, and significant tricuspid and mitral insufficiency (Table 3). Hepatomegaly, ascites, and right-sided hydrothorax were verified by ultrasound.

Right heart catheterization showed decreased cardiac index (2.1 l/min/m²) and stroke volume (40 ml/beat), increased pulmonary artery pressure (43/33/21 mmHg), transpulmonary gradient (12 mmHg), and pulmonary vascular resistance (2.7 Wood). Right ventricular endomyocardial biopsy did not verify acute myocarditis, but post-myocarditis changes were found (Table 4).

Within a complex examination, due to the witnessed apneas, full polysomnography was performed. It showed severe mixed sleep apnea (apnea-hypopnea index – 43/h, mean \(O_2\) saturation – 93.9%) and periodic breathing [10]. A strong association between sleep-disordered breathing and NREM sleep was found: in rapid eye movement (REM) sleep apnea-hypopnea index – 3.7/h, in NREM sleep – 56.4/h (Figure 1A).

### Table 2. Laboratory analyses at baseline and after heart transplantation.

| Parameter                          | Baseline, on admission | One month after heart transplantation | Reference values |
|-----------------------------------|------------------------|---------------------------------------|------------------|
| **Clinical blood analysis**       |                        |                                       |                  |
| Hemoglobin, g/l                   | 96.0                   | 161.4                                 | 130–160          |
| Red blood cells, 10¹²/l           | 3.17                   | 4.87                                  | 4.00–5.00        |
| Hematocrit, %                     | 28.3                   | 46.1                                  | 40.0–48.0        |
| Platelets, 10⁹/l                  | 142                    | 292                                   | 180–320          |
| White blood cells, 10¹²/l         | 9.0                    | 6.9                                   | 4.0–9.0          |
| **Biochemistry**                  |                        |                                       |                  |
| C-reactive protein, mg/l          | 70.55                  | 0.57                                  | 0.00–5.00        |
| Total protein, g/l                | 57.00                  | 65.00                                 | 64.00–83.00      |
| Albumin, g/l                      | 34.0                   | 42.0                                  | 35.00–50.00      |
| Creatinine, mcmol/l               | 112                    | 75                                    | 64–111           |
| eGFR, ml/min/1.73 m²              | 73.15                  | 109                                   | >60              |
| Alaninaminotransferase, IU/l      | 20.0                   | 14.0                                  | 0.0–55.0         |
| Aspartataminotransferase, IU/l     | 47.0                   | 14.0                                  | 5.0–34.0         |
| N-terminal pro-brain natriuretic peptide, pg/ml | 2071.00                | –                                     | 0.00–125.00      |
| Myoglobin, ng/ml                  | 204.2                  | –                                     |                  |
| Glucose, mmol/l                   | 6.5                    | 4.55                                  | 3.89–5.83        |
| **Blood gases and acid-base balance (arterial)** |                        |                                       |                  |
| pH                                | 7.46                   | –                                     | 7.35–7.45        |
| pCO₂, mmHg                        | 31                     | –                                     | 32–48            |
| \(\text{sO}_2\)%                   | 98                     | –                                     | 95–99            |
| HCO₃⁻ (P), mmol/l                 | 19                     | –                                     | 21–28            |
| BE, mmol/l                        | –5.5                   | –                                     | –2.5–2.5         |
In light of unsuccessful conventional therapy and HF progression despite intensive care, orthotopic heart transplantation was considered the only possible treatment strategy. The operation and postoperative period were successful, and ejection fraction was 53% and 62% at early and 1-month postsurgery follow-up (Table 2), respectively. No signs of HF were present and immunosuppression therapy was started (Table 1). Repeated endomyocardial biopsies did not show acute cellular rejection (Table 4, Figures 2–4). Based on pathology data, primary dilated cardiomyopathy as a result of lymphocyte myocarditis was verified (Figures 2–5).

The repeated polysomnography (1 month after the operation) did not show sleep-disordered breathing (apnea-hypopnea...
In this reported case, severe sleep apnea of the evident central origin was observed during NREM sleep in a patient with severe systolic HF; it completely disappeared after successful treatment of HF and restoration of cardiac systolic function.
The prevalence of sleep apnea in systolic HF is 50% and higher, and, according to some authors, it is associated with worse outcomes [6]. However, the data on the effects of HF treatment, including heart transplantation, on sleep apnea are controversial, and sleep-stage-dependency of sleep-disordered breathing has not received much research attention.

The pathophysiology of sleep apnea in HF includes combinations of different mechanisms. Hypoxia and hypocapnia (due to high respiration rate), prolonged circulation time, and diminished pulmonary volume are considered possible causes, although they are not themselves pathogenetic mechanisms [6]. Recently, White and Bradley suggested a novel theory of sleep apnea development in states associated with fluid-retention (such as HF) [11], giving some new insights into the classical concept of central breathing patterns in HF. According to this hypothesis, posture-dependent fluid shift (from legs to upper body) due to gravity can augment venous return to the thorax and heart, increasing pulmonary capillary wedge pressure, pulmonary congestion, and interstitial pulmonary edema. These factors lead to hyperventilation, thus decreasing PCO₂ below the apnea threshold [6,9,11] causing cessation of breathing, which in turn results in CO₂ accumulation, chemoreceptor activation, and respiration resumption. The impaired chemosensitivity observed in HF causes higher ventilation response and more abrupt fluctuations [6]. In our patient, pulmonary thromboembolism further decreased the ventilation volume, worsening hypoxia and hypercapnia and leading to hyperventilation, thus contributing sleep apnea onset.

There is an evidence of sleep-stage dependent differences of ventilator control. Ventilation during sleep, especially in NREM-sleep, is thought to be dependent on chemoreceptor stimulation associated with arterial PCO₂ level, and apneic threshold plays a pivotal role. This was confirmed in animal models, and is assumed to be a possible mechanism of sleep apnea onset.
in HF [12,13]. In contrast, in REM sleep, ventilator responses to the changes in PO$_2$ and PCO$_2$ are less prominent, which can lead to a more stable breathing pattern during this sleep phase, as observed in our patient [6,14,15].

The prognostic role and possible treatment of central and mixed sleep apnea in HF need further clarification. There is rather contradictory evidence of the effects of oxygen and there are few medication options (including acetazolamide, and theophyllines) for sleep-disordered breathing [6]. Positive airway pressure therapy, especially adaptive pressure support ventilation, seemed promising, although low compliance is common in HF patients. However, preliminary results of the SERVE-HF study demonstrating higher cardiovascular mortality rate in patients with systolic HF who used the devices compared to non-users (10% vs. 7.5%, respectively), prompted discussion about the possible role of central breathing patterns in systolic HF being somehow protective [16]. There are reports showing improvement or complete elimination of sleep-disordered breathing following successful treatment of HF, including medications, biventricular assist devices, and heart transplantation [6,17,18], although the data on sleep-stage association of sleep-breathing disorders is lacking. Our case report confirms the possibility of the complete elimination of NREM-associated mixed sleep apnea after successful treatment of severe systolic HF by heart transplantation.

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Conclusions and Implications for Clinical Practice

Our clinical case demonstrates that NREM sleep-associated mixed sleep apnea occurring in patients with severe systolic HF due to dilated cardiomyopathy is reversible in case of successful elimination of HF. We suggest that it might be a marker of HF and the possible mechanisms of sleep apnea elimination include improvement of systolic heart function, decrease in circulation time, and beneficial changes in neurohumoral regulation, which play pivotal roles in ventilation control, especially during NREM sleep.

Thus, we strongly suspect that NREM sleep-associated mixed sleep apnea occurs at initial stages of HF, when the brain centers regulating ventilation are intact, and that compensation of HF might be highly effective in NREM sleep-associated mixed sleep apnea without non-invasive ventilation. This is important to know, especially with the regard to the recently published data of potentially unfavorable effects of adaptive pressure support support servoventilation in systolic HF, and the lack of other treatment options.

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