LETTER TO THE EDITOR

Cheyne-stokes respiration associated with hypertrophic cardiomyopathy and normal left ventricular ejection fraction

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INTRODUCTION

Cheyne-Stokes respiration (CSR) is a form of periodic breathing in which central apneas and hypopneas alternate with periods of hyperventilation, producing a waxing and waning pattern of tidal volume. This brief case described an interesting association of CSR and hypertrophic cardiomyopathy (HCM) in a patient with normal left ventricular ejection fraction, providing physiological insights for the genesis of CSR.

CASE DESCRIPTION

A 64-year-old male patient was admitted for a routine cardiac evaluation with complaints of witnessed apnea during sleep. He had previous history of HCM and permanent atrial fibrillation. He was on regular use of carvedilol 50 mg/d; enalapril 40 mg/d, furosemide 80 mg/d and warfarin 5 mg/d and was on NYHA stage III heart failure. Echocardiography demonstrated interventricular septum wall thickness of 20 mm and posterior wall thickness of 11 mm, without left ventricle outflow tract obstruction. The left ventricle ejection fraction was in the normal range (69%). The right ventricle systolic pulmonary pressure was 35 mmHg. Echocardiographic diastolic function evaluation was impaired due to atrial fibrillation. Technetium (^{99m}Tc) radionuclide ventriculography showed normal biventricular systolic function and a median pulmonary transit time of 13 seconds (normal <10 seconds), denoting diastolic dysfunction. Cardiac nuclear magnetic resonance also demonstrated normal global biventricular function. Arterial blood gas while awake showed pH:7.41; pCO_2:33 mm Hg; paO_2: 78 mm Hg; Sat: 97%; HCO_3: 20.6 mMol/L; BE: -2.6 mMol/L. A full-overnight polysomnography indicated a sleep efficiency of 95% with predominantly light sleep (9.9% of stage 1, 75.9% stage 2, 4% of delta sleep (non REM stage 3/4) and 10.2% stage REM). The study showed an apnea-hypopnea index of 34.3 events per hour divided in: obstructive apneas = 8; central apneas = 12.1; mixed apneas = 5.3 and hypopneas = 8.9 events/

hour. CSR pattern of breathing was present during the entire night (Figure 1). The respiratory pattern characteristics were averaged over 10 consecutive cycles of apnea at stage 2 sleep and the results are presented as mean±SD. Hyperpnea duration was 42±3 seconds (calculated as the time between the beginning of inspiration during the ventilatory cycle and the onset of the subsequent apnea). Apnea duration was 19±3 seconds (defined as the time between the end of inspiration of the breath preceding a central apnea and the onset of inspiration of the breath terminating the apnea) resulting in a cycle duration of 62±5 seconds (calculated as the sum of the hyperpnea and apnea durations). The circulation time from the lungs to the peripheral chemoreceptors was increased (29±2 seconds-estimated by measuring the lung-to-ear circulation time [LECT]), which is the time from the first breath after a central apnea to the subsequent nadir of SaO_2 detected at the ear by an oximeter. This measure reflects the circulatory delay due to cardiac dysfunction.

DISCUSSION

HCM is the most common hereditary cardiac disease and is characterized by left ventricular hypertrophy that may lead to diastolic heart failure. The annual rate of sudden cardiac death, the most feared complication of HCM, ranges from 0.5% to 1.5% per year for most age groups.[1] We have recently reported a high prevalence of obstructive sleep apnea in 80 consecutive patients with HCM.[2] Obstructive sleep apnea was independently associated with heart remodeling and atrial fibrillation in this population.

In patients with systolic heart failure, CSR is an independent marker of poor prognosis[3] and may be part of a vicious cycle, further stressing the failing heart in patients with congestive heart failure. CSR is characterized by a prolonged waxing and waning pattern of breathing interposed by central apneas. CSR has been extensively described among patients with systolic congestive heart failure with low ejection fraction. The prevalence of CSR among patients with systolic congestive heart failure is strikingly high and ranges from 30% to 50%.[3] One of the key features of CSR is hyperventilation and low arterial $PaCO_2$ that, when it falls below the apnea threshold during sleep, triggers central apneas.[4] Patients with CSR present a low $PaCO_2$ both awake and asleep. Our patient also presented a low awake $PaCO_2$ (33 mmHg). The mechanisms leading to
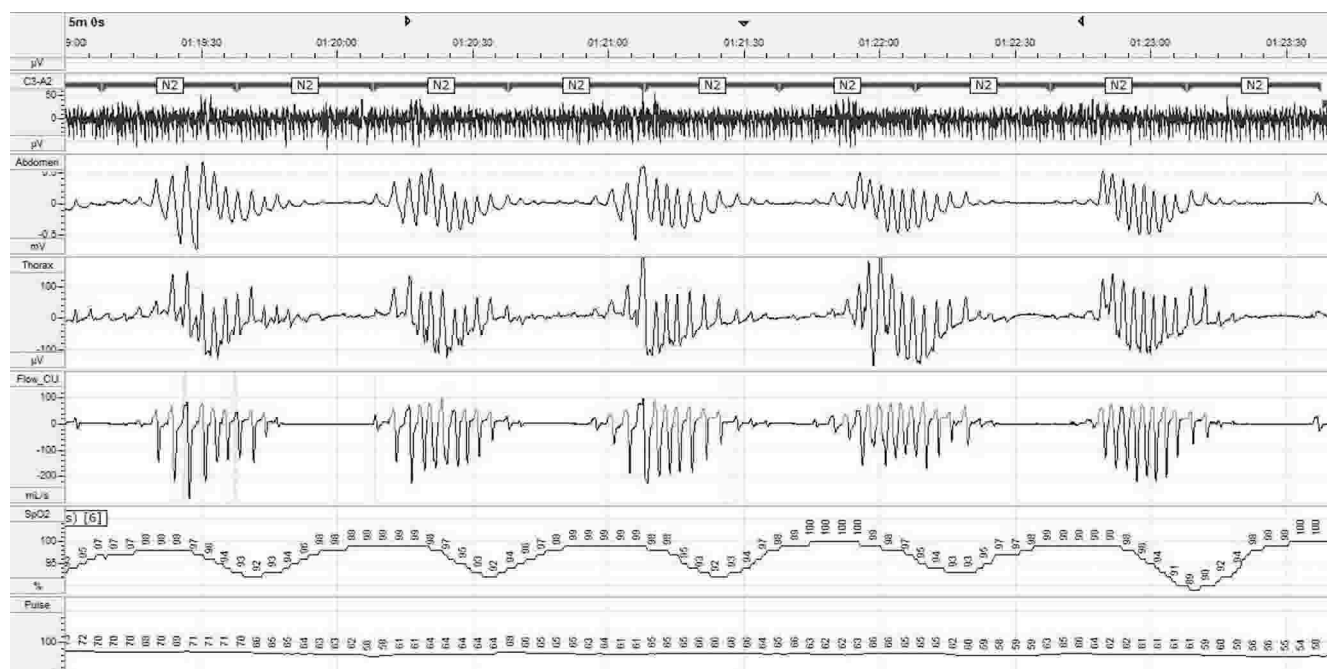
Figure 1 - Polysomnographic recording (5 minutes tracing) of an HCM patient with normal left ejection fraction presenting a Cheyne-Stokes respiration during sleep. The patient was on stage 2 sleep; top channel is related to sleep recordings. ←The following channels, from top to bottom, trac respiration by monitoring motion of the thorax, abdomen, respiratory flow (nasal canulla), ear lobe oxymetry, and derived heart rate. Black arrows show how the circulation time is measured (time from the first breath after a central apnea to the subsequent nadir of SaO$_2$ detected at the ear by an oximeter).

hyperventilation are not completely understood. Increased pulmonary capillary vascular pressures may trigger hyperventilation through stimulation of pulmonary vagal afferent-nerve activity. Left ventricular systolic dysfunction has been suggested as the cause of pulmonary congestion, but diastolic dysfunction could also lead to pulmonary congestion. Diastolic dysfunction has also been associated with increased hypercapnic ventilatory responsiviness.[5] Increased chemorreflex could contribute to respiratory instability due to increased loop gain.[3] A previous study that evaluated 20 patients with diastolic dysfunction found that 2 patients presented central sleep apnea and CSR pattern of breathing.[6] The present case report extends these findings by showing that CSR may also be present in patients with HCM. To the best of our knowledge, this is the first time this association was presented in a patient with hypertrophic cardiomyopathy and normal systolic function. It is important to stress, however, that the presence of atrial fibrillation is a marker for loss of atrial contraction and poor cardiac pumping function and may contribute to the genesis of CSR in the present case.[7] Atrial fibrillation is 8 times more common among patients with central sleep apnea than among normal controls.[8] Another important finding encountered in this patients that helps explain the respiratory pattern is that mean pulmonary transit time was prolonged, denoting increased circulation time, a hallmark of CSR, previously described in association with systolic dysfunction. It also has been found that the duration of hyperpnea is directly proportional to the lung to peripheral chemoreceptor circulation time, and inversely proportional to cardiac output. Patients with heart failure and CSR present with the periodic cycle duration averaging approximately 60 seconds, compared with only 35 seconds in patients with

idiopathic central sleep apnea or high-altitude periodic breathing without heart failure.[9] Hall et al.[10] compared central apnea in patients with normal systolic function versus patients with systolic dysfunction. While the duration of apnea was similar, patients with normal heart function presented a significantly shorter hyperpnea and cycle length time than patients with systolic dysfunction. The investigators concluded that prolonged periodic breathing cycle and hyperpnea durations, typical of CSR, are a consequence of left ventricular systolic dysfunction, low cardiac output, and prolonged circulation time. However, the patient described presented values of cycle length, apnea length, and LECT similar to those described in patients with CSR and heart failure due to systolic dysfunction:[11] hyperpnea time (42 ± 3 vs 35 ± 7), apnea time (19 ± 3 vs 27± 3), cycle length (62 ± 5 vs 62 ± 10) and LECT (29 ± 2 vs 27 ± 3). Therefore, we extend the concept proposed by Hall et al.[10] by showing that prolonged circulation time can also occur in patients with normal left ventricular systolic function but impaired left ventricular diastolic function. We conclude that patients with normal left ventricular function but with severe diastolic dysfunction and atrial fibrillation may present the typical CSR.

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