

Exertional and nocturnal periodic breathing after successful cardiac transplantation. A case report

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Abstract

We present a case report of a heart failure patient who underwent cardiopulmonary exercise testing and sleep screening 12 months before and after heart transplantation (HTx). Severe Cheyne-Stokes respiration (CSR) with central sleep apnoea (CSA) was identified either before and after HTx, while periodic breathing during exercise vanished. We suggest that optimization of

hemodynamics and medical therapy (low dose of diuretic) did not withdraw the central mechanisms underlying the diathesis for CSR-CSA. While periodic breathing during exercise reversal may support a closer link with an exertional central hemodynamic. This observation indirectly neglects the possible unifying mechanistic background of CSR and periodic breathing, during exercise, in this setting.

Introduction

Heart transplantation (HTx) has been a life-saving and life-extending intervention for end-stage heart failure patients since the 1980s [1]. Periodic breathing disorders (PBD) might be uncovered at rest, during exercise and overnight in heart failure, due to left ventricular dysfunction (HFrEF). Although sleep Cheyne-Stokes respiration (CSR) with central sleep apnoea (CSA) and exertional periodic breathing (EOV) are independently linked to mortality [2], when EOV is associated to CSR-CSA has a particular worst outcome connate [3].

CSR and EOV are uncommon if left ventricular ejection fraction (LVEF) is above 40: causes of CRS-CSA may be prolonged circulation time, pulmonary congestion with diminished pulmonary gas stores, or consecutive “underdamping” of breathing control, or a combination of these [4]. Increased respiratory drive as well as changed chemosensitivity of chemoreceptors are main factors, too.

We describe a case report on the effect of successful HTx on both PBD, daily (during exercise) and nocturnal.

Case Report

R.S. is a male and he was born in October 1941. An ischaemic cardiomyopathy was diagnosed in 1999 and at the age of 60 years, a triple vessel myocardial revascularization was undertaken. In 2006, he was on optimal pharmacological therapy, in NYHA class II, free of angina pectoris. Ambulatory sleep screening (SS) study and cardiopulmonary exercise testing (CPET) were completed, as described elsewhere [3]. Chest X-ray was defined as normal. EOV and CSR-CSA were identified.

CSA was defined as cessation of airflow lasting at least 10 seconds, in absence of flow and thoraco-abdominal movements while hypopnea was defined as $\geq 50\%$ decrease in the sum of thoraco-abdominal movements lasting ≥ 10 seconds, followed by a reduction in oxygen blood saturation (SaO₂) of at least 4%; CSR was defined as periodic waxing and waning of the depth of respiration with regularly recurring periods of apnoea or hypopnea [2].

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Consent for publication: The patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

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Key words: heart transplantation; Cheyne-Stoke respiration; exertional periodic breathing.

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EOV was visually determined by cyclic fluctuations in minute ventilation, lasting more than 66% of the exercise duration and with an amplitude of more than 15% of the average amplitude of cyclic fluctuations at rest [5].

In 2007, he complained intractable muscle fatigue and breathlessness in NYHA Class III-IV: the clinical course was further deteriorated by repeated sustained ventricular beats occurrences. On August 13th, 2007, he underwent an orthotropic HTx. In October 2008, the patient was in NYHA class I, on cyclosporine, mycophenolate mofetil, furosemide (12.5 mgr, daily), enalapril (10 mg daily), aspirin, atorvastatin. After HTx, CPET and SS were repeated with the same modality, as before: data are reported in Table 1. EOV disappeared while CSR-CSA was confirmed after HTx, although circulatory and cycle length were (marginally) reduced. Chest radiography was normal. In 2010, CSR-CSA was still preserved, and it was corrected with Auto-Titrating Positive Airway Pressure (At-PAP) treatment.

After almost 10 years (2019), the patient is still alive. He had asymptomatic HF_rEF: he underwent myocardial revascularization with angioplasty of interventricular anterior vessel on 2015, November 6th, and of right coronary on 2017, February 10th.

The recipient suffered diabetes mellitus not insulin-dependent, that can confuse the clinical scenario of vasculopathy graft.

Discussion

Few experiences had evaluated PBD before and after HTx. This case report confirms that EOV is sensible to HTx [5], highlighting a relationship between the degree of hemodynamic improvement: none of the recipients had EOV during exercise [7], when Kremser's criteria are assumed [4]. Improvement of cardiac function by HTx might abolish CSR [4,8-9]; most of the patients

Table 1. Clinical, spirometric and sleep characteristics of the heart failure patient's (1-year) pre- and post-heart transplantation (HTx).

	Pre-HTx	Post-HTx
Age (years)	61	62
Body mass index (kg/m ²)	24.6	26.6
NYHA functional class (I-IV)	III	I
Echocardiographic evaluation		
Left ventricular ejection fraction (%)	22	61
Serum chemistry		
Creatinine (mg/dl)	1.20	1.29
Urea (gr/l)	0.57	0.69
Arterial blood sample		
PaCO ₂ (mmHg)	31.6	27.7
PaO ₂ (mmHg)	83.3	89.2
HCO ₃ (mmol/l)	23.3	18.3
Base excess (mmol/l)	1.1	-7.5
SaO ₂ (%)	97.6	96.7
Cardiopulmonary exercise test		
Peak workload (watts)	80	100
Peak VO ₂ (ml/kg/min)	12.5	18.0
Percent predicted peak VO ₂ (%)	57	68
Peak RER	1.15	1.12
VE/VCO ₂ slope	39	32
EOV (yes/no)	yes	no
Polysomnography		
TST (minutes)	424	402
Total AHI (n/hour)	40.7	40.2
AHI in supine position (n/hour)	43.3	39.4
ODI (n/hour)	28.6	26.8
Percentage of duration of SaO ₂ <90% (%)	10	4
Minimum SaO ₂ (%)	86	80
Circulatory length (seconds)	60	40
Cycle length (seconds)	180	120

NYHA, New York Heart Association; PaCO₂, carbon dioxide arterial pressure; PaO₂, oxygen arterial pressure; HCO₃, bicarbonate; VO₂, oxygen consumption; RER, respiratory exchange ratio VE/VCO₂ slope, relationship between ventilation (VE) and carbon dioxide production (VCO₂); EOV, exertional (oscillatory) periodic breathing; TST, total sleep time; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; SaO₂, oxygen saturation; cycle length, time from the beginning of an apnea to the end of ventilation.

suffering from pre-existing CSR will normalize their breathing pattern disorder, however, some recipients continue to show periodic breathing. Although a remarkable progress has been made, including changes in surgical techniques, immunosuppression therapy, donor and recipient selection, and post-transplant care, we showed that apnoea-hypopnea index (AHI) was almost unchanged (Table 1), while a reduction in both the circulatory and cycle length was observed, after successful HTx. The association of EOv and CSR [3], implicitly indicating a common mechanistic background in HFrEF, is largely a matter of speculation.

In HFrEF, beside periodic fluctuations in cardiac output, that directly affect chemoreflex regulation by introducing variations in gas exchange and circulatory delays, ventilatory instability and variability contribute to CSR-CSA development and perpetuation: furthermore, the instability of the respiratory control system arise either from feedback instability due large differences in hypercapnic and hypoxic chemosensitivities across individuals, or from external non-respiratory influences [10]. CSR-CSA persistence might be related to a complex interplay between different pathogenetic contributors, after HTx; both an increased central controller gain and/or baseline hypocapnia may mask the effect of optimization of heart function.

EOv turnaround is unclear, after HTx, as well. EOv is related to a lower pCO₂ at rest, a greater chemosensitivity to CO₂, a higher left ventricular filling pressure and pulmonary venous pressure and a prolonged lung to chemoreceptor circulatory delay. Although invasive hemodynamic evaluation was not performed, EOv overturn underscores that an enhanced exertional hemodynamic might play a foremost role.

We cannot exclude that CSR-CSA might be associated to worst outcome, even if this patient lived long after HTx, and also because he responded well at non-invasive respiratory device (At-PAP).

Conclusions

This case report debates about a HFrEF patient who underwent HTx. Severe CSR-CSA was identified either before and after HTx, while EOv vanished. These data suggest that optimization of hemodynamics and of medical therapy does not withdraw the

mechanisms, underlying the diathesis for CSR-CSA. While EOv reversal may support a closer link with an exertional central hemodynamic.

References

1. Braith RW, Edwards DG. Exercise following heart transplantation. *Sports Med* 2000;30:171–92.
2. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2015;8:597-619.
3. Corrà U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006;113:44–50.
4. Braver HM, Brandes WC, Kubiet MA, et al. Effect of cardiac transplantation on Cheyne-Stokes respiration occurring during sleep. *Am J Cardiol* 1995;76:632-4.
5. Kremser CB, O’Toole MF, Leff AR. Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1987;59:900-5.
6. Ribeiro JP, Knutzen A, Rocco MB, et al. Periodic breathing during exercise in severe heart failure. Reversal with milrinone or cardiac transplantation. *Chest* 1987;92:555-56.
7. Corrà U, Piepoli M, Giordano A. Difference in prevalence of exertional oscillatory between healthy subjects and patients with cardiovascular disease. *Monaldi Arch Chest Disease* 2020;90:1203.
8. Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. *Chest* 2003;124:1675-81.
9. Thalhofer SA, Kiwus U, Dorow P. Influence of orthotopic heart transplantation on breathing pattern disorders in patients with dilated cardiomyopathy. *Sleep Breath* 2000;4:121-5.
10. Khoo MCK. Determinants of ventilatory instability and variability. *Respir Physiol* 2000;122:167-82.