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CASE STUDY

Central sleep apnoea in congestive heart failure despite vagal denervation after bilateral lung transplantation

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Central sleep apnoea in congestive heart failure despite vagal denervation after bilateral lung transplantation. P. Solin, G.I. Snell, T.J. Williams, M.T. Naughton. ©ERS Journals Ltd 1998.

ABSTRACT: Nonhypercapnic central sleep apnoea is a disorder of respiratory control characterized by hyperventilation previously attributed to the stimulation of either pulmonary vagal afferent nerve fibres or respiratory chemoreceptors. This report describes central sleep apnoea in a patient with congestive heart failure following bilateral lung transplant in whom pulmonary vagal afferent nerve activity was absent.

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Nonhypercapnic central sleep apnoea (CSA) is a disorder caused by respiratory control instability during nonrapid eye movement (NREM) sleep [1]. CSA occurs commonly in patients with congestive heart failure (CHF) and is also known as Cheyne-Stokes respiration. The pathophysiology of CSA can be attributed to an increase in either central controller gain (respiratory drive to hyperventilate), plant gain (reduced lung volume and gas diffusion with impaired capacity to dampen oscillations in arterial blood gases) or circulatory delay where there is a prolongation of communication from plant to central controller [2].

Of these factors, increased controller gain with resultant hyperventilation, which drives arterial CO_2 levels below the apnoea threshold, resulting in central apnoea, is thought to be the major determinant of CSA in patients with CHF [1]. Hyperventilation has been attributed to stimulation of either pulmonary vagal afferent nerve fibres or to respiratory chemoreceptors. Pulmonary vagal afferent nerve fibres (C-fibres) have "J-receptors" that are sensitive to, and increase their rate of firing in response to increased pulmonary vascular pressure and pulmonary oedema [3], as would occur in patients with CHF. Increased central and peripheral chemosensitivity (hypercapnic and hypoxic ventilatory responses) has been described in patients in whom cardiac function is normal [4] or impaired [5]. Whether intact pulmonary vagal afferent nerve activity alone is necessary for the development of CSA is not known.

This report describes CSA in a patient with CHF and bilateral lung transplant in whom pulmonary vagal afferent nerve activity was absent.

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Case report

A 45 yr old Caucasian male presented for bilateral sequential lung transplantation in 1995. He had end-stage respiratory failure due to progressive idiopathic bronchiectasis. Although there were no symptoms of CHF pretransplant, routine assessment had revealed a mildly reduced left ventricular ejection fraction (44%) with mild global hypokinesis, but normal right ventricular ejection fraction, pulmonary artery pressures and coronary arteries. Echocardiography showed fractional shortening of 28% (normal value >28%).

Surgery was uncomplicated and postoperative recovery was routine. Triple immunosuppression was continued as maintenance therapy comprising cyclosporin A, azathioprine and prednisolone. The patient had weekly reviews until 3 months, when he was discharged to his rural home and the care of his referring physician and was seen every 3 months thereafter.

At 12 months he presented with severe orthopnoea, paroxysmal nocturnal dyspnoea, fragmented sleep, hypersomnolence, uncontrolled hypertension and fluid retention. Chest radiography demonstrated cardiomegaly and pulmonary venous congestion, and subsequent transbronchial biopsy with bronchoalveolar lavage showed no evidence of infection or rejection. There was no evidence of occult neurological disease. A diagnostic polysomnogram showed severe CSA with an apnoea hypopnoea index (AHI) of 78 events·h^{-1}, moderate hypoxaemia (94% total sleep time spent with the arterial oxygen saturation (S_{a,O_2}) <90%) and hypocapnia (mean overnight transcutaneous CO_2 pressure (P_{tc,CO_2}) 4.1 kPa (31 mmHg)). The apnoea-hyperpnoea cycle length was 62.5 s. Ventilation was regular during wakefulness. Awake lung function testing revealed a forced vital capacity (FVC) of 67% predicted (table 1). His clinical

Table 1. – Serial clinical and sleep study results

	Pretransplant	12 months	16 months	23 months
NYHA class	3	3	1	3
Fractional shortening %	28	20	24	21
pH	7.39	7.46	7.41	7.45
P_{a,CO_2} mmHg	44	33	38	26
P_{a,O_2} mmHg	69	62	76	89
FEV1 L % pred	1.12 (30)	2.56 (71)	3.16 (87)	2.56 (71)
FVC L % pred	3.40 (69)	3.30 (67)	4.19 (85)	3.67 (75)
$D_{L,CO}$ mL·min^{-1}·mmHg % pred	23.4 (80)		22.8 (79)	19.7 (69)
K_{CO} mL·min^{-1}·mmHg % pred	5.37 (112)		3.98 (84)	3.84 (82)
Total sleep time min		171	331	403
Stages 1 and 2 %		41.7	55.7	67
Stages 3 and 4 %		0	17.3	14.3
Stage REM %		0	19	7.6
AHI events·h^{-1}		78	15	79
Arousals events·h^{-1}		25	12	7
Mean sleep S_{a,O_2} %		87	95	92
Minimum sleep S_{a,O_2} %		81	90	80
Total sleep time S_{a,O_2} <90% %		94	0	16
Mean sleep P_{tc,CO_2} mmHg		31	37	33
Mean sleep f_C beats·min^{-1}		98	69	80
VL s		37	15	40
AL s		25	20	26.3
Cycle length s		62.5	35	66.3
VL:AL ratio		1.48	0.75	1.52

NYHA: New York Heart Association; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; K_{CO}: carbon monoxide transfer coefficient; REM: rapid eye movement; AHI: apnoea hypopnoea index; S_{a,O_2}: arterial oxygen saturation; P_{tc,CO_2}: transcutaneous carbon dioxide tension; f_C: cardiac frequency; VL: ventilatory length; AL: apnoea length. (1 mmHg=0.133 kPa.)

state rapidly improved with diuresis, antihypertensives, dobutamine infusion and 8 cmH_2O nasal continuous positive airway pressure (CPAP). CPAP was used for 7 days to treat the pulmonary oedema. Echocardiography after 7 days treatment showed fractional shortening of 20%.

At 16 months, when the patient was clinically stable, compliant with immunosuppressive and heart failure therapy and free of any symptoms of CHF, a repeat overnight sleep study demonstrated mild CSA (AHI 15 events·h^{-1}, 0% total sleep time spent with S_{a,O_2} <90%, mean P_{tc,CO_2} 4.9 kPa (37 mmHg) and apnoea-hypopnoea cycle length 35 s). Awake left ventricular fractional shortening was 24% and lung function testing revealed FVC to be 85% pred.

Following this clinical improvement, the patient represented at 23 months post-transplant with unstable CHF after self-withdrawal of heart failure treatment due to side-effects. Transbronchial biopsies again excluded rejection. Left ventricular fractional shortening was reduced, at 21%. A repeat overnight sleep study revealed severe CSA (AHI 79 events·h^{-1}, 16% of total sleep time spent with S_{a,O_2} <90%, mean P_{tc,CO_2} 4.4 kPa (33 mmHg) and apnoea-hypopnoea cycle length 66.3 s). Awake lung function revealed FVC to be reduced, at 75% pred normal. Vagal activity, as measured by high-frequency power spectrum analysis of variability in cardiac frequency (f_C), was markedly depressed, at 3.6 ms^2, consistent with vagal denervation [6, 7].

Discussion

This case report provides two unique observations that further our understanding of nonhypercapnic CSA associated with heart failure. Firstly, it is the only description of hyperventilation associated with nonhypercapnic CSA in the absence of pulmonary vagal innervation. This would suggest that pulmonary vagal afferent nerve stimulation due to venous congestion is not essential to the development of CSA in patients with CHF [3, 8]. Secondly, it describes the effects of medical therapy, targeted at the underlying CHF, on the pattern of ventilation during NREM sleep in a patient with CHF and CSA. With optimal medical therapy the AHI decreased, the cycle length shortened, the ventilatory length to apnoea length ratio (VL:AL) decreased and FVC increased from 67 to 85% pred (table 1). Withdrawal of medical therapy resulted in the opposite changes, with increased AHI, cycle length and VL:AL, and a reduction in FVC. This would suggest that improved medical treatment of CHF had a beneficial effect on ventilatory control during NREM sleep, through reduced plant gain (increased FVC) and improvement in left ventricular performance (shortened circulatory delay) [9, 10].

Patients who undergo bilateral lung transplantation have completely denervated lungs distal to the bronchial anastomoses for periods of at least 4 yrs [11–13], thereby offering a unique opportunity to examine the mechanisms responsible for the development of ventilatory abnormalities, including CSA. Studies in recipients of bilateral lung transplantation have demonstrated the absence of sympatho-inhibitory effects of lung inflation [13], loss of the Hering-Breuer reflex [12] and reduced cough frequency with ultrasonically nebulized distilled water [11]. Moreover, there is a paradoxical increase in bronchial responsiveness to physical stimuli such as exercise and cold air [14, 15] and methacholine, independent of airway inflammation [11, 16], due to vagal denervation hypersensitivity of muscarinic receptors [17].

The absence of vagal activity in this case report is indicated by the high-frequency power spectrum analysis of f_C variability, which was markedly depressed at 3.6 ms^2. Our laboratory has previously confirmed the highly significant

relationship between vagal blockade and high-frequency power spectrum analysis of *f*C variability. The mean value observed in normal subjects is 303 ms^2, compared with 47 ms^2 in CHF and 5.0 ms^2 in those with vagal blockade [6].

Therefore, in the absence of vagal innervation, hyperventilation seen in this patient with CSA must have been due to alternative mechanisms such as increased chemosensitivity. Increased chemosensitivity may result from hypoxaemia [18], increased levels of circulating catecholamines [19] or, perhaps, immunosuppressive drugs. Marked hypoxaemia was observed on the first and third sleep studies, and there was no significant hypoxaemia on the second study when the CHF was under good clinical control. As CSA has been shown to occur following arousal-induced hyperventilation and hypocapnia, in the absence of hypoxaemia [1, 20], it is likely that mechanisms other than hypoxaemia were responsible for hyperventilation and CSA in this case report.

An alternative explanation for hyperventilation may be the effects of elevated levels of circulating catecholamines on the chemoreceptors. CHF is characterized by elevated catecholamines [21], particularly when associated with CSA [22]. Moreover, infusions of noradrenaline have resulted in substantial increases in minute ventilation, an effect blocked by propranolol [19]. Therefore, it is possible that circulating catecholamine levels due to CHF may be sufficiently increased to stimulate ventilation, and thereby destabilize control of ventilation during sleep in vagally denervated patients [19]. Alternatively, acute elevation in blood pressure as part of the systemic hypertension, seen in post-lung transplant patients, may episodically suppress ventilatory drive and result in the propagation of central apnoeas, as suggested by GARPESSTAD *et al*. [23]. Both cyclosporin and prednisolone can cause systemic hypertension, which may have contributed to the CSA in this manner.

CHF patients are particularly prone to increased plant gain and restrictive ventilatory defect due to space-occupying effects of pleural effusion and increased cardiac volume and possible underlying respiratory muscle weakness. As a result, patients with stable chronic heart failure have reduced capacity to dampen oscillations in arterial blood gases when asleep. The improvement in FVC in response to medical treatment in this patient is similar to that reported elsewhere with medical therapy [24] and would suggest that plant gain was reduced with medical therapy.

Finally, the changes in ventilatory pattern during sleep are instructive and may shed light on underlying cardiac performance. Previously, it has been shown that the cycle length (ventilatory length plus apnoea length) in CSA is greater in patients with CHF than in those without CHF [9, 10] and correlates inversely with left ventricular ejection fraction [9]. Moreover, the VL:AL ratio is >1.0 in patients with CHF, while it is <1.0 in those without CHF [9, 10]. The case presented herein had characteristic features of CHF on the first and third studies when the patient had unstable CHF, and features of a non-CHF CSA on the second study when clinically stable, thereby suggesting that ventilatory patterns, namely the VL:AL ratio, obtained from sleep studies may be a useful adjunct in determining the adequacy of CHF control.

In summary, this case report describes severe nonhypercapnic central sleep apnoea in a patient with cardiac failure and vagally denervated lungs after bilateral sequential lung transplant. This indicates that intact pulmonary vagal innervation is not essential for the development of central sleep apnoea in congestive heart failure. Moreover, changes in ventilatory patterns on sequential sleep studies with medical treatment would suggest that improved cardiac function is associated with shorter cycle length and a ratio of the ventilatory length to apnoea length of <1.0.

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