The Effect of Successful Heart Transplant Treatment of Heart Failure on Central Sleep Apnea*

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Study objective: Central sleep apnea (CSA) associated with Cheyne-Stokes respiration in patients with congestive heart failure (CHF) is thought to be an acquired pattern of respiratory control instability, related at least in part, to elevated sympathetic nervous system activity. The effect of restoring heart function to normal with heart transplantation in patients with CHF and CSA has only been reported within weeks of the transplant and with varying results. The purpose of the study was to evaluate the impact of successful heart transplant on sympathetic nervous system activity and CSA severity in patients with CHF.

Design: Controlled prospective trial.

Setting: University hospital.

Patients: Twenty-two patients with CHF (13 patients with CSA, and 9 patients with no sleep-disordered breathing [SDB]).

Interventions and measurements: Polysomnography, left ventricular ejection fraction (LVEF), and overnight urinary norepinephrine excretion (UNE) were measured before and >6 months after successful heart transplantation.

Results: In the CSA group, there was a fall in apnea-hypopnea index (AHI) [mean ± SD, 28 ± 15 to 7 ± 6/h; p < 0.001] and UNE (48.1 ± 30.9 to 6.1 ± 4.8 nmol/mmol creatinine, p < 0.001) associated with normalization of LVEF (19.2 ± 9.3% to 53.7 ± 6.1%, p < 0.001) at 13.2 ± 8.3 months following heart transplantation. Of the CSA group following transplantation, seven patients had no SDB (AHI < 5/h), three patients had persistent CSA (AHI, 12.3 ± 0.9/h) and four patients acquired obstructive sleep apnea (OSA) [AHI, 11.2 ± 7.4/h]. In comparison, none of the control group acquired CSA or OSA after transplantation.

Conclusions: We conclude that CSA may persist despite normalization of heart function and sympathetic nerve activity.

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Key words: central sleep apnea; heart failure; sleep-disordered breathing

Abbreviations: AHI = apnea-hypopnea index; CHF = congestive heart failure; CSA = central sleep apnea; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OSA = obstructive sleep apnea; SDB = sleep-disordered breathing; SpO2 = pulse oximetric saturation; UNE = urinary norepinephrine excretion

Central sleep apnea (CSA) associated with Cheyne-Stokes respiration is observed during stages 1 and 2 sleep in approximately 30% of patients with congestive heart failure (CHF), and is characterized by typical waxing and waning hyperventilation interspersed with central apneas or hypopneas. It has been shown that hyperventilation results from acquired changes in ventilatory responses to hypercapnia and hypoxia within a few weeks in experimentally induced CHF, and probably relates to changes in carotid body nitric oxide or elevated catecholamines. Moreover CSA severity can be attenuated in humans by the introduction of anti-heart failure therapy and improvement in heart function over several weeks. The responsible mechanisms for altered respiratory control are thought to relate to...
sympathoexcitation,5 circulatory delay,7 and possibly pulmonary congestion with vagal afferent stimulation.8

Whether normalization of heart function should lead to complete abolition of CSA has not been shown. Early case reports suggested normalization of heart function with transplantation led to complete abolition of CSA9 or the development of obstructive sleep apnea (OSA).8,9 However, CSA persisting within a few days after heart transplantation has also been reported10; more recently, a series of patients was reported11 in which CSA persisted 3 to 9 weeks following successful heart transplantation in approximately 20% of 29 patients with CHF and CSA despite normal heart allograft function. Those authors postulated that respiratory control centers may have been permanently altered in those patients with persistent CSA. However, no such study has assessed whether CSA persists after the initial peri-transplant period (ie, > 6 months) with normalization of allograft function. The aim of this study was to test the hypothesis that normalization of heart function, and associated attenuation of sympathetic activity, would lead to abolition of CSA.

MATERIALS AND METHODS

Subjects and Protocol

Patients with a diagnosis of ischemic or idiopathic cardiomyopathy, and selected for heart transplantation assessment were included in the study. Patients with congenital, valvular, or restrictive heart disease were excluded. All patients were opti- mally treated and considered medically stable at the time of heart transplantation assessment.

At the time of heart transplantation assessment, patients underwent 99Tc radionuclide equilibrium measurement of left ventricular ejection fraction (LVEF), overnight polysomnography, and measurement of sympathetic nerve activity with overnight urinary norepinephrine excretion (UNE). Patients with plasma creatinine level of > 180 mmol/L were not included.

Patients with CSA who subsequently underwent successful heart transplantation were re-evaluated for the presence of sleep-disordered breathing (SDB) at a minimum of 6 months after transplantation. A group of patients with severe CHF and no SDB who also underwent successful heart transplantation with repeat overnight polysomnography at a minimum of 6 months after transplantation and were matched for posttransplant medical therapy, served as a control group. All patients were in stable condition and had maintained normal function of the heart allograft. The study was approved by the Alfred Hospital Ethics Committee, and all patients provided written informed consent.

Polysomnography

Full overnight polysomnography was performed using a computerized system (Somnostar; SensorMedics; Yorba Linda, CA). Sleep staging was determined manually by monitoring with two-channel EEG, two-channel electrooculogram, and submen-

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tal electromyogram. Oronasal airflow was monitored by thermistor (ProTech Services; Woodinville, WA). Thoracabdominal movement was recorded using calibrated respiratory effort bands (Resp-ez; EPM Systems; Midlothian, VA). ECG recorded heart rate and rhythm from lead II. Pulse oximetric saturation (SpO2) was monitored using ear probe pulse oximetry (Fastrac; Sensor-Medics).

Sleep was manually staged according to standard criteria.12 A central apnea was defined as absence of oronasal airflow during sleep for ≥ 10 s associated with absent respiratory effort. A central hypopnea was defined as any reduction in oronasal airflow for ≥ 10 s associated with in phase thoracabdominal movement and ≥ 2% fall in SpO2. Obstructive apnea was defined as cessation of oronasal airflow for ≥ 10 s in the presence of out of phase thoracabdominal effort. An obstructive hypopnea was defined as a fall in oronasal airflow for ≥ 10 s with out-of-phase thoracabdominal movement associated with ≥ 2% fall in SpO2. A mixed apnea was defined using the above criteria, when a central apnea included or terminated with obstructive components. Mixed apneas were classified as obstructive events. Patients were described as having CSA if ≥ 80% of all respiratory events were central in origin with total central AHI ≥ 5/h. OSA was described as AHI ≥ 5/h with < 20% central in type. No SDB was defined as an overall AHI < 5/h. The ventilation, apnea and cycle lengths were determined during a period of continuous cyclic central apneas in stages 1 or 2 sleep and the average taken of 10 cycles as previously described.13

UNE

Sympathetic nervous system activity was estimated from overnight UNE. Subjects were asked to void prior to sleep. Subsequent overnight urine and first morning voided samples were collected into acidified containers of 6 mol/L hydrochloric acid (20 mL) and stored at 4°C. Urinary norepinephrine was determined by high-performance liquid chromatography with fluorescent detection,14 and concentrations were expressed as nanomol per millimol creatinine to adjust for effects of urine volume and renal function.15 Values for normal subjects in our laboratory are 13.4 ± 5.6 nmol/mmol creatinine.16

Statistics

The data were expressed as mean ± SD, and paired and unpaired t tests and one-way analysis of variance were used to compare groups; p < 0.05 was assumed to indicate significance.

Results

Between the years of 1999 and 2000, 37 patients with severe CHF underwent heart transplantation workup that included full polysomnography who subsequently received a heart transplant: 16 patients had CSA, 6 patients had OSA, and 15 patients had no SDB (control group). In the CSA group following heart transplantation, one patient was excluded due to allograft dysfunction, one patient due to failure to achieve clinical stability, and one patient refused repeat polysomnography. The 13 remaining patients agreed to follow-up polysomnography and were included in the analysis, of whom 10 patients underwent orthotopic transplantation, and 3 patients un-
derwent heterotopic transplantation. In the control group, two patients failed to achieve clinical stability and four patients refused repeat polysomnography, leaving nine patients to act as a matched control group, each of whom had an orthotopic transplant. None of the patients studied had any clinical evidence of neurologic impairment following transplantation.

The pretransplant baseline characteristics for both CSA and control groups are shown in Table 1. The two groups had similar degrees of CHF, as indicated by similar LVEF and New York Heart Association (NYHA) class plus type of cardiomyopathy; however, the CSA group tended to be older.

Following heart transplantation, both groups had significant improvements in LVEF and NYHA classification, associated with significant reductions in UNE (Table 2). Sleep efficiency and sleep stage distribution were not significantly different at baseline between the CSA and control groups, nor did they change in either group following transplantation (Table 3). The arousal index was greater at baseline between the CSA and control groups, compared with the control group in which there was no change. Arterial blood gas estimates were unchanged following transplantation. Overnight oxygenation improved in the CSA group following transplantation.

Of the 13 patients with CSA before transplant, 3 patients had persistent CSA, 4 patients had OSA, and 6 patients had no SDB (AHI, 36.1 ± 10.0 to 12.3 ± 0.9/h, 18.0 ± 4.2 to 11.2 ± 7.4/h, and 31.4 ± 6.5 to 1.3 ± 0.9/h, respectively) on follow-up sleep studies. The characteristics of the CSA changed significantly with transplantation, such that cycle length shortened significantly (65 ± 14 to 31 ± 7 s, p < 0.01) [Table 3, Fig 1], and the ventilation:apnea length ratio diminished (2.6 ± 0.9 to 0.7 ± 0.3, p < 0.01) [Table 3]. There was a tendency for greater hypocapnia in the posttransplant CSA group compared with the OSA or no-SDB groups (37.5 ± 0.7 mm Hg, 40.4 ± 4.4 mm Hg, and 38.0 ± 0.6 mm Hg, respectively), but this failed to reach statistical significance. The severity of CSA pretransplant did not predict posttransplant apnea status. In the pretransplant no-SDB control group, all patients remained free of SDB after transplantation.

Four patients from the CSA pretransplant group acquired posttransplant OSA, whereas none of the no SDB pretransplant control group acquired SDB after transplant. The percentage of OSA events in the pretransplant CSA group were similar in those who went on to acquire posttransplant CSA, OSA, and no SDB (12 ± 17%, 12 ± 16%, and 12 ± 19%, respectively).

The UNE levels fell significantly following transplantation (48.1 ± 30.9 to 6.5 ± 4.8 nmol/mmol creatinine, p < 0.01) in the CHF group with CSA, and a similar trend was demonstrated in the CHF control group with no SDB (21.1 ± 15.5 to 5.8 ± 4.0 nmol/mmol creatinine, p = 0.20) [Table 3, Fig 2]. The UNE values were not statistically significantly different between the posttransplant CSA, OSA, and no-SDB groups (10.5 ± 2.1 nmol/mmol creatinine, 7.3 ± 4.8 nmol/mmol creatinine, and 4.7 ± 2.9 nmol/mmol creatinine, respectively).

Table 1—Patient Characteristics *

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group</th>
<th>CSA Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>44 ± 10</td>
<td>54 ± 9</td>
<td>0.02</td>
</tr>
<tr>
<td>Male/female</td>
<td>5/4</td>
<td>13/0</td>
<td></td>
</tr>
<tr>
<td>Pretransplant LVEF, %</td>
<td>26.4 ± 11.4</td>
<td>30.8 ± 3.2</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0 ± 1.2</td>
<td>1.9 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>89 ± 12</td>
<td>90 ± 8</td>
<td>0.05</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>40 ± 3</td>
<td>43 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.03</td>
<td>7.41 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2—Patient Characteristics Before and After Heart Transplant *

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group</th>
<th>CSA Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>25.5 ± 3.5</td>
<td>26.5 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26.4 ± 11.4</td>
<td>30.8 ± 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0 ± 1.2</td>
<td>1.9 ± 0.3</td>
<td>0.05</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>89 ± 12</td>
<td>90 ± 8</td>
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<td>43 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.03</td>
<td>7.41 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 1 for expansion of abbreviation.
Posttransplant medications are shown in Table 4 and reveal no significant difference in the medication usage between the CSA, OSA, and no SDB groups. Standard posttransplant medications were prescribed for immunosuppressive, cholesterol-lowering, and antihypertensive actions.

**DISCUSSION**

This study demonstrated two unique observations: first, CHF patients with CSA who undergo heart transplantation may have persistent CSA beyond the peritransplant period (>6 months) despite normalization of heart function and sympathetic activity. Second, CSA severity is attenuated and the cycle length plus ventilation:apnea ratio are altered in appearance, similar to that seen with idiopathic nonhypercapnic CSA,13 a condition characterized by normal heart function, after successful heart transplantation. Therefore, mechanisms other than heart dysfunction and heightened sympathetic activation are likely for the development or persistence of CSA.

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Table 3—Polysomnography and Catecholamine Data Before and After Heart Transplantation*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group</th>
<th>CSA Group</th>
<th>p Value</th>
<th>Control Group</th>
<th>CSA Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed, min</td>
<td>416 ± 30</td>
<td>396 ± 64</td>
<td>NS</td>
<td>280 ± 78</td>
<td>69 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>321 ± 72</td>
<td>377 ± 62</td>
<td>NS</td>
<td>376 ± 47</td>
<td>67 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>SPT, min</td>
<td>401 ± 36</td>
<td>26 ± 16</td>
<td>NS</td>
<td>27 ± 9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>77 ± 15</td>
<td>69 ± 15</td>
<td>NS</td>
<td>67 ± 12</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Wake, % SPT</td>
<td>21 ± 14</td>
<td>26 ± 16</td>
<td>NS</td>
<td>27 ± 9</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stages 1 and 2, % SPT</td>
<td>57 ± 12</td>
<td>58 ± 11</td>
<td>NS</td>
<td>56 ± 6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Slow-wave sleep, % SPT</td>
<td>10 ± 6</td>
<td>5 ± 7</td>
<td>NS</td>
<td>5 ± 6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Rapid eye movement, % SPT</td>
<td>12 ± 3</td>
<td>11 ± 7</td>
<td>NS</td>
<td>13 ± 10</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Arousal, No./h</td>
<td>27 ± 38</td>
<td>43 ± 36</td>
<td>NS</td>
<td>27 ± 26</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71 ± 14</td>
<td>69 ± 10</td>
<td>NS</td>
<td>80 ± 15</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>CSA, % total sleep time</td>
<td>2 ± 2</td>
<td>28 ± 15</td>
<td>NS</td>
<td>7 ± 6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CSA cycle length, s</td>
<td>65 ± 14</td>
<td>65 ± 14</td>
<td>&lt;0.01</td>
<td>31 ± 71</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>CSA ventilation: apnea length ratio</td>
<td>2.6 ± 0.9</td>
<td>0.7 ± 0.3</td>
<td>&lt;0.01</td>
<td>0.7 ± 0.3</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Mean SpO₂, %</td>
<td>95.2 ± 2.9</td>
<td>94.7 ± 1.8</td>
<td>NS</td>
<td>96.3 ± 1.6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Minimum SpO₂, %</td>
<td>91.7 ± 4.6</td>
<td>85.5 ± 3.9</td>
<td>NS</td>
<td>90.7 ± 5.2</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Time SpO₂ &lt; 90%, % total sleep time</td>
<td>6.6 ± 12.5</td>
<td>5.2 ± 10.8</td>
<td>NS</td>
<td>1.4 ± 4.9</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>UNE, nmol/mmol creatinine</td>
<td>21.1 ± 15.5</td>
<td>48.1 ± 30.9</td>
<td>0.2</td>
<td>6.5 ± 4.8</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 1 for expansion of abbreviation. SPT = sleep period time; sleep efficiency = total sleep time/sleep period time; p values represent level of significance between before and after transplant in each group.
†Subset with persistent CSA only (three patients).
Figure 2. **Top, A**: Polysomnography of patient before heart transplantation demonstrating typical CSA with Cheyne-Stokes pattern of respiration during stage 2 non-rapid eye movement sleep. Note the crescendo-decrescendo ventilation interspersed by absence of ventilation associated with an arousal at peak ventilation, a cycle length of approximately 72 s, and a ventilation:apnea length ratio of approximately 2.0. **Bottom, B**: Polysomnography of same patient 10 months following successful heart transplantation demonstrating CSA with a similar Cheyne-Stokes pattern of respiration to that of top, A, except for the markedly shortened cycle length of approximately 31 s and a ventilation:apnea length ratio of approximately 0.7. EOG = electrooculogram; EMG = electromyogram.
Although our observations of apnea type changing from central to obstructive following transplantation confirms previous observations,9 we observed it to occur only in the group with pretransplant CSA. While hyperventilation, related to heightened central and peripheral chemoreceptor function, is the physiologic entity which underpins CSA,17–19 the precise factors which contribute to the altered chemosensitivity are unknown. In CHF, it is assumed that circulating norepinephrine20 or possibly loss of endothelial production of nitric oxide4 are responsible for the changes in chemosensitivity. Alternatively changes to chemoreceptor function may result from increased pulmonary vagal afferent stimulation, due to elevated pulmonary vascular pressures, in some patients but not in all.21 Importantly, the change in the pattern of CSA, namely shortening of the cycle length with successful transplantation, indicates that CSA may occur despite normalization of heart function.13 The current study would suggest that factors other than heart dysfunction and sympathetic activity are responsible.

An alternative explanation is that medications that are required after heart transplantation affect chemosensitivity. Cyclosporin has been shown to contribute to hypertension through mechanisms of direct renal vasoconstriction, rather than via elevations in sympathetic nerve activity,22 while its effect on chemosensitivity is not known. Swings of heightened systemic BP could contribute to the brief central apneas23,24; however, we believe this mechanism is unlikely to be responsible for persistent CSA in our study, as no patient in the control group, matched for medications, acquired CSA.

A third of patients with CSA before transplant acquired OSA after transplant. This alteration in apnea type cannot be explained by variations in body weight or dosage of prednisolone between the three patient groups after transplant, nor could we identify upper airway anatomic differences. No patient in the control group acquired OSA despite a similar medication profile. Therefore, we believe it possible that these patients may have had OSA prior to the development of CHF and CSA, which was uncovered by the eradication of CSA. This conclusion remains to be confirmed with rigorous prospective studies.

Thalhofer et al11 demonstrated persistence of CSA 3 to 9 weeks following transplantation in approximately 20% of patients with CHF and CSA. The severity of CSA was unchanged from the pretransplant value, prompting the conclusion that respiratory control centers were permanently damaged as a result of chronic CHF. In contrast, we have demonstrated that in those in whom CSA persists, there is substantial attenuation of severity over time. Furthermore, we have extended the observations of Thalhofer et al11 by demonstrating that correction of heart function translates to a reduction in both the CSA cycle length and the ventilation:apnea length ratio to levels similar to that observed in patients with idiopathic nonhypercapnic CSA, in whom heart function is normal and that persistence of CSA may occur despite normalization of sympathetic nerve activity. Our study confirms our previous observation that cycle length correlates inversely with heart function13; therefore, we postulate that persistent abnormalities of chemosensitivity may underpin the persistence of CSA in these patients.

In summary we have demonstrated that CSA may persist for >6 months following successful heart transplantation albeit with a significant attenuation in severity. This is despite the demonstration of normal heart function and reduction of sympathetic activity to the normal range. Further studies on chemoreflex and baroreflex activity, upper airway function and autonomic activity are required to further our understanding of SDB in this posttransplant group.

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