

# Obstructive Sleep Apnea Induced Sinus Pause After Heart Transplantation: A Manifestation of Parasympathetic Reinnervation

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## Background

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing and is estimated to occur in 4% of men and 2% of women aged 30-65 years.<sup>1,2</sup> Obesity, male gender, increasing age, and craniofacial abnormalities are major risk factors for this disorder. OSA is defined by periods of repetitive episodes of apnea or hypopnea. An apnea-hypopnea index of > 5 is considered mild OSA; whereas a value > 15 represents a moderate to severe disease state. The syndrome of OSA may manifest as a combination of apnea along with daytime tiredness, recurrent awakenings or gasping episodes.<sup>1-3</sup> The majority of cases can be effectively treated with continuous positive airway pressure (CPAP) or if necessary a tracheostomy. However, not all patients are responsive to therapy with CPAP. Cardiac arrhythmias are known to be associated with OSA. The development of sinus pauses and asystole during sleep are postulated to be a vagally mediated phenomenon.<sup>1-3</sup> Following orthotopic heart transplant (OHT), recipients lack heart rate variability secondary to both sympathetic and parasympathetic denervation of the heart.<sup>4</sup> Sympathetic reinnervation in transplant recipients has been shown to occur as early as 4 years post-transplant, but parasympathetic reinnervation is not well reported.<sup>4</sup> In a published case-series of 5 OHT recipients with OSA, there was no change in baseline heart rate during periods of hypoxia because of lack of parasympathetic innervation.<sup>5,6</sup> The following case report is the first in which an OHT patient with documented OSA developed sinus pause and arrest during periods of apnea while asleep suggestive of a vagal mediated bradyarrhythmia consistent with parasympathetic reinnervation.

## Keywords

Obstructive sleep apnea, Heart transplantation

## Case Report

A 54 y/o gentleman, who had a combined kidney and orthotopic heart transplant in 2004, and documented OSA since 2002 treated with bilevel positive airway pressure (BIPAP) therapy presented to our institution for recurrent lower extremity osteomyelitis. His heart transplant operation was performed via bicaval anastomosis with an aortic cross-clamp time of 108 minutes and total bypass time of 2 hours and 47 minutes. On telemetry he was observed to have marked sinus bradycardia and multiple sinus pauses during sleep. (Fig 1) The patient was compliant with his BIPAP therapy and had been wearing it during these episodes. During these episodes, it was documented that he had a pulse oxygen saturation of 88% while wearing BIPAP (Fig 2). He was not receiving sinus or atrioventricular (AV) nodal blocking agents. These episodes occurred on a nightly basis and since the patient was asymptomatic, permanent pacemaker placement was not recommended. A physical examination revealed an obese gentleman with a body mass index of 41kg/m<sup>2</sup>. He was afebrile with normal vital signs. Cardiopulmonary examination revealed clear lungs with no murmurs or gallops. An echocardiogram showed normal left ventricular ejection fraction, moderately dilated right ventricle, mild tricuspid regurgitation and pulmonary hypertension with pulmonary artery systolic pressure of 35mmHg. He was diagnosed with obstructive sleep apnea prior to his transplants, and his Apnea-Hypopnea Index was noted to be 30 consistent with severe apnea. The patient eventually underwent a below-the-knee amputation during this admission and was treated with antibiotics. Serial negative blood cultures were collected throughout the entire hospital course and were negative.

## Discussion

The exact mechanism regarding the link between OSA and bradyarrhythmias is not well understood. However, it has been established that the severity of bradyarrhythmias is directly related to the number of apneic episodes and the severity of hypoxemia observed.<sup>1,3</sup> In our patient, sinus pause and periods of sinus arrest were observed during apnea with resumption of normal sinus rhythm once the apneic episodes terminated. It is hypothesized that hypoxemia along with prolonged apnea elicit a cardiovagal reflex which can perpetuate bradyarrhythmias.<sup>1-3</sup> There is some evidence to suggest that there is increased production of adenosine during hypoxemia in patients with OSA, however, it is unclear whether this increase in plasma adenosine level mediate bradyarrhythmias.<sup>7</sup> Furthermore, to assess the effects of adenosine in the denervated heart, Ellenbogen et al., evaluated the electrophysiological effects of adenosine on sinus and AV nodal properties.<sup>8</sup> They found that the denervated sinus node had a 3 to 4.5-fold increased response to adenosine as measured by the sinus node slowing effects of adenosine on the

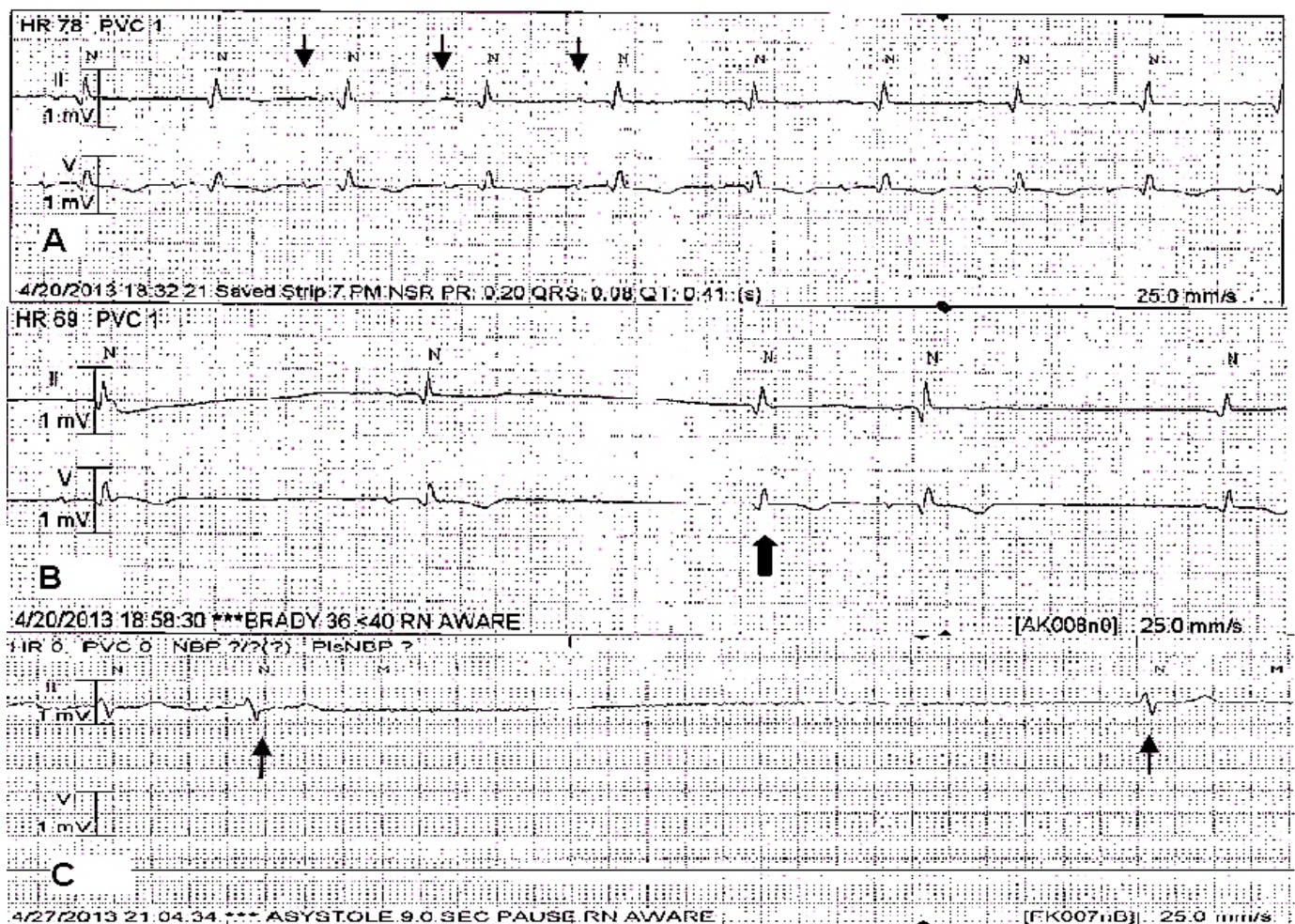
donor heart as compared to the recipient sinus node. Similarly, following adenosine administration, the donor AV node demonstrated a 3 to 5-fold increase in the PR interval as compared to control subjects. They concluded that the denervated sinus and AV node response to adenosine was of greater magnitude than that observed in innervated patients suggestive of adenosine supersensitivity in the denervated heart.

In cardiac transplant recipients, the estimated prevalence of OSA ranges from 2.5% to 43%. During cardiac transplant surgery there is complete cardiac denervation resulting in lack of heart rate variability (HRV) and a higher resting heart rate (HR). Parasympathetic reinnervation in heart transplantation is not well documented; however few studies have highlighted this phenomenon. In a study of sympatho-vagal tone in heart transplant recipients followed up to 10 years postoperatively, only a minority of patients in the subgroup showed reinnervating patterns of heart rate variability.<sup>4</sup> Recently, a study published by Imamura et al., employing HRV spectral analysis showed that a shorter cardiopulmonary-bypass time correlated with improvement of parasympathetic reinnervation in as little as six months after operation.<sup>9</sup> They studied 16 heart transplant recipients, and measured mean HR and HRV for 5 minutes in a supine position under a fixed 0.25Hz of respiratory rate along with fasting serially up to 6 months after transplant. Eventually these measurements were translated into low frequency (LF) and high frequency (HF) signals, where the HF signals corresponded to parasympathetic activity and LF/HF correspond to sympathetic activity. After twenty weeks post operatively, HF and LF / HF power were notably increased. Imamura et al, demonstrated that the increase in HF and LF/HF power represented parasympathetic reinnervation which occurred in under 1 year post-transplant. This was especially noted in patients who had shorter cardiopulmonary bypass time with a mean of 181 minutes (p=0.035). Our patient had a bypass time of 167 minutes.

In this case presented, our heart transplant patient had normal sinus rhythm at baseline and sinus pause with sinus arrest during periods of apnea while asleep associated with brief oxygen desaturation while on BIPAP therapy. OSA is usually effectively treated with CPAP or BIPAP; however since many patients have a combination of central and obstructive components or a mixed disorder, it is feasible that a combined disorder may not afford the patient complete abstinence from apneic episodes. Moreover, positive airway pressure may not prevent pharyngeal collapse or airway obstruction in all patients undergoing such therapy. Although the patient was admitted for infection, he received complete antibiotic therapy and serial blood cultures remained negative during the entire hospitalization. It is unlikely that these bradyarrhythmias and sinus pauses were due to severe infection or other etiologies as

bradycardia and pauses only occurred during sleep thus excluding sinus node dysfunction which would be expected to occur perhaps intermittently but not exclusively related to sleep. Subsequent admissions later for other medical issues still demonstrated sinus pauses on telemetry. It is our belief that parasympathetic or vagal reinnervation of the heart has occurred in this patient and postulate that activation of a cardiovagal reflex allowed transient sinus bradycardia to abruptly occur only in conjunction with apneic episodes. A predilection for parasympathetic reinnervation has been reported in patients with a short cardiopulmonary bypass time which also was the case in our patient.<sup>9</sup>To the best of our knowledge this the first case report of OSA mediated sinus bradycardia and sinus pause following OHT.

## Figures



**Figure 1:** Telemetry recording during sleep apnea episodes. (A) Baseline recording demonstrating normal sinus rhythm (arrows demonstrate baseline p waves) at a rate of 78 bpm with 1<sup>st</sup> degree AV block. (B) During apnea the patient developed sinus bradycardia with sinus pause followed by junctional escape complex (arrow). (C) On a separate evening, sinus arrest with an actual 4.7 second pause (a 9.0 second pause was erroneously indicated on the monitor) occurred during apnea.



18																			
19			4	2	4	6	15		BiPAP	18	88%								
20																			
21																			

**LIMB MOVEMENT**

5. Normal - Ability to move an entire extremity without assistance to a position and hold against gravity and resistance.

4. Lift and Hold - Ability to move an entire extremity without assistance to a position but cannot sustain against resistance.

3. Lift - ability to lift an entire extremity without assistance but cannot sustain against resistance.

2. Move laterally - ability to move entire extremity without assistance but cannot lift.

1. No movement.

Date: APR 20 2013 / \_\_\_ / \_\_\_

**PATIENT CARE FLOW SHEET**

**Figure 2:** Displays the nursing documentation of oxygen desaturation to 88%, and the time thereof which is consistent with the recorded time of the bradycardic event. The 2 columns on the left represent right and left extremity movement scale; whereas the next 4 columns are the Glasgow coma scale illustrating eye, motor and verbal responses with a total of 15 out of 15 score. BiPAP therapy and a respiratory rate of 18 is shown.

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