

Nocturnal Overdrive Pacing Reduces Circulation Delay

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Abstract

Sleep apnea affects 24% of men and 9% of women. Circulation delay (CD) is the time from end of an apnea to oxygen saturation nadir. To evaluate effects of cardiac pacing on sleep apnea, 19 patients were enrolled in a two center, single blind, randomized crossover study comparing Nocturnal Overdrive Pacing (NOP, 75 bpm lower night rate) to Control (45 bpm lower night rate). Patients underwent two sleep studies measuring Apnea-Hypopnea Index (AHI, [# (apneas+hypopneas)/hour of sleep] and finger oxygen saturation. CD was measured with an adaptive window in 14 patients. NOP improved AHI ≥ 10 events/hour in 4 (Responders), and not in 10 (Non-responders). NOP decreased CD in all patients. CD was 25.6 ± 5.5 sec, Control, and 20.9 ± 3.7 sec, NOP, ($p=0.03$). Changes in CD were not different in Responders vs. Non-responders (4.8 ± 2.0 sec vs. 4.6 ± 3.9 sec, $p=0.9$). NOP reduced CD, however, CD did not predict relative changes in severity of sleep apnea as measured by AHI.

1. Introduction

Sleep apnea syndrome (SAS) is characterized by recurrent episodes of apnea during sleep, typically producing excessive daytime sleepiness [1,2]. Moderate to severe sleep apnea affects 24% of middle-aged men and 9% of middle-aged women [3].

Obstructive sleep apnea (OSA) is the most common form of sleep apnea and is caused by the collapse of the upper airway during inspiration. Central sleep apnea (CSA), in which apneas and hypopneas are due to a cessation of airflow and respiratory effort, is significantly less common [4]. For congestive heart failure (CHF) patients, it has been hypothesized that low cardiac output leads to lung-to-carotid chemoreceptor circulatory delay causing instability in respiratory control that triggers sleep apnea [5]. The cessation of airflow reduces the oxyhemoglobin saturation (SaO_2) and increases the partial pressure of carbon dioxide (PaCO_2) in the blood. Hyperpnea (hyperventilation) occurs at the termination of apnea increasing SaO_2 and decreasing PaCO_2 . The SaO_2 begins to rise in the lungs immediately following the

onset of breathing, however due to the blood's transport time to the periphery, the rise in peripheral SaO_2 is delayed (as measured in customary locations such as finger tip or ear lobe). The interval from the restoration of breathing to the onset of rise in SaO_2 in these locations has been labeled Circulation Delay (CD) (Fig. 1). It is thought to reflect the status of cardiac pumping and varies in inverse proportion to cardiac output. It is defined as the time from the end of an apnea to the nadir of SaO_2 .

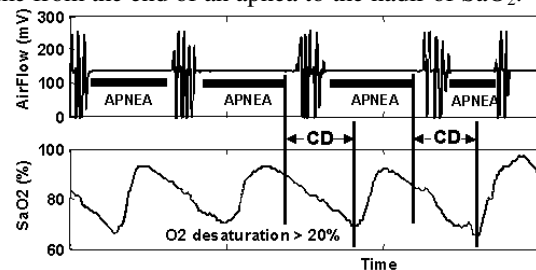


Figure 1: Circulation Delay (CD) is the time delay from the end of an apnea to the nadir of SaO_2 .

A recent study by Garrigue et al, reported improvements in SAS in patients during nocturnal atrial overdrive with DDD pacing [6]. They hypothesized that atrial pacing at a high rate relative to that of spontaneous sinus bradycardia may counteract sustained increases in vagal tone by maintaining sympathetic activity. Fifteen patients with dual chamber pacing systems and mild to moderate SAS were randomized, in a crossover design, to DDD pacing at 15 bpm above the spontaneous nocturnal heart rate or spontaneous rhythm with VVI backup pacing at 45 bpm. There was a 60% reduction in AHI during nocturnal atrial overdrive pacing. We conducted a study to test the hypothesis that atrial or dual chamber nocturnal overdrive pacing (NOP) can reduce the number and total duration of apnea and hypopnea compared to spontaneous rhythm with backup dual chamber pacing in subjects with SAS. The primary endpoint of this study was to test the effect of nocturnal overdrive pacing on AHI. In addition, we conducted an analysis to examine effects of NOP on CD. We hypothesized that NOP would reduce CD for those patients in whom AHI improved as compared to control.

2. Methods

Nineteen patients previously implanted with Medtronic pacemakers with the sleep function, and diagnosed with sleep apnea or symptoms of excessive daytime sleepiness were enrolled in the randomized, single blind crossover study design. Patients were studied using two nocturnal pacing rates. Control arm pacing was programmed to dual chamber (DDD(R)) or atrial (AAI(R)) mode at a lower pacing rate of 45 bpm at night and 60 bpm during the day while the treatment arm with NOP was DDD(R) or AAI(R) mode at a pacing rate of 75 bpm at night and 60 bpm during the day. Pacing rate was switched automatically using the pacemaker's Sleep function. Patients remained in each arm for 7-10 days. An in-hospital polysomnography (PSG) sleep study was conducted after 7-9 days in each therapy arm.

Pacemaker patients without persistent atrial fibrillation/flutter were selected based on previous diagnosis of SAS or the presence of risk factors highly predictive of moderate to severe SAS. Patients were enrolled in the study if they were able to tolerate a lower rate of 45 bpm, were ≥ 18 years of age, had a prior diagnosis of SAS with AHI ≥ 15 or high probability of SAS based on an Epworth Sleepiness Scale score ≥ 10 [7] and Sleep Disorders Questionnaire Sleep Apnea section score of >32 for females and >36 for males [8] and signed an informed consent. Patients were screened with questionnaires or ambulatory multichannel sleep recorders. All subjects screened with ambulatory recorders had an AHI ≥ 15 before entry into the study.

Patients were excluded for atrial arrhythmia(s) preventing programming of DDD(R) or AAI(R) mode, current use of CPAP therapy or use of an oral appliance for the treatment of sleep apnea. Patients were also excluded if they had CHF exacerbation, severe nasal congestion or other respiratory conditions which prevented nasal breathing during sleep and which would interfere with monitoring airflow. Airflow was monitored indirectly using an oro-nasal cannula that monitors changes in oro-nasal pressure.

Patients were randomized to Control or NOP arms and their pacemaker was programmed accordingly. They returned after one week for an in-hospital PSG study. Following the PSG, patient's pacemakers were reprogrammed to the opposite therapy arm. Patients returned after a second week for another in-hospital PSG study. Following study completion, the pacemaker was returned to the permanent settings.

DDD(R) or AAI(R) mode was used depending on the implanted pacemaker and was kept constant for both arms of the study.

In-hospital, overnight PSG recorded 4 EEG channels, 2 channels of EOG, chin and anterior tibialis EMG, ECG,

airflow, respiratory effort, SaO₂, body position, and snoring. SaO₂ data was collected by a pulse oximeter on the fingertip. PSGs were scored by a registered sleep technologist and interpreted by a board-certified Sleep Medicine specialist using standard scoring procedures [9]. Standard sleep events including: sleep onset; sleep stages; arousals; obstructive apneas; central apneas; mixed apneas; hypopneas; periodic limb movements; and sleep offset were identified.

The complete PSG recording and a summary of the scored sleep study was used to determine the number and timing of sleep events. Nocturnal heart rate was calculated from the ECG recorded by the PSG system or Holter.

Circulation delay analysis was performed on patients with >5 apneas in both the Control and NOP night. Fourteen of 19 patients had >5 apneas per night and were included in the analysis. Circulation delay was measured for apneas only. Hypopneas were not considered due to small oxygen desaturations making it difficult to accurately detect the nadir of SaO₂.

An algorithm was developed, which read patient data from the sleep studies and measured circulation delay for apnea events. CD was determined by searching for the nadir of SaO₂ in a window following the termination of an apnea. The window size was determined to be slightly longer than the average apnea-hyperventilation cycle length of the patient. The search window was terminated before the search window for a consecutive apnea began.

In order to avoid quantization errors, we considered apneas with large desaturations. The criteria used were:

1. Desaturations had to exceed 3% from baseline SaO₂.
2. SaO₂ had to return to within 2% of baseline following the apnea.

Figure 2 shows an example of an SaO₂ waveform that met these criteria. While the definition of apnea included a minimum duration of 10 seconds, we took a more conservative approach by using 15 seconds as the cutoff for evaluation. These requirements helped ensure that a nadir in SaO₂ could be unambiguously associated with a specific apnea.

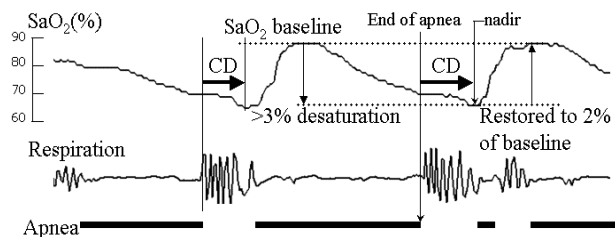


Figure 2: Apnea with significant oxygen desaturation restored to within 2% of baseline.

The algorithm implemented the selection criteria and measured circulation delay from the end of the apnea to the nadir of SaO₂. CD results for all 14 patients were recorded and normalized by height to account for variation in arm-length.

3. Results

Patient demographics are shown in Table 1. Indications for pacing were sinus arrest in 5, AV block in 7 and bradycardia in 2. Patients had a low level of heart failure.

Table 1: Baseline patient demographics (N=14)

Age	71.3±9.1 yrs
Gender	12 M/ 2 F
Systolic BP	133.2 ± 14.0 mm Hg
Diastolic BP	84.6 ± 9.7 mm Hg
BMI	29.5 ± 6.1 kg/m ²
Pacing Indication	5 Sinus Arrest, 7 AV Block, 2 Brady
NYHA class	0=1; I=6, II=5, III=1, unknown=1

Circulation delay was calculated for Control and NOP. Table 2 shows a significant reduction in CD from 25.6±5.5 sec at control to 20.9±3.7 during NOP, p<0.03. However, AHI was not different between Control (30.6±18.5) and NOP (27.4±17). By design, heart rate increased from 58±9 bpm during Control to 77±3 bpm during NOP. All other parameters including minimum SaO₂ and the percent of time below 90% SaO₂ were not significantly different from Control to NOP.

AHI determines the severity of sleep apnea and based on its value sleep apnea can be classified as Normal (AHI < 5), Mild (AHI 5-15), Moderate (AHI 15-30), or Severe (AHI >30) [10]. Patients showing an improvement in classification due to NOP were called responders (N=4) while patients showing no change or worsening AHI were called non-responders (N=10).

We compared the reduction in circulation delay in responders and non-responders. No difference in the

circulation delay reduction was noted between responders and non-responders (4.8±2.0 sec vs. 4.6±3.9 sec, p<0.9).

Table 2: Effect of NOP on CD and severity of sleep apnea as measured by AHI and other indices (N=14)

	Control	NOP	p
CD (sec)	25.6±5.5	20.9±3.7	0.03
AHI	30.6±18.5	27.4±17.0	0.64
AI	17.7±19.8	16.3±16.0	0.84
OSA index	8.3±10.3	7.0±8.5	0.73
CSA index	3.8±3.3	4.7±5.8	0.63
Min SaO ₂	74.5±15.5	79.3±13.5	0.39
% time<90% SaO ₂	6.6±7.4	10.2±17.5	0.48
Mean HR (bpm)	58±9	77±3	< 0.001

4. Discussion and Conclusions

Our study did not show an overall reduction in AHI with NOP, although 4 of 14 patients did demonstrate a reduction in AHI. The sample size was small making it difficult to draw conclusions as to whether some patients received benefit or whether various factors, which were not controlled, influenced certain nights of sleep during which they were studied. For example, we did not control sleep stage and body position which had been known to influence sleep disorders [11]. There are many factors affecting one's sleep, including the environment of the sleep laboratory. To understand the effect of cardiac pacing upon sleep apnea, we conducted an analysis of CD in 14 patients. Our hypothesis was that NOP would improve cardiac output (CO) in those patients who were considered 'responders'. The improvement in CO would be reflected in a corresponding reduction in CD as measured at the fingertip. This reduction in CD would then stabilize respiratory control, preventing or reducing sleep apnea episodes. CD decreased in all patients but was not different between NOP responders and non-responders. However, the decrease in CD does not predict or explain NOP responders. The explanation eludes us and continues to be a topic of research.

While fingertip blood oxygen saturation is modeled to reflect that of the lung with an associated delay due to circulation, in fact, we observed a decrease in SaO₂ immediately upon apnea, not accounting for circulation delay. Thus, measurement of CD was most effective from the end of apnea to the nadir of SaO₂. Contiguous episodes made it difficult to unambiguously detect the nadir associated with each apnea. We sought to design an algorithm for automatic analysis without requiring visual inspection. Thus, we excluded some CD measurements that might otherwise have been of use but felt we had sufficient measurements for significance. We were encouraged to analyze CD trends during the entire night.

CD decreased in all patients, however, so reduction of CD did not predict or identify those who responded to cardiac pacing therapy. CD may be useful in helping elucidate the mechanisms of response to nocturnal overdrive pacing.

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