

# Investigating Sleep Fragmentation By Autonomic Arousals in Depressed Patients With Obstructive Sleep Apnea

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## Abstract

*The aim of this study is to look at if there is any difference of arousal patterns in polysomnography (PSG) and Pulse Transit Time (PTT) recordings in Obstructive Sleep Apnea (OSA) patients with Major Depressive Disorder (MDD) and without MDD subjects. Nine overnight PSG recordings (7~8 hours) were acquired from OSA subjects (AHI: 15~60; 36.68±13.55 events/hour) with MDD diagnoses [OSAMDD](5 cases) and OSA subjects (AHI: 15~60; 38.37±19.61) without MDD [OSA] (4 cases) from a local psychiatric clinic. Selection criteria include the age [39.5±5 vs 41.4±3.5 yrs;  $p>0.05$ ] and weight [120.2±10 vs 118.6±12 Kgs;  $p>0.05$ ] matched subjects. Diagnoses of MDD were made by the Mini-International Neuropsychiatric Interview with ICD-10 questionnaire. A PTT arousal (ArPTT) was defined as a decrease in PTT by at least 15 milliseconds of the baseline lasting at least 5 seconds. Expert scored EEG based cortical arousals (ArEEG) include respiratory, movement, periodic leg movement and spontaneous arousals. Mann-Whitney U test showed that ArPTT index (events per hour) of OSA+MDD was significantly ( $p<0.05$ ) higher than that of OSA groups [36.56±5.6 vs 28.78±4.6]. In contrast, ArEEG indices in both groups were not found significantly different [24.18±6.7 vs 25.74±8.3].*

## 1. Introduction

Obstructive Sleep Apnea (OSA) is defined as the repetitive blockage of the upper airway, resulting in interrupted breathing during sleep. To restore breathing, arousal is needed to reopen the airway to activate the throat muscles. During sleep, the serotonergic system in the body regulates sleep through the release of serotonin and the activity of serotonergic neurons, which are at

maximum during wakefulness, lower during slow wave sleep (SWS), and at minimum during REM sleep [1].

Major Depressive Disorder (MDD) is associated with a decrease in serotonergic and an increase in cholinergic neurotransmissions. So, antidepressants like selective serotonin reuptake inhibitors (SSRI) could activate the serotonergic system receptors causing an increase in the serotonergic activity and thus an inhibition of REM sleep. This could be one of the reasons why MDD patients often suffer from insomnia, early wake-ups and frequent awakenings during sleep. Compared to nondepressed subjects, depressed patients tend to have higher beta power, rapid eye movement (REM) activity, REM latency [2].

The relationship between Obstructive Sleep Apnea (OSA) and Major depressive disorder (MDD) is complex which may share neurological risk factors. Arousal (Ar) from sleep is an important mechanism for reestablishing upper airway patency in OSA. When EEG frequency changes are not seen at event termination by visible cortical arousals but accompanied by sudden drop in pulse transit time (PTT), those are known as autonomic arousals.

Pulse transit time (PTT) is a non-invasive cardiovascular measure which was used in the diagnosis of OSA in the past. PTT is the time taken for the arterial pulse pressure wave to travel from the left ventricle to a peripheral level (e.g. finger). The travel time of the pulse wave is inversely related to the arterial wall stiffness, which is determined by blood pressure. Hence, PTT may be inversely correlated to blood pressure [3]. The feasibility of PTT in detecting subcortical arousals and respiratory effort has been assessed in adults and recently also in children [4,5,6]. However, there are no studies on PTT based arousals in relation to mental illness such as MDD. Recently decreased arterial stiffness was correlated with acute and chronic mental stress [8], depression and anxiety [9]. Oulis and co-researchers documented reversal of arterial stiffness in a small group of severely depressed women, after a 6-week

antidepressant therapy [Selective serotonin re-uptake inhibitors, Serotonin–norepinephrine reuptake inhibitors or a combination thereof in adequate dosages] [7], suggesting a pathophysiological connection.

It still remains to be answered if sleep quality measured by number of arousals per night sleep in OSA patients is different from OSA patients with co-morbidity of MDD. The aim of this study is to look at if there is any difference of arousal patterns in polysomnography (PSG) and PTT recordings in OSA patients with MDD and without MDD subjects.

## 2. Methods

### 2.1. Subjects

The overnight polysomnogram (PSG) data with psychiatric assessment profiles were collected from 9 patients at American Center for Psychiatry and Neurology (ACPN) in Abu Dhabi and analyzed by Miniscreen Software. The study protocol was approved by ACPN Ethics and Research Committee in 2017. Nine overnight PSG recordings (7~8 hours) were acquired from OSA subjects (AHI: 15~60; 36.68±13.55 events/hour) with MDD diagnoses [OSAMDD](5 cases) and OSA subjects (AHI: 15~60; 38.37±19.61) without MDD [OSA] (4 cases) from a local psychiatric clinic. Selection criteria include the age [39.5±5 vs 41.4±3.5 yrs; p>0.05] and weight [120.2±10 vs 118.6±12 Kgs; p>0.05] matched subjects. Diagnoses of MDD were made by the Mini-International Neuropsychiatric Interview with ICD-10 questionnaire.

Each PSG study included electroencephalogram (channel C3-A2 and C4-A1), left and right electro-oculogram (EOG), leg movements, body positions, thoracic and abdominal wall expansion (by respiratory inductive plethysmography), oronasal airflow (by nasal pressure), arterial oxygen saturation SpO2 (by pulse oximetry) and PPG (sampling frequency = 100 Hz with a resolution of 16 bits/sample). All subjects were free of any cardiac history. Diagnosis was based on clinical symptoms and PSG outcomes. Arousals were scored manually according to ASDA criteria using the EEG signal and marked using Miniscreen software.

### 2.2. Pulse Transit Time (PTT)

PTT was calculated as the time elapsing between the occurrence of the electrocardiographic R-wave and the point on the pulse waveform that is 50% of the maximum value [13].

### 2.3. PTT based arousals

PTT arousals (ArPTT) was defined as a fall in PTT of ≥15 ms lasting for ≥3 s [6,10,12]. Ar PTT includes both respiratory and non-respiratory related arousals. Uninterpretable or spurious PTT signals extracted from artifacts in the electrocardiogram or pulse waveform were removed from the analysis.

Table 1: Patient Characteristics

	OSA	OSA+MDD
Number (N)	5	4
Age (years)	39.5±5	41.4±3.5
Weight (Kgs)	120.2±10	118.6±12
AHI (events/hr)	36.68±13.55	38.37±19.61
SWS of TST (%)	26.56±10.6	27.6±12
REM of TST (%)	20.4±6.7	26.5±9.4*

\* significant difference at p<0.05. SWS= Slow Wave Sleep; TST= Total Sleep Time; REM= Retinal Eye Movement.

Table 2: Cortical (EEG based) ArEEG Microarousals (respiratory and non-respiratory related) [events/hour]

	OSA	OSA+MDD
Stage 1-2	5.4±3.2	6.2±2.2
SWS	7.2±4.7	4.3±7.5*
REM	13.74±8.3	15.18±6.7
Total	25.74±8.3	24.18±6.7

Table 3: Autonomic (PTT based), ArPTT (Microarousals (respiratory and non-respiratory related) [events/hour]. \*= $p<0.05$ .

	OSA	OSA+MDD
Stage 1-2	5.78±3.5	4.34±2.1
SWS	7.78±5.4	6.89±8.5
REM	18.78±4.6	26.56±5.6*
Total	28.78±4.6	36.56±5.6*

## 3. Results and Discussion

Figure 1 shows an example of arousal patterns of an OSA subject with MDD. Table 2 and 3 show that ArPTT index (events per hour) of OSA+MDD was significantly ( $p<0.05$ ) higher than that of OSA groups [36.56±5.6 vs 28.78±4.6]. In contrast, ArEEG indices in both groups were not found significantly different [24.18±6.7 vs 25.74±8.3].

In the previous research [15] it was reported that

subcortical arousals due to increased upper airway resistance could be detected by PTT signals. Factually increased inspiratory resistive load is considered a main trigger mechanism for autonomic arousal and sleep disruption [13]. These upper airway resistance-related arousals apart from traditional respiratory events detected by PTT changes could be useful as a non-invasive diagnostic tool in the therapeutic management of MDD with OSA patients.

The relationship between autonomic arousals and the main factors affecting PTT is complex. The sympathetic nervous system is considered one of the major elements involved in the regulation of mean arterial pressure, affecting heart rate, left ventricular contractility, and systemic vascular resistance [14] and thereby PTT changes. How the magnitude of PTT is related to MDD is still unknown and remains to be investigated. It is however possible that the higher PTT based arousals could be related to changes in serotonergic pathways or other mechanical properties of the resistance of vessels of MDD patients.

However, understanding the neurobiological mechanism of autonomic arousals and serotonergic pathways needs further study.

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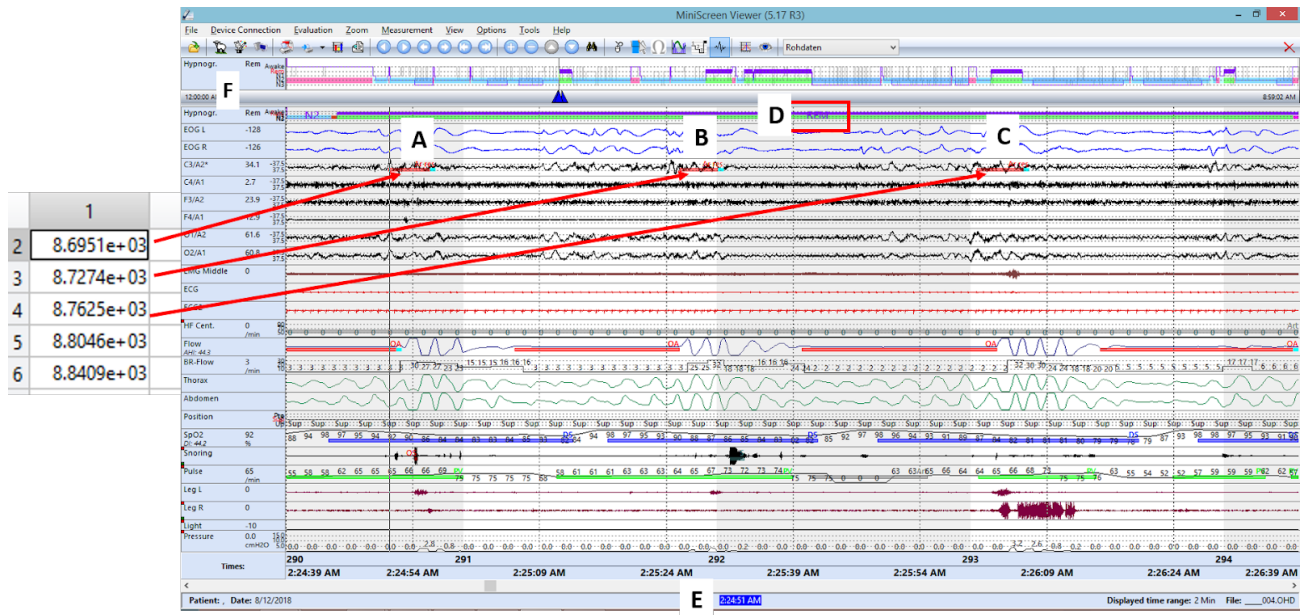


Figure 1: An screenshot of an OSA patient with MDD profile in Miniscreen software. A, B, and C indicates the timings of three arousals detected in the EEG signal during REM stage. F indicates the hypnogram (sleep profile of the patient).