

# Sudden Cardiac Death In Patients With Obstructive Sleep Apnea: Is It Due To Ventricular Arrhythmias?

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## Abstract

Obstructive sleep apnea is a growing problem and it has attracted everyone's attention due its effect on various chronic medical conditions like atrial fibrillation, insulin resistance, chronic kidney disease and coronary artery disease. There is new evidence associating obstructive sleep apnea with sudden cardiac death as an independent risk factor. The most common rhythm causing sudden cardiac death or arrest is a ventricular arrhythmia. It is possible that the increased risk of ventricular arrhythmia due to obstructive sleep apnea could explain the increased risk of sudden cardiac death in patients with obstructive sleep apnea.

## INTRODUCTION

Obstructive Sleep apnea has been associated with the occurrence of different kinds of arrhythmias which include sinus bradycardia, AV block and ventricular arrhythmias. In this article, we would like to explore the association of obstructive sleep apnea (OSA) with ventricular arrhythmias and sudden cardiac death (SCD). There is some new evidence showing the association of obstructive sleep apnea with sudden cardiac death. The most common arrhythmias noted in the events of sudden cardiac death are ventricular fibrillation (VF) and sustained ventricular tachycardia. The question we want to answer in this article is "Does obstructive sleep apnea cause sudden cardiac death due to its potential to cause fatal ventricular arrhythmias ? ". In order to answer this question, we have attempted to present the existing knowledge of association between OSA and sudden cardiac death, ventricular arrhythmias and sudden cardiac death and most importantly between OSA and ventricular arrhythmias. The question is are these associations significant enough to establish OSA as a risk factor for sudden cardiac death due to ventricular arrhythmias and is the available evidence of potential morbidity and mortality compelling enough to come up with new treatment strategies to address this problem .

## SUDDEN CARDIAC DEATH

In the 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines, the following definition was presented:

(Sudden) cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal.

There factors which increase the risk of SCD are advanced age, male sex and history of underlying cardiac disease [32, 33, 34]. Men are two to three times more likely to experience SCD than women. The risk of SCD is increased six- to ten-fold in the presence of clinically recognized heart disease, and two- to four-fold in the presence of coronary artery disease (CAD) risk factors [32,35].

## SUDDEN CARDIAC DEATH AND VENTRICULAR ARRHYTHMIAS

In this discussion, our main focus is on ventricular arrhythmias as a cause of SCD. Ventricular fibrillation is thought to be the main event leading to SCD, however, we cannot restrict SCD to the documented cases of ventricular fibrillation only. In most of the cases the underlying rhythm is not known. 70% of all cases of SCD are attributed to structural heart disease mainly coronary artery disease (CAD).

The question we have is whether OSA is a independent risk

factor of SCD due its possible role in causing ventricular arrhythmias. There is evidence of association between OSA and CAD (50,51,52,53) . Studies also reported association between OSA and cardiomyopathy (54,55,56,57). Therefore, one can hypothesize that due its associated risk with CAD and cardiomyopathy, OSA increases the risk of SCD. In a longitudinal study done by Gami et al., OSA and nocturnal hypoxemia in particular strongly predicted SCD independently of the well-established risk factors of SCD (31). It is therefore important to explore the other causes of SCD in the absence of structural heart disease. It is important to note that the absence of structural heart disease doesn't necessarily mean normal heart. This category includes people with congenital or acquired prolonged QT interval, Brugada pattern electrocardiographic changes (a pseudo-right bundle branch block and persistent ST-segment elevation in the leads V1 to V3) and early ventricular repolarization as noted in cases of idiopathic VF. Another entity that we feel needs to be mentioned is Familial Polymorphic VT, also called catecholaminergic polymorphic ventricular tachycardia (CPVT) . The catecholaminergic state like hypoxia and direct sympathetic activation that are seen in OSA can be triggers for the fatal polymorphic VT in these patients. The underlying mechanisms predisposing to this problem are mutations of cardiac ryanodine receptor (RyR) (An autosomal dominant form of CPVT was initially linked to chromosome 1q42-q43) (40). One report suggested that RyR2 mutations may account for at least one in every seven cases of sudden unexplained death (42). The other cause which may not be very relevant to our discussion involves the mutation of calsequestrin 2 gene (CASQ2). This has an autosomal recessive inheritance with mean age of death being around 7 years (43,44).

### **OBSTRUCTIVE SLEEP APNEA AND SUDDEN CARDIAC DEATH**

Gami et al. have studied the association of OSA with SCD (1). In that study, they have observed that the incidence of SCD in patients with OSA have occurred between 12 am to 6 am (sleeping hours) which is a striking contrast to the incidence of sudden cardiac deaths due to other cardiac causes which have predominantly occurred between 6 a.m. to 12 p.m. This study again shows that there is an alteration in the day night pattern but does not show that OSA is an independent risk factor for SCD. A recent breakthrough was made by Gami et al. when they presented the longitudinal study in which 10,701 patients were included. These patients were followed for 15 years and 142 patients had either a fatal SCD or have been resuscitated. The study revealed that

OSA predicted incident SCD, and the magnitude of risk was predicted by multiple parameters characterizing OSA severity and nocturnal hypoxemia (31).

### **SLEEP APNEA AND VENTRICULAR ARRHYTHMIAS**

The relation between OSA and Ventricular arrhythmias remains unclear. In this section we tried to put together various studies that have showed an association between OSA and ventricular arrhythmias. A study done by Aydin et al. showed that cardiac autonomic activity may be altered in patients with OSA throughout a 24-hour period (18). In a study done by Mohanan et al. a total of 2815 patients with polysomnograms were screened for paroxysmal atrial fibrillation and nonsustained ventricular tachycardia. These patients had normal sinus rhythm at baseline. This study showed that though the absolute arrhythmia rate is low in these patients, the incidence of arrhythmias after an event of respiratory disturbance (sleep disordered breathing) has significantly increased. The odds of an arrhythmia during the apneic episodes was as high as 18 . 57 patients had 62 arrhythmic events of which 76% were runs of nonsustained ventricular tachycardia (NSVT) (4). Roche et al. did a prospective cohort study in the patients who were referred for OSA evaluation (5). 66% of these patients had OSA. The noted that there were frequent episodes of nocturnal nonsustained supraventricular tachycardias that were predominantly found in patients with severe sleep related breathing disorders; however, an increased risk of ventricular arrhythmias was not found. In another prospective trial done by Araújo et al., with 53 patients with stable CAD, patients were divided into 3 groups based on apnea hypopnea index (AHI) (AHI=15, AHI>15, AHI>30). They did not see any significant increase in ventricular arrhythmias in the patients with OSA (6). Another prospective cohort study done by Harbison et al., included 45 patients with sleep disordered breathing. Mean AHI in these patients was 23. These patients were monitored by holter monitoring for 18h and 36 patients in this study group (80% of the study group) showed some kind of cardiac rhythm disturbance. Of these 32 patients who showed cardiac arrhythmias, 8 patients (22%) showed significant ventricular arrhythmias.

It is known from various studies that ventricular late potentials (VLP) are associated with SCD. Scanner et al. prospectively studied 118 patients and polysomnographically verified OSA. They used 21 snorers without OSA as controls. Signal averaged

electrocardiograms and 24 hour holter monitoring were done for all patients and only 7 patients showed VLP. On following all these patients for about 45 months they recorded 2 syncopal episodes and 1 event of sudden cardiac death. None of these events occurred in the 7 patients who had VLP indicating that VLP is not a prognostic marker in patients with OSA (21).

In 2008, Serizawa et al. presented a study done in patients with history of Congestive Heart Failure (CHF) with significant cardiomyopathy (EF < 35%) (7). The study included a total of 71 patients and SDB in these patients was defined as AHI > or = 10. 66% of these patients had SDB and 43% of these patients had life threatening ventricular arrhythmias requiring Automated Implantable Cardioverter Defibrillator (AICD) therapy as opposed to 17% in patients without SDB. This study very convincingly showed that SDB was common and an independent predictor of life-threatening ventricular arrhythmias that were more likely to occur during sleep. Another study done by Fitcher et al. included 36 patients with history of significant cardiomyopathy and AICD placement. and AHI > 10 was defined as SDB in these patients. Holter monitoring was done during sleep study in these patients. The study showed ventricular arrhythmias occurred significantly more often in association with SDB in patients at high risk for arrhythmias and reduced left ventricular ejection fraction (LVEF). A study showing contrasting results was done by Fries et al. in Germany (22). In this study, they included a total of 40 patients with history of cardiomyopathy and AICD placement. These patients underwent polysomnography and 16 patients (40%) among them were diagnosed with sleep apnea (Central or Obstructive Sleep Apnea) and the occurrence of AICD shocks for ventricular arrhythmias occurred in 42% of these patients without OSA or CSA and 42% respectively in patients with OSA and CSA.

A study done by Suzuki et al., in 2006 showed an improvement in the frequency of PVCs in patients with CHF and OSA with oxygen treatment. In 2004, a study done by Leung et al. showed that cheyne stokes respiration in patients with central sleep apnea provokes ventricular ectopy that is most pronounced during the hyperpneic phase. Such an increase in ventricular premature beats might contribute to the higher mortality rates reported in heart failure patients with CSR-CSA (15). These findings can possibly be applied to the OSA patients as well.

The association between OSA and ventricular arrhythmias can also be due to left ventricular dysfunction. Somers et al.

studied 47 patients with LVEF < 40% with. In this study central sleep apnea was defined as AHI > 15. In this study central sleep apnea was associated with impaired cardiac autonomic control and higher frequency of NSVT (25). These results, again could possibly be applied to OSA as well. A study done with one hundred and fifty seven patients showed that severe OSA is associated with high prevalence of concentric LV geometry. This increased prevalence may in part explain the increased rate of cardiovascular events in these patients (26). The association between LV dysfunction and OSA has been established by several studies (27, 28, 29).

### **PATHOPHYSIOLOGY**

The possible underlying pathophysiology in patients with OSA who had ventricular arrhythmias is related to sympathetic activation. Recurrent apneas and hypoxia as a consequence of these apneic episodes leads to the heightened sympathetic drive which will continue while the person is awake too (45). Patients with sleep apnea have faster heart rates even during their resting time indicative of increased cardiac sympathetic drive (46). The mechanism for heightened sympathetic drive are not known. One of the possibilities is tonic chemoreflex activation even during resting wakefulness (normoxic periods) with consequent increase in sympathetic activity (47). Treatment with 100% oxygen to treat tonic chemoreflex lowered sympathetic activity during daytime in patients with OSA (47).

### **TREATMENT OPTIONS**

The role of sleep apnea in causing ventricular arrhythmias that may lead to SCD is not well established therefore treatment strategies or guidelines (therapeutic or preventive) have not been developed. The effect of treating OSA on ventricular arrhythmias has been studied. Roche et al. did a comparative study with 38 patients with polysomnographically diagnosed OSA matched with 38 control subjects with 24 hour holter, ECG monitoring the results showed that QT length related to heart rate was found significantly altered in patients with OSA compared to the controls. This flattened relationship was significantly improved with the treatment of the OSAS with Continuous Positive Airway Pressure (CPAP) treatment. There was no significant impact of CPAP therapy on ventricular ectopic activity as well as on static repolarization parameters (QT, RT, QTc, RTc) measured separately over daytime and nighttime (13). A randomized control study was done by Ryan et al. in which they tested the hypothesis that treatment of OSA with CPAP in patients with CHF would reduce the

frequency of ventricular premature beats (VPBs) during sleep in association with reduced sympathetic nervous system activity. 8 CHF patients with OSA and >10 VPBs per hour of sleep were randomized to a control group (n = 8) or a treatment group who received CPAP (n = 10). The frequency of VPBs and urinary norepinephrine (noradrenaline) concentrations during total sleep time were determined at baseline and after 1 month. The results showed that in patients with HF, treatment of co-existing OSA by CPAP reduces the frequency of VPBs during sleep. These data suggest that reductions in VPBs and other ventricular arrhythmias through treatment of OSA might improve the prognosis in patients with CHF (14). The role of oxygen treatment in preventing ventricular arrhythmias in patients with sleep apnea has been demonstrated in several other studies as well (10,11,19). The role of other treatment strategies like prophylactic anti-arrhythmic treatment or beta blockade and defibrillation have not been studied.

### CONCLUSIONS

The main question we attempted to answer in this article is based on the evidence that sleep apnea is an independent risk factor for sudden cardiac death. The most important and probably the only evidence is provided by Gami et al. in their study which we think can be called a landmark study with 10,701 patients. A systematic review of several studies did not show any convincing evidence of direct association of sleep apnea with ventricular arrhythmias however there is one study which did show evidence of increased episodes of NSVT with sleep apnea (REF). The studies done in patients with cardiomyopathy with OSA seem to show an increased incidence of ventricular arrhythmias compared to the cardiomyopathy patients without OSA. This association was also seen retrospectively with treatment as patients with cardiomyopathy who have OSA when treated with CPAP did show reduced frequency of ventricular arrhythmias. (Rewrite this) In conclusion, there seems to be a significant association between sleep apneas and ventricular arrhythmias but we did not find any evidence to see whether this association can explain the association between OSA and SCD. There is a need to design a bigger study to study the type of arrhythmias which were present at the time of the event of SCD in patients with OSA. If there is evidence of OSA being an independent risk factor for ventricular arrhythmias leading to the SCD, then there will be a need to come up with prophylactic strategies.

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