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Association of Cardiac Arrhythmias with Obstructive Sleep Apnea & Role of CPAP

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Abstract: ***Sleep related breathing disorders (SRBD), manifesting as hypopneas and apneas include Obstructive sleep apnea (OSA) in its ultimate form. Obstructive sleep apnea is characterized by episodic incomplete or complete obstruction of the upper airways, manifesting as apnea, which is complete cessation of breathing and closure of pharyngeal airways. Besides other medical complications, cardiac arrhythmias are one of the commonest medical complications associated with OSA. Cardiac arrhythmias, depending on their complexities are directly related to morbidity and mortality in patients of OSA. Recurrent stressful episodes of complete breathing cessation followed by restlessness due to arousals leads to hypoxemia and neuroharmonal catecholamine surge as a suggested trigger for cardiac arrhythmias orchestrating acute and chronic cardiovascular changes. Despite of advancement in diagnosis and treatment modalities, it is impossible to predict the prognosis and response to various modalities of treatment like continuous positive airway pressure (CPAP), cardioversion, and tracheostomy. Therefore, this update review of the literature is aimed to elaborate epidemiology and underlying pathophysiology of cardiac arrhythmias associated with OSA and to assess the impact of OSA management on cardiac arrhythmia.***

Keywords: OSA - Obstructive Sleep apnea, Arrhythmia, Hypopnea, Apnea

1. Introduction

Sleep - disordered breathing (SDB) or Sleep related breathing disorders (SRBD) are comprised of abnormalities in frequency and depth of breathing during sleep. Various risk factors for SRBD are age, obesity, short neck, and craniofacial abnormalities [**1, 2**]. Grouped as SRBD, include hypopnea and obstructive sleep apnea syndrome (OSA), central sleep apnea, hypoventilation syndrome, upper airway narrowing and cheyne - stokes breathing [**3, 4**]. Among these OSA, as extreme variant of SRBD, is manifesting as incomplete or complete obstruction of upper pharyngeal airways during sleep, disrupting normal ventilation and sleep pattern, resulting in snoring and daytime somnolence [**5 - 8**]. With increasing awareness and diagnosis obstructive sleep apnea affects about 4% of males and 2% females aged 30 - 5 years which is comparable to the prevalence of diabetes type - 1 [**9**]. A diagnosis of OSA based on polysomnography, is accepted with reported rate of apnea - hypopnea index (AHI) or as respiratory distress index (RDI) per hour of sleep >5 with associated snoring and somnolence. [**10**]

In the recent past, cardiac arrhythmia associated with sleep obstructive apnea has been the focus of research in various medical sub - specialties [**10 - 12**]. Cardiac arrhythmias are a recognized and common association of OSA, having typical episodic heart rate variations in SRBD. The frequency and complexity of these arrhythmias in a particular patient of OSA, has prognostic value in terms of morbidity and mortality [**13, 14**]. The prevalence and clinical relevance of cardiac arrhythmias including their possible mechanisms which are not yet full known, but could be same as purposed in other cardiovascular diseases associated with OSA. Obstructive sleep apnea causes episodic pharyngeal collapse during sleep, leading to oxygen desaturation, sustained inspiratory effort against obstructed upper airways, terminating in an arousal [**15**]. Hemodynamic, autonomic, humoral and neuroendocrine mechanisms play a role in evoking acute and chronic cardiovascular events [**16 - 18**]. Commonest arrhythmias during obstructive sleep apnea include non - sustained ventricular tachycardia, 2nd degree heart block, frequent premature atrial and ventricular beats [**19 - 23**]. Actual Incidence and prevalence of cardiac arrhythmias associated with OSA are not well defined due to lack of extensive studies on this subject, therefore questions will remain whether OSA causes cardiac arrhythmias as a primary condition or the patients having OSA have pre - existing cardiovascular conditions [**24 - 27**]. Similarly prognosis of cardiac arrhythmias associated with OSA remains unclear, in terms of whether treatment of one has any significant effect on the other.

This extensive review article includes underlying pathophysiological mechanisms on the interrelationship of OSA and cardiac arrhythmias in epidemiological terms and to evaluate the impact of OSA treatment.

Epidemiology

Obstructive sleep apnea is not an uncommon condition, it affects about 2 - 4% of populations with a double prevalence in males than females [**28 - 30**]. Even today in developed western countries 5% of the cases of OSA - Syndrome (OSAS) remain undiagnosed [**31**]. Different types of cardiac arrhythmias associated with OSAS include premature, atrial, ventricular beats, sinus arrest, non - sustained ventricular tachycardias and atrioventricular conduction defects in about 30 - 50% of cases, and their severity and frequency is linked to the degree and duration of hypoxemia [**32 - 34**]. Patients having OSA and organic heart diseases together are more likely to have all kinds of cardiac arrhythmias [**35**]. Bradycardias are also reported in some of the case reports representing conduction defects associated with sinus node depression [**36**]. Among nocturnal cardiac arrhythmias occurring during sleep, commonest (50%) are reported in those diagnosed having OSA. Whereas in general population, prevalence of atrial fibrillation (AF) is 0.4%, it is said to be more common (>6%) in those age above 80yeras [**37**]. In the presence of OSA, the frequency of AF is increased many fold and is reported 24% in middle aged men and 9% of females [**38**]. Although there is controversy in the reported prevalence of OSA related cardiac arrhythmias [**39, 40**]. Therefore conclusion, that cardiac arrhythmias are reported more frequently among those having SRBD remains questionable. [**39, 40**]. **Table - A** is showing data from various studies on association of OSA and cardiac arrhythmias.

Table A: Studies on prevalence of cardiac arrhythmias and obstructive sleep apnea

Studies	Subject	prevalence
Mehra et al.[18]	566	Non - sustained ventricular tachycardia in 5.3%, complex Complex ventricular ectopy 25%, AF 4.8%
Gulleminault et al, [22]	400	Bradyarrhythmias in 18% of patients, Sustained ventri cular tachycardia in 2%, sinus arrest in 11%
Flemons et al, [39]	263	Complex ventricular ectopy (including ventricular tachy Tachycardia) in 1.3% of patients. Frequent ventricular. PVCs (>30/hr) in 2.6%, 2nd degree atrio - ventricular block in 1.3%, sinus arrest in 5.2% patients.
Tilkian et al, [45]	15	Marked sinus arrhythmia in 14 patients, extreme sinus Bradycardia in 6, asystole in 5, 2nd degree atrioventricular. Block in 2, Ventricular arrhythmias - complex premature Ventricular beats in 10, ventricular tachycardia in 2 Patients.
Becker et al, [46]	239	Sinus arrest and atrioventricular (AV) block in 30% of Patients.
Mooe et al, [47]	121	Atrial fibrillation (AF) in 32% of patients with apnea Hypopnea index (AHI) >5 or = 5 and in 18%patients. With oxygen desaturation index (ODI) <5
Javaheri et al, [48]	81	Atrial fibrillation in 32% of patients.
Simantirakis et al, [50]	23	Rhythm disturbances in 48% of patients
Gami et al, [51]	524	OSA more prevalent in patients with AF= (n=151) than In high - risk patients with organic heart disease.
Porthan et al, [52]	115	Sleep apnea syndrome common in lone Atrial fibrillation.
Xiofan Wu, et al.9[1]	390	Treatment of OSA reduces the risk of repeat re - vascularization after percutaneous coronary intervention.
Fatmia Dumas Cintra [95]	101	Cardiac arrhythmias occur more frequently in patients OSA, and prevalence increases with disease severity, age, sex

While apnea - hypopnea index (AHI) were predictors of arrhythmias.

It appears from the data given in various studies, that arrhythmias were more frequent in SRBD patients having severe nocturnal hypoxemia especially in phase of rapid eye movement sleep. [**40**]. it is reported in a recent study that among patients who went through successful cardioversion for supraventricular arrhythmia as atrial fibrillation, there is high recurrence rate of about 82% over a period of one year. It is in contrast to 42% and 53% rate reported among OSA treated with CPAP and those controls who were not investigated by sleep studies. None of these studies has commented on an independent role of obstructive sleep apnea on deaths related to arrhythmias, other than attributing to co - existing cardiovascular organic disease and diabetes [**43**]. Further studies are required to strengthen the evidence on association of cardiac arrhythmias and OSA.

OSA in children manifests by central hypoventilation and respiratory muscle disorders. Children suffering from genetic disorders associated with altered upper airway anatomy, central ventilatory control and associated respiratory muscle dysfunction represent a large percentage of children having OSA. Other common condition is hypertrophied adenoids and tonsils causing narrowing of pharyngeal airways besides obesity. OSA and its association with cardiovascular risk in children however lack sufficient evidence in today's literature [**44**].

Evidence in favor of association of cardiac arrhythmias with OSA

The association of SRBD and cardiac arrhythmias was first time reported, 30 years ago in a study by Tilkian[45] et al; where overnight effect of tracheostomy, and atropine was studied on cardiac arrhythmias during sleep and wakefulness in 15 patients of OSA, and as part of sleep studies, keeping them under continuous monitoring and recordings by holter [**45**]. Among the findings, marked sinus tachycardia was observed in 93%, sinus bradycardia 40%, asystole 33%, atrioventricular block 13%, premature ventricular contractions (PVCs) 66 % and ventricular tachycardia 13%. Main type of Arrhythmias during wakefulness were PVCs in 40%. Sinus arrhythmia was more characteristic of OSA, and was usually accompanied by serious tachy - brady arrhythmias.

A study by Guilleminault [22]et al, on 400 patients with OSA, reported 48% patients (n=192) having cardiac arrhythmias including bradyarrhythmias in 18% (n=72), sustained ventricular tachycardia 2% (n=8), sinus arrest 11% (n=44), 2nd degree atrioventricular (AV) block 8% (n=32) and PVCs 19% (n=76) [22]. There was no significant difference in number of apneic episodes, weight, age and oxygen desaturation during sleep than those having arrhythmias and conduction defects. The commonest abnormalities were non

- sustained ventricular tachycardia in 8 patients, sinus arrest lasting for at least 2.5 - 13 seconds in 43 patients, 2nd degree AV block in 31 patients. Frequent (>2/min) PVCs were reported in 75 patients during sleep. Fifty patients with significant arrhythmias required tracheostomy and were monitored after surgery. No other type of arrhythmias except PVCs were observed in this group of patients after tracheostomy.

Flemons[39] et al, reported prevalence of arrhythmias in 263 patients of OSA [39]. Here reported prevalence of arrhythmias in patients with or without sleep apnea included, complex PVCs and ventricular tachycardia 1.3% vs 4.1%, frequent PVCs 2.6% vs 6.2%; 2nd degree AV block - 1.3% vs 4.1% and sinus arrest - 5.2% vs 1.0% (>30/hr). The difference was statistically not significant and was independent of severity of sleep apneas.

Becker [46]et al, performed Holter monitoring studies on 239 patients of OSA using a validated recording device dependent on recordings of heart rate, oxygen saturation (SaO2), snoring and body position in the bed [46]. This observation reported that bradycardia occurred exclusively during apneas and hypopneas and were absent during hyperventilation, thereby demonstrating a clear link between bradyarrhythmias and severity of apnea related hypoxemia.

Becker study in 1995 was followed by another study conducted by Mooe et al, which revealed that pre - operatively diagnosed SRBD with nocturnal hypoxemia was an independent predicting factor of atrial fibrillation after coronary bypass surgery [**47**].

Javaheri [48]et al, studied 81 male patients with stable heart failure without other major comorbidities. Among these, 51% suffered from SRBD, of which 40% was central sleep apnea and 11% OSA [**48**]. Atrial fibrillation and ventricular arrhythmias were higher in those having sleep apnea. Same way, patients with an AHI>5, and post coronary bypass surgery were reported having a higher incidence of postoperative AF 32% vs 18% in patients without SRBD. Continuous cardiac monitoring by defibrillator showed that onset of nearly 75% of episodes of persistent atrial fibrillation occurred during sleep between 8pm and 8am, which strongly points towards its association with OSA [**49**].

In their important study, Simantirakis et al, used loop recording devices in 23 patients with OSAHS in whom other cardiac and lung diseases were excluded by exercise testing, invasive electrophysiological studies, echocardiography and spirometry, those having diabetes were excluded [50]. After continuous recording over 2months, 48% had significant rhythm abnormalities occurring during sleep. It was also noted that after 48 hours of Holter monitoring, no significant bradycardia was detected.

A prospective study by Gami [51]et al; studied simultaneously patients undergoing electro - cardioversion for AF (n=151) and patients without past or current AF referred to a general cardiology practice (n=312) [51]. The presence of OSA was confirmed by the Berlin questionnaire, a validated questionnaire to identify individuals having high risk of OSA. Atrial fibrillation was more common among patients having OSA, than those in general cardiology practice (n=312) [**51**]. The rate of fibrillation was more frequent among patients having OSA, than in general cardiology group 49% vs 32%. The new finding in this study was that a strong association exists between OSA and AF, Such that OSA was significantly more prevalent with AF than in high risk patients with other cardiovascular diseases. In contrast another relatively smaller Finnish study[52], used objective sleep studies (Autoset portable Plus device), did not agree with the previous findings and actually reported no difference in the prevalence of OSAHS in 59 patients with isolated AF, compared with 5 controls matched for age, gender and cardiovascular morbidity [**52**].

A recent study, 2014 shows that patients having OSA if not treated by CPAP, has increased incidence of coronary artery disease and associated arrhythmias. However, when treated by CPAP, there is significance reduction in the in the incidence of coronary artery disease and associated arrhythmias before and after subcutaneous intervention [**90**].

A subgroup analysis of the Sleep Heart Study revealed a four times increase in the prevalence of AF in subjects with an AHI>30 as compared with patients with no SRBD, matched for age, ethnicity, sex and body mass index (BMI) [**18**]. Moreover, a strong relationship was reported between SRBD and number of ventricular PVCs/hr.

In the light of above findings, it can be said that patients with severe SRBD were found to have 2 to four times more frequent complex cardiac arrhythmias than those without SRBD.

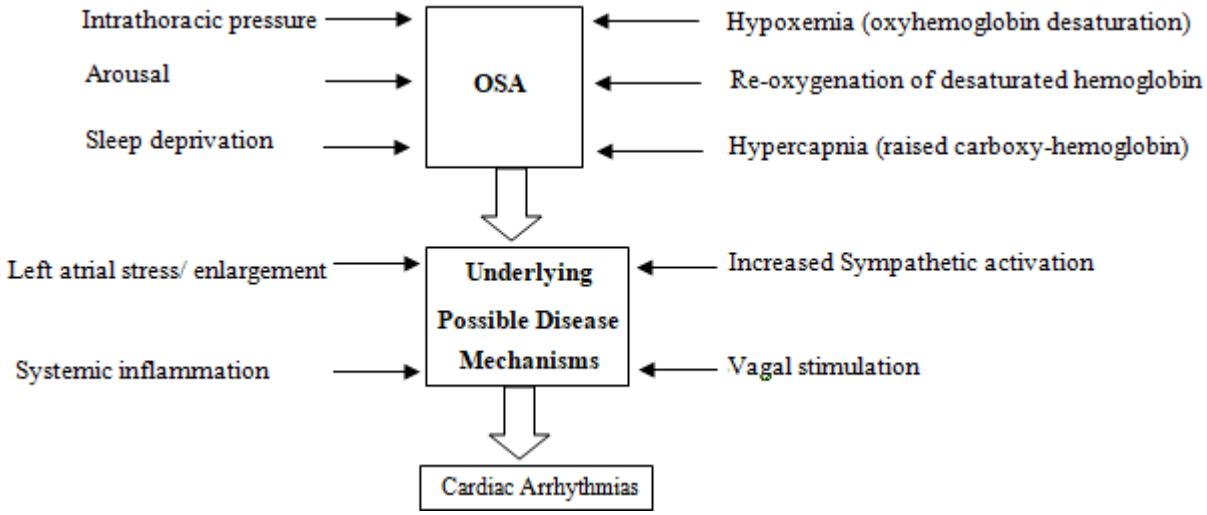
In a largest recent study2002 - 2012 by Xiaofan Wu et al; on 390 patients of OSA treated with CPAP application and treated simultaneously for coronary heart disease with percutaneous angioplasty reported clear benefits of CPAP modality of treatment. Those patients who were treated with CPAP and had gone under a percutaneous intervention, they had significant reduction in their need for repeat re - vascularization [**91**].

The prevalence of OSA is 2 - 3 times more in patients with diabetes and cardiovascular disease when compared to general population and so is true for associated cardiac arrhythmias [**92 - 94**].

A latest study 2014, on 101 volunteers by Fatima Dumas Cintra. et al[95], has reported that nocturnal cardiac arrhythmias are more frequent in patients with OSA, and there frequency and prevalence increases with disease severity, age, and sex, while apnea hypopnea index were the predictors of cardiac arrhythmias in this population sample [**95**].

Pathophysiological mechanisms in OSA related arrhythmias.

Despite of poor understanding about the mechanisms involved in cardiac arrhythmias associated with OSA, there are several observations where arrhythmias would occur more commonly in patients with OSA [**Figure - 1**].



There are recurrent desaturations and co - existing rise in arterial blood carbon dioxide levels due to attenuated chemo - reflexes [**53, 54**]and baro - reflexes [**55, 56**] leading to autonomic sympathetic neural stimulation. Recurrent or persisting sympathetic activation leads to rise in blood pressures in systemic and pulmonary circulation with increased stress on heart and large vessels. Episodic or sustained stress on atrial tissue leads to generation of abnormal electrical signals giving rise to ectopic beats as well as supraventricular arrhythmias like AF [**57**]. Stress on heart chambers on one hand can lead to supra ventricular arrhythmias, and on the other hand leads to remodeling of conducting system manifesting sinus block with associated atrial arrhythmias [58]. Again hyper stimulation of sympathetic nervous system in association with respiratory hypopneas and apneas triggers sinus node automaticity [**59**].

There are a number of other reports on the strong association of hypertension and OSA [**60, 61**], whereas association of AF and hypertension is also very well recognized [**62, 63**]. Although not definite, relationship between AF and OSA could be just due to remodeling of right atrial tissue as happens in patients with hypertensive heart disease [**64**]. The effortful ventilation against closed upper airways during apneas leads to enhanced shift in cardiac chamber pressures and thus increasing their dimensions [**65, 66**]. Sudden changes in pressure induced stress as well as changes in chamber anatomical structure could promote triggered stretch on activation of depolarization channels [**67**]. The frequency of SRBD and severity of OSA is said to be independently associated with enhanced systemic inflammation accompanied by rise in C - reactive protein like acute inflammatory markers [**68**]which is said to be directly linked to the frequency of AF [**69**]. Despite reports that apnea leads to left atrial enlargement via systemic hypertensive stress as part of hypertensive heart disease [**70**]. This is said to be a triggering factor for AF, this may not be appealing and may remain an unproved hypothesis, because the sinus node is on the right atrium which is enlarged due to 2ndry pulmonary hypertension (corpulmonale) associated with recurrent hypoxemia in OSA. [**71**]. Contrary to this, brady - arrhythmias are said to be associated with prolonged apneas and hypoxia in OSA that give rise to vagal stimulation reflex resulting in depression of the cardiac conducting system with simultaneous stimulation of sympathetic supply of peripheral vessels, muscles, renal and splanchnic system [**72 - 75**]. Despite of the vagal response producing a notable brady - arrhythmias, such as atrioventricular block and asystole may develop even when there is no cardiac conduction disease [**22**]. It is likely to occur during rapid eye movement phase of sleep associated with 4% reduction in oxygen saturation [**76**]. Reentry mechanisms may be related to the vagal stimulation that results from breathing against partially collapsed upper pharyngeal airways leading to bradycardia [**77, 78**].

In addition, mechanical effects related to SRBD cause negative intra - thoracic pressure on the atrial and ventricular musculature promoting remodeling and predispose to development of cardiac arrhythmias [**79**].

2. Treatment

In the absence of any under lying cardiac conduction system abnormality and significant arrhythmias or heart block associated during apneas, it may be treated effectively with continuous positive airway pressure (CPAP) application and in some cases if necessary by tracheostomy [**53, 80**]. There are no interventionalor epidemiological studies related in particular to the severity, prevalence and outcomes of cardiac arrhythmias and management of OSA. According to a study by Becker et al[46]; in 1995 on 239 patients reported that 7% (n=17) of their patients with OSAHS were having significant bradyarrhythmias and out of these 17 patients, one continued to endure Brady - arrhythmias despite of CPAP application. Majority of these patients were already diagnosed having cardiac disease or newly discovered cardiac abnormalities like pulmonary hypertension, congestive heart failure, hypertension, therefore OSAHS as a sole cause of cardiac arrhythmias was difficult to determine.

In an observational study by Kanagala et al, reported 80% increased rate of recurrence of AF after successful cardioversion in patients with OSAHS who received inadequate treatment as compared to those without OSAHS and adequately treated OSAHS patients [**41**]. A study by Harbison et al, reported significant cardiac arrhythmias in 45 patients who had confirmed OSAS and assessed the outcome

of nasal CPAP application [**45**]. Seven of eight patients improved having no more rhythm abnormalities, who had pathological rhythm disturbances like ventricular tachycardia or fibrillation, complex PVCs or new supraventricular tachycardia.

In another controlled randomized study with one - month trial on 18 patients with OSA and having systolic dysfunction, Ryan et al, observed the effects of CPAP application on the ectopic ventricular arrhythmias [**81**]. Treatment of OSA with CPAP showed improved prognosis in these patients having co - existing congestive heart failure (CHF) and reduction in PVCs during sleep by 58%.

In a 10 years long prospective cohort study published by Marin et al, they reported a higher risk of fatal and not fatal cardiac events in males with severe OSA, who were non - compliant to CPAP application as compared to snorers, CPAP –treated patients with OSA and healthy males. [**82**]. This study advocates that OSA has adverse effects on long term cardiovascular prognosis. However atrial pacing as part of long term management would favor a link between OSA and atrial fibrillation. There is increased risk of recurrence of AF 2 In cardioverted patients of atrial fibrillation, presence of untreated sleep apnea increases 2 fold their risk of recurrence of atrial fibrillation within. When observed over a period of one year following cardioversion, there was still a significant increase in recurrence of AF in patients not treated with CPAP, when compared with those treated by CPAP application [**41**].

In a recent study2002 - 2012 by Xiaofan Wu et al; on 390 patients of OSA treated with CPAP application and treated simultaneously for coronary heart disease with percutaneous angioplasty reported clear benefits of CPAP modality of treatment. Those patients who were treated with CPAP and had gone under a percutaneous intervention, they had significant reduction in their need for repeat re - vascularizationThe prevalenc of OSA is 2 - 3 times more in patients with diabetes and cardiovascular disease when compared to general population and so is true in associated cardiac arrhythmias [**91**].

Cardiac Pacing in OSA

This modality of treatment to begin with however has created a new hope in patients of obstructive sleep apnea (**83**). Correction of cardiac arrhythmias with overdrive pacing may lead to a significant reduction in the morbidity associated with central or OSA. Similar findings however were not reported in subsequent prospective studies, when 16 patients with the OSA were treated with overdrive pacing and reassessed after 24 hours and after 1 month and outcomes were compared with use of nasal CPAP [**84 - 86**]. The results showed that atrial overdrive pacing was not very useful on the degree of OSA, whereas benefit of CPAP was overwhelming as treatment of OSA. Another prospective, single blinded, randomized crossover trial in population of patients having moderate to severe OSA also showed that temporary atrial pacing does not prove useful in improving symptoms of OSA, therefore regular use of permanent atrial pacing in these patients at present doesn't seems very promising [**87**]. Recent data has confirmed only this much that overdrive atrial pacing is partially effective in relieving respiratory symptoms, in patients having co - existing OSA and heart failure. Atrial overdrive pacing as a therapeutic modality however was not effective in improving respiratory function related to sleep [**88**].

3. Future Prospects

Anticipation of any significant prognostic improvement in the presence of SRBD related cardiac arrhythmias, remains doubtful in the patients of OSA. This observation demands more research in this field to detect and report OSA associated cardiac arrhythmias during sleep studies [**89**]. In the presence of multiple co - morbidities and risk factors for SRBD and OSA, like obesity, cardiac failure, pharyngo - facial anatomical anomalies, and neuroendocrine abnormalities make it very challenging. Treatment with technology based devices is not tolerated equally by all. In the absence of a strong evidence, it remains uncertain that only treating OSA, in the presence of cardiac arrhythmias could prove beneficial. Underlying mechanisms still being unclear, present literature however do suggest based on prevalent studies, that SRBD and OSA are not only arrhythmogenic in their own right, but act as an exacerbating factors as well. Therefore, when one is present, clinicians as a practice point, must look for the other, because early recognition and referral in time certainly will reduce morbidity and mortality. So far CPAP application has proved quite useful in relieving patients either having OSA alone or in association with cardiovascular diseases. Trials on the benefits of CPAP application focused on the population of patients having OSA and cardiovascular risk may prove very useful. There is a need of more prospective studies and trials aimed not only to understand the relationship of OSA and cardiac arrhythmias, but also to observe the effect of treatment of one on the other. Reduction of incidence as well as recurrence of atrial fibrillation in response to an effective treatment of OSA requires more trials on large scale to gather more concrete evidence [**64, 90**].

4. Conclusion

This review has highlighted the association of cardiac arrhythmias with SRBD, OSA, their possible mechanisms, and usefulness of various modalities of treatments advocated in the present literature. Despite of enormous research on this association, still there is a dire need not only to determine underlying mechanisms with clarity, as well to recognize early those patients who will benefit when offered various treatments like CPAP, cardioversion and tracheostomy. Early recognition and prompt proper intervention has a great prognostic importance for patients of SRBD, OSA with or without associated cardiac arrhythmias. For this further research needs to be continued. CPAP application remains a first choice treatment tool in patients of OSA, which clearly reduces the risk of coronary heart disease and associated cardiac arrhythmias.

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