

# A Systematic Review of the Association between Obstructive Sleep Apnea and Ventricular Arrhythmias

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**Introduction:** Obstructive sleep apnea (OSA) is an independent risk factor for sudden cardiac death. The aim of this review was to study the relationship between OSA and ventricular arrhythmias.

**Methods:** PubMed, Medline, and Cochrane databases were searched with MESH headings to find studies linking OSA and ventricular arrhythmias including ventricular ectopy, ventricular tachycardia (VT), and ventricular fibrillation (VF). Studies were graded by a scoring system, and an attempt was made to pool data.

**Results:** There were no matched cohort or case control studies to study the association between OSA and ventricular arrhythmias. Given data heterogeneity, pooling and meta-analysis of data were not possible. An attempt was made to judge the quality of evidence and present a systematic review. Patients with OSA were noted to have higher odds of ventricular ectopy, and were at a higher risk for ventricular arrhythmias. Associations included higher QTc dispersion and

HR variability. We did not, however, find any clear evidence for a direct correlation between increased apnea hypopnea index and increased VT or VF.

**Conclusions:** Pooling and meta-analysis of studies linking OSA and ventricular arrhythmias were not possible due to heterogeneity of data. In a systemic review of studies, patients with OSA were noted to have higher odds of ventricular ectopy and arrhythmias. A single study showed that CPAP may help lower arrhythmogenicity; however, it was unclear if CPAP lowered the risk of VT. Further research should focus on studying the association of OSA and causes of sudden cardiac death, including ventricular arrhythmias.

**Keywords:** OSA, sleep apnea, ventricular fibrillation, ventricular tachycardia, arrhythmia

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Obstructive sleep apnea (OSA) is a common, treatable, chronic disorder that affects more than 18 million Americans.<sup>1-5</sup> Its associated healthcare costs are substantial, and a large number of individuals remain undiagnosed and untreated.<sup>1-6</sup> It is characterized by recurrent complete (apnea) or partial (hypopnea) closure of the upper airway, often terminated by brief arousals and associated with intrathoracic pressure changes. This results in sleep fragmentation, increased sympathetic nervous system stimulation at night, and an increase in circulating inflammatory markers of endothelial dysfunction.<sup>7,8</sup>

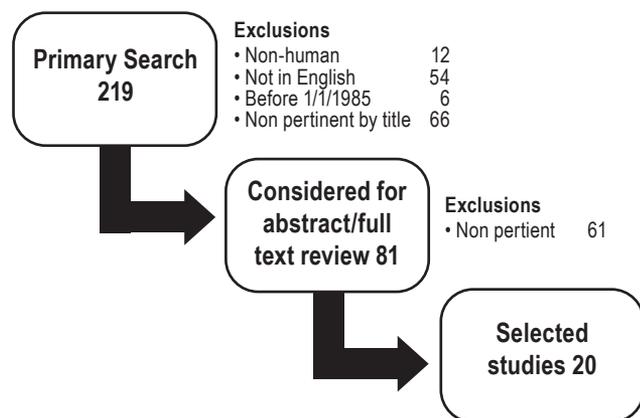
Cardiovascular problems have been increasingly linked to OSA. Evidence has shown that patients with OSA were more likely to have nocturnal “non-dipping” of blood pressure in sleep.<sup>9,10</sup> Studies have also shown that patients with decreased total sleep time and OSA are at a higher risk for hypertension; continuous positive airway pressure (CPAP) lowers blood pressure in these patients.<sup>11</sup> Improvement in blood pressure has also been described in patients with OSA using an oral appliance.<sup>12</sup> Uninterrupted sleep reduces ventricular ectopy. This reduction is stronger than that observed with commonly used antiarrhythmic agents such as quinidine, procainamide, or propranolol.<sup>13</sup> In patients with OSA, sleep is interrupted by frequent arousals. An increase in severity of OSA is associated with an increased sleep fragmentation, potentially increasing the risk of cardiac arrhythmias.<sup>14</sup>

Ventricular arrhythmias can be classified electrocardiographically into ventricular tachycardia (VT), ventricular fibrillation

(VF), premature ventricular contraction (PVCs), and accelerated idioventricular rhythm.<sup>15</sup> Premature ventricular contractions (PVCs) are early occurring beats with widened QRS complexes that have a distinct morphology; these generally by themselves are considered benign. VT is a cardiac arrhythmia of three or more consecutive complexes in duration emanating from the ventricles at a rate of greater than 100 beats per minute (bpm) (cycle length < 600 ms). Non-sustained VT is a series of at least three repetitive ventricular beats that have durations of less than 30 seconds or do not require emergency therapy. Sustained VT lasts for more than 30 seconds or requires termination earlier because of hemodynamic compromise. Ventricular fibrillation is identified by grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude. This leads to sudden cardiac arrest. Non-sustained ventricular tachycardia (NSVT) has been described as a risk factor for sudden cardiac death.<sup>16-19</sup> Patients with congestive heart failure (CHF) are at higher risk for sudden cardiac death from VT.<sup>20-22</sup>

Among patients with an implantable cardiac defibrillator (ICD), those with SDB have a higher risk of receiving treatment for life-threatening arrhythmias.<sup>23,24</sup> Prior review articles have focused on the association between OSA and atrial arrhythmias; however, there is little known about OSA and ventricular arrhythmias.

Our aim was to review available literature for associations between OSA and ventricular arrhythmias. A secondary goal

**Figure 1**—Search strategy.

was to identify changes in the prevalence of ventricular arrhythmias among patients treated with CPAP.

## METHODS

### Data Sources

Three electronic databases (MEDLINE, PubMed, and Cochrane) were searched from dates 1985 to current to locate potential good quality peer-reviewed articles. The following MESH terms were used in various combinations, “OSA,” “obstructive sleep apnea,” “sleep disordered breathing,” “ventricular arrhythmias,” “ventricular ectopy,” “premature ventricular contraction,” “automatic implantable defibrillator,” “Ventricular tachycardia,” “ventricular fibrillation,” and “sudden cardiac death.” Studies focusing on central sleep apnea were excluded by including “NOT central sleep apnea” in the search strategy. The search strategy was limited to English language abstracts and adult human population. Duplicate records, if any, were removed from the final search result. The reference lists of relevant articles were then reviewed to retrieve other studies that were missed in the original search.

### Study Selection and Rejection

Complete randomized control trials, case control trials, as well as observational studies were included. Abstracts were excluded, as were letters, animal studies, and studies in languages other than English. The articles were evaluated by three authors (AR, RK, AK) and classified as being adequate or not based on an a priori established set of criteria. Those that were adjudged to be of poor quality were rejected. Common reasons for exclusion were studies with exclusively central sleep apnea or obesity hypoventilation and studies without use of a control population. A large proportion of OSA is now diagnosed with home sleep studies and not by in-lab polysomnography (PSG). A lack of PSGs alone was therefore not regarded a reason for exclusion.

Conflicts of interest were assessed in all articles included. Sources such as industry affiliation or funding, if noted, are indicated in **Table 1**. Any conflicts regarding inclusion or exclusion of studies in this review were resolved by consulting the senior authors (LT, AK).

## Data Extraction and Quality Assessment

Three independent reviewers (AR, RK, AK) validated, extracted, and recorded study related data. Each study was graded according to guidelines by the Cochrane Collaboration, and a scoring system was employed, in which 1 point was awarded if the study was described as a randomized control study, 1 point for appropriate method of randomization, 1 point for appropriate control group, and 1 point for blinding of evaluator.<sup>25</sup> Studies were then rated on a scale from 1-4. Any discrepancy in the scoring of trials was resolved in discussion between the 3 reviewers and input from the senior authors.

## RESULTS

**Figure 1** summarizes the results of the literature search. In the first selection of articles, 210 search results were obtained. Of these, 138 were excluded either due to being non-human studies, or studies not in English language by review of the title. Eighty-one studies were then considered for an abstract or a full-text review. Of these, 61 were excluded as being non-pertinent based on the review of either the abstract or full text of the article. Twenty articles were included in the final review. These consisted of 10 observational studies, 8 case control studies, one case series, and one CPAP interventional study. No double-blind cohort studies were found. Sample sizes varied from 22 to 1,911 patients.

### Study Characteristics and Quality

**Table 1** summarizes the characteristics of the studies and the study populations included in the final analysis. The studies fell into 2 broad categories. The first category consisted of studies in ICD recipients, which compared the prevalence of OSA in this group versus non-ICD recipients. Some compared the rate of ICD therapy between individuals with and without OSA, and others compared rates of recurrence of arrhythmias between patients with and without OSA after catheter ablation of arrhythmias. The second category of studies compared the prevalence of ventricular arrhythmias between OSA patients and non-OSA patients. Many such case control studies had age-matched controls; however, there were a few observational cohort studies without matched controls. Lastly, there were a number of studies of patients with CHF, since this group of patients has a higher prevalence of ventricular arrhythmias.

The quality scores of the included articles ranged from 0 to 4. These varied in the outcome measured, inclusion criteria, definition of sleep apnea, and sample size. Due to the heterogeneity of the studies we were not able to pool data for a meta-analysis. We therefore proceeded to perform a systematic review.

## DISCUSSION

OSA affects 2% to 4% of adults and is associated with diabetes, impaired glucose metabolism, and increased cardiovascular mortality.<sup>4,26-35</sup> In this review, we identified 20 studies evaluating the effect of OSA on ventricular arrhythmias. We attempted to perform a meta-analysis, but were limited by heterogeneity in the definition of OSA, in the diagnostic methods for OSA detection and in inclusion criteria such as ICD recipients or CHF.

**Table 1—Studies included in systemic review.**

Study Name	Design	Population	Definition of OSA	Diagnosis of OSA	Outcome and conclusion
Marin 1998 <sup>42</sup>	Case-control	AMI in ICU. 55 cases, 196 controls	ODI $\geq$ 10 (4% desaturation) with snoring & H/O EDS	Holter & nocturnal SpO <sub>2</sub>	$\uparrow$ PVCs p (< 0.05) & $\uparrow$ couplet PVCs p (< 0.05).
Noda 1998 <sup>59</sup>	Case-control	18 cases, 10 age matched controls	Controls = no OSA AI < 20 = mild AI $\geq$ 20 = severe	PSG	AHI $\geq$ 20 had $\downarrow$ HRV. $\uparrow$ Time with SpO <sub>2</sub> < 90% $\downarrow$ HRV.
Fries 1999 <sup>60</sup>	Prospective observational	40 ICD recipients, 2 year f/u	AHI $\geq$ 10	PSG (post ICD)	16/40 patients had SDB, 8 CSA, and 7 OSA. $\uparrow$ 2 y mortality with CSA
Harbison 2000 <sup>57</sup>	Prospective observational	45 patients with OSA, studied pre and post CPAP	Mean AHI 50 $\pm$ 23	PSG	35/45 subjects had nocturnal dysrhythmia, 8/45 had pathologic dysrhythmia in 7/8 dysrhythmia resolved with CPAP
Fichter 2002 <sup>61</sup>	Observational cohort	38 ICD recipients with LVEF 36 $\pm$ 13%	AHI $\geq$ 10	PSG	Prevalence of SDB 14/38. $\uparrow$ AHI associated with $\uparrow$ Arrhythmias
Roche 2003 <sup>62</sup>	Observational prospective cohort	147 consecutive patients	AHI $\geq$ 10	PSG + Synchronized Holter	No increase in ventricular arrhythmias, Nocturnal paroxysmal asystole was more prevalent in OSA (10.6 vs 1.2%; p < 0.02) and $\uparrow$ with severity of OSA
Roche 2005 <sup>63</sup>	Case-control	38 cases and 38 age matched controls	Mean AHI 56.9 $\pm$ 28.4	PSG	No difference in ventricular ectopy or Qtc, RTc, QT, or RT intervals. QT/RR slope was altered b/w OSA and no OSA and improved with CPAP
Mehra 2006 <sup>36</sup>	Case-control	Sleep Heart Health Study	RDI $\geq$ 30 = OSA (cases) vs. RDI < 5 no sleep apnea (controls)	PSG	SDB was associated with $\uparrow$ in prevalence of NSVT (OR = 3.4), CVE (OR = 1.74), and AF (OR 4.02).
Javaheri 2006 <sup>45</sup>	Observational cohort	100 CHF patients with EF < 45%	Average AHI > 49/h. (49% patients had SDB, 37% CSA & 12% OSA)	PSG	No correlation between OSA and VT. CSA was associated with ventricular arrhythmias.
Aytemir 2007 <sup>38</sup>	Case-control	80 cases and 55 age matched controls	AHI > 5	PSG & Holter	OSA patients had $\downarrow$ HRV, $\uparrow$ HR turbulence, and $\uparrow$ QT dynamicity, all predictors of myocardial vulnerability.
Craig 2009 <sup>41</sup>	Interventional trial	83 men, before & after CPAP for 1 month	ODI $\geq$ 10, 4% desaturation (Av. 41.2 $\pm$ 24.3)	Cardiorespiratory Study	CPAP $\uparrow$ HR, no difference in arrhythmias
Mehra 2009 <sup>64</sup>	Case-control, post hoc analysis	1,911 patients from the MrOS Study	OAI < 2.9, vs. OAI 2.9-6.5, OAI 6.5-12.7, vs. OAI > 12.7	PSG	$\uparrow$ RDI associated with $\uparrow$ risk of AF, and CVE, $\uparrow$ OSA associated with $\uparrow$ CVE but not AF. $\uparrow$ hypoxia associated with CVE.
Monahan 2009 <sup>65</sup>	Observational cohort	57 patients from SHHS who presented with arrhythmias	RDI > 30.	PSG	Odds of arrhythmias after a respiratory disturbance were 18 times odds of arrhythmias occurring after normal breathing, overall incidence of arrhythmias associated with respiratory disturbances was low.
Tomaello 2010 <sup>23</sup>	Case-series	22 consecutive male patients with LVEF < 45% with ICD and BMI < 35	AHI > 10	Cardiorespiratory Study	Incidence of SDB was 17/22 (77.2%), NYHA class, AHI and hypoxia associated with appropriate ICD discharge. ICD was programmed to discharge for VT and VF.
Koshino 2010 <sup>66</sup>	Observational cohort	44 patients with VT and PVCs without structural heart disease underwent EP ablation, and f/u for mean of 13.5 months	AHI > 10	PSG	$\uparrow$ VT and PVC recurrence post EP ablation among patient with SDB.
Zeidan-Shwiri 2011 <sup>49</sup>	Observational cohort	45 ICD recipients over 1 year f/u	AHI > 10	PSG	SDB present in 26 (57.1%), appropriate ICD therapy higher in SDB (73% vs 47%, p = 0.02), SDB predicted ICD therapy (OR = 4.4) and nocturnal arrhythmias needing ICD discharge (OR = 5.6), SDB not associated with wake ICD discharge (OR = 0.7, p = 0.61).
Bitter 2011 <sup>46</sup>	Observational Cohort study	283 CHF patients with ICD and untreated SDB, 113 with moderate to severe SDB (cases) and 117 with mild or no sleep apnea (controls) with 48 month f/u	AHI was $\geq$ 15 was (cases) and AHI was b/w 5-14 (controls)	Cardiorespiratory Study	In CHF patients, CSA and OSA were independent predictors for ventricular arrhythmias and appropriate ICD therapy. Patients with CSA received $\uparrow$ ICD therapies than OSA patients.
Voigt 2011 <sup>40</sup>	Case-control	135 cases (50 females and 77 males) and 100 controls (50 female and 50 males)	Undefined	Undefined	QTc dispersion $\uparrow$ in patients with OSA vs. controls
Sakakibara 2012 <sup>67</sup>	Observational cohort	24 patients with history of sudden cardiac arrest.	AHI > 15	PSG	SDB prevalence was 45.8%, SDB was a risk factor for SCA in sleep in patients with inducible coronary spasm by acetylcholine provocation test. VF was primary etiology for SCA.
Javaheri 2012 <sup>68</sup>	Observational cohort	86 CHF patients with EF < 45%	AHI $\geq$ 15	PSG	$\uparrow$ arousal index was associated with $\uparrow$ in VT. $\uparrow$ AHI was only associated with couplets, not VT.
Grimm 2013 <sup>47</sup>	Prospective observational cohort	204 ICD recipients, 29 (14%) with OSA	AHI $\geq$ 5	Cardiorespiratory Study	CSA incidence 105 (51%), OSA incidence 29 (14%), AHI was higher in CSA vs. OSA
Gami 2013 <sup>44</sup>	Observational cohort	10,701 adults	AHI > 20	PSG	OSA was associated with SCD (HR = 1.6)

AHI, apnea-hypopnea index; AMI, acute myocardial infarction; ICU, intensive care unit; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PVC, premature ventricular contractions; HR, heart rate; BMI, body mass index; CSR, Cheyne-Stokes respiration; CSA, central sleep apnea; SDB, sleep disordered breathing; ICD, implantable cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; QT, QT interval; QTc, corrected QT interval; AF, atrial fibrillation; OAI, obstructive apnea index; f/u, follow up; EDS, excessive daytime sleepiness; h/o, history of; PSG, polysomnography; AI, apnea index; HRV, heart rate variability; SpO<sub>2</sub>, oxygen saturation by pulse oximetry; SDB, sleep disordered breathing; CPAP, continuous positive airway pressure; RDI, respiratory disturbance index; EF, ejection fraction; OAI, obstructive apnea index; CVE, complex ventricular ectopy; Holter, Holter monitor; NYHA, New York Heart Association; SCA, sudden cardiac arrest.

We were able to find a large number of case reports and observational studies that showed an association between ventricular arrhythmias and OSA. However, given the nature of the outcome, we did not find any randomized control trials that

studied this relationship. We therefore proceeded with a systematic review and found that OSA creates an environment ripe for occurrence of VT and VF by increasing ventricular ectopy, is associated with sustained ventricular arrhythmias treated by

ICD therapies, and is independently associated with sudden cardiac death. We were unable to demonstrate that CPAP lowered the arrhythmogenicity. Given the small number of studies available, we included studies including patients with central sleep apnea or Cheyne-Stokes breathing pattern, but only used the OSA subgroup for the review.

### **Sleep Disordered Breathing and Ventricular Arrhythmias in Patients without CHF**

We found a number of case reports and observational cohort studies (some with age matched controls) that attempted to describe this relationship. These noted a significant increase in the prevalence of EKG predictors of ventricular arrhythmias and sudden cardiac death such as ventricular premature beats, Qtc prolongation, Qtc dispersion, T wave alternans, and heart rate “turbulence”; however, because of the heterogeneity of these studies we were limited in the data we could meaningfully pool. Mehra et al. noted that among participants in the Sleep Heart Health Study, atrial fibrillation, VT, and complex ventricular ectopy were more prevalent in the SDB subgroup than non-SDB subgroup.<sup>36</sup> They also noted that nocturnal atrial fibrillation and complex ventricular ectopy were more frequent in the SDB subgroup than non-SDB subgroup. Similarly Noda et al., Aydin et al., and Aytemir et al. noted an increased prevalence of heart rate variability among patients with SDB than those without.<sup>37-39</sup> Voigt et al. found that among patients with OSA, there was a higher prevalence of QTc dispersion.<sup>40</sup> Other EKG abnormalities described include R-R interval and QTc shortening and P-R interval lengthening by Craig et al.<sup>41</sup> Even in the acute MI population, Marin found an increase in PVCs and couplets among the OSA group when compared with the non OSA group.<sup>42</sup> Similarly in 2 population-based studies, patients with OSA were more likely to have sudden cardiac death (SCD) at night, and the incidence of SCD was increased with the severity of OSA.<sup>43,44</sup> Another recent retrospective study of 10,701 patients who presented for a diagnostic PSG showed that at average follow-up of 5.3 years, OSA with AHI > 20 was an independent predictor of SCD.<sup>44</sup> Since a large proportion of these deaths were outside the hospital, it was not possible to attribute all these to ventricular arrhythmia. In this study in a multivariate analysis, independent risk factors for SCD were age, hypertension, coronary artery disease, cardiomyopathy or heart failure, ventricular ectopy or nonsustained ventricular tachycardia, and lowest nocturnal O<sub>2</sub> saturation. While the risk of SCD was low (annual rate 0.27%), the severity of OSA (quantified by AHI and nocturnal hypoxemia) predicted the magnitude of risk for SCD.

### **Sleep Disordered Breathing and Ventricular Tachycardia in Patients with CHF and ICD Placement**

We found considerable published literature describing the prevalence of ventricular arrhythmias and sudden cardiac death among OSA patients in patients with advanced CHF. Javaheri et al. noted an increase in prevalence of VT and PVCs in CHF patients with SDB compared to those without.<sup>45</sup> Bitter et al. showed that OSA was an independent risk factor for malignant ventricular arrhythmias requiring ICD therapy.<sup>46</sup> Grimm et al. noted an increased prevalence of SDB among ICD recipients.<sup>47</sup> Serizawa et al. noted that among CHF patients with ICD, SDB

patients had a higher rate of ICD therapy, particularly more nocturnal ICD therapy.<sup>48</sup> Zeidan-Schwiri et al. noted a similar increase in prevalence of nocturnal ventricular arrhythmias in a similar population.<sup>49</sup> Tomaello et al. noted that SDB patients had a high incidence of appropriate ICD discharge when compared with patients without SDB.<sup>23</sup>

### **Does CPAP Therapy Prevent Ventricular Arrhythmias and Sudden Cardiac Death?**

The secondary aim of this review was to study the role of CPAP therapy in preventing sudden cardiac death and ventricular arrhythmias in patients with OSA. Given the nature of the intervention, this was conducive to a randomized control study design and blinding. We only found one study (by Craig et al.) that met all 4 of the Cochran criteria, and this study showed no significant change in ventricular arrhythmias in OSA with the initiation of CPAP.<sup>41</sup> In a study by Ryan et al., patients with 10 or more PVCs/h despite receiving  $\beta$ -blockers had improvement in PVCs after CPAP therapy.<sup>50</sup> In another study, the prevalence of PVCs was reduced, but the prevalence of VT remained unchanged.<sup>51</sup> Other studies showed an increase in Qtc length and dispersion on withdrawal of CPAP in patients with SDB, showing that withdrawal of CPAP worsened potentially arrhythmogenic substrate in SDB.<sup>52</sup> While one well-designed study showed that CPAP did not decrease event-free survival among elderly heart failure CSA patients despite symptomatic improvement, another showed that in a population of patients with known pulmonary and cardiovascular disease and comorbid OSA, appropriate treatment with CPAP reduced hospital admissions in the 2 years following initiation of therapy.<sup>53,54</sup> These conflicting findings underscore the need for more research with well-designed randomized control trials with compliance data.

Furthermore, observational evidence supports the use of CPAP in OSA patients as a means for improved cardiovascular outcomes.<sup>55</sup> An early study showed that PVCs were statistically more likely to occur when nocturnal arterial oxygen saturation decreased below 60%.<sup>56</sup> In fact, a recent study showed that nocturnal hypoxemia (to < 78%) was another risk factor for sudden cardiac death, in a large population-based study with a hazard ratio (HR) of 2.6, in addition to age > 60 years (HR: 5.53), apnea-hypopnea index > 20 (HR: 1.60), and mean nocturnal oxygen saturation < 93% (HR: 2.93).<sup>44</sup> A cause-and-effect relationship between the pathophysiology of SDB and ventricular arrhythmias is also suggested from data from the Sleep Heart Health Study, which shows that NSVT and paroxysmal atrial fibrillation were statistically more likely to occur within 90 seconds of a respiratory disturbance, suggesting that CPAP use does may reduce the prevalence of ventricular arrhythmias.<sup>57</sup>

Sleep disordered breathing is associated with increased cardiovascular morbidity and mortality.<sup>43,44</sup> Gami proposed that patients with OSA lose the cardio-protective period of increased vagal tone and autonomic stability during normal sleep by showing that OSA patients have higher levels of sudden cardiac death during sleeping hours compared with the rest of the population.<sup>43,44</sup>

It is not surprising that most of the studies we reviewed showed an association between an increase in ventricular ectopy and ventricular irritability in patients with CHF who also had OSA. Repeated pathologic fluctuations in intrathoracic

pressure during OSA episodes increase LV afterload and impair LV relaxation working against therapeutic goals in heart failure.<sup>58</sup> Cycles of repeated apnea and arousal increase adrenergic activity, adversely influencing heart failure outcomes. It is possible that the association between OSA and ventricular arrhythmias is underreported, as the incidence of SCD is low among non-CHF patients, approximately 0.27%.<sup>44</sup> Among the studies we excluded, many did not have sufficient follow up time to detect differences in ventricular arrhythmias and SCD. The outcomes, where the studies showed significant differences, such as PVCs and QTc lengthening and dispersion, are more prevalent, allowing their detection with smaller sample size and shorter follow up time.

## CONCLUSIONS

OSA is independently associated with sudden cardiac death and sustained ventricular tachycardia with appropriate ICD therapies. There is insufficient evidence that appropriate and adequate CPAP use leads to a significant decrease in either VT or VF. There is, however, indirect evidence that CPAP therapy prevents arrhythmias in patients with SDB, particularly those with an AHI  $\geq$  20. In addition, given that there is reduction in ectopy and adverse ventricular remodeling and an improvement in EKG markers, CPAP therapy remains an important modality in the treatment of OSA with benefits that stretch far beyond a good night's sleep. Given the lack of well-designed studies, larger, age-matched, randomized studies are needed with better compliance data, and longer follow-up to examine these relationships.

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