Sleep Disordered Breathing And Ventricular Arrhythmias: Mechanisms and Implications

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Sleep-Disordered breathing (SDB) describes a group of disorders characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. Sleep disordered breathing, including the sleep apnea syndrome, is demanding the attention of clinicians and researchers due to its high prevalence, detrimental impact on quality of life and association with a myriad of morbidities in multiple body systems. SDB has been associated with an increased risk for cardiovascular diseases. Life-threatening cardiac arrhythmias are of utmost importance because of their clinical implications. Atrial fibrillation (AF) has received most of the attention and its associations with SDB are well characterized.[1,2] This is in part, due to an increased risk of stroke in patients with SDB. Increased AF prevalence among patients with SDB is considered the main physiopathological explanation for this morbid association.

Recent evidence also aids to establish the association between SDB and ventricular arrhythmias. Previous reports have suggested a high prevalence of SDB in populations at risk for ventricular arrhythmias and sudden cardiac death (SCD). The prevalence of SDB has been shown to be 50% or higher in patients with symptomatic heart failure and depressed left ventricular ejection fraction (LVEF), asymptomatic systolic dysfunction, and diastolic dysfunction.[3-5] These clinical conditions correspond to the populations of patients currently receiving implantable cardioverter defibrillators (ICDs) for the prevention of SCD due to ventricular arrhythmias,[6] specifically patients having survived ventricular tachycardia or fibrillation (secondary prevention) and patients with prior myocardial infarction (MI) and advanced left ventricular dysfunction (primary prevention).[7-9] The pathophysiological mechanisms that link SDB to ventricular arrhythmia remain undetermined. The following speculative mechanisms are worth mentioning:[1,2,10]

1-SDB has been linked to increased incidence of non fatal cardiovascular events including non-fatal MI, stroke, coronary insufficiency, revascularization (OR: 3.17, 95% CI 1.12-7.51, p>0.05).[11] This may represent an increased risk of post-MI associated arrhythmias and a long-term risk mediated by deterioration of left ventricular (LV) function.[10]

2-SDB may have a detrimental effect on LV function. It is postulated that this effect could be mediated by increased negative intrathoracic pressure, intermittent hypoxia impairing cardiac contractility, and increased pulmonary artery pressure and/or myocardial ischemia.

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It is speculated that the deleterious effects on LVEF may lead to hormonal and cellular changes, which may predispose to SCD. Continuous Positive Airway Pressure (CPAP) treatment has been shown to improve LVEF in a group of 24 patients with SDB over a period of one month (25.0 ± 2.8 to 33.8 ± 2.4%, P<0.001).[12] SDB also has well-defined associations with hypertension (HTN) (OR: 2.89, 95% CI: 1.46 -5.64 for AHI ≥ 15 vs AHI =0) and (OR 1.37, 95% CI: 1.03-1.83; P=0.005 for AHI >30 vs. AHI<1.5).[13,14]

3-Premature ventricular contractions are common in hypertensive patients with LV hypertrophy (RR 8.9, p < 0.01).[15,16] Hypertension is significantly associated with SDB.[1,2,13,14]

4-Intermittent hypoxemia is a consequence of SDB. Acutely severe hypoxemic episodes can induce ventricular ectopy,[17] a potential trigger for more complex ventricular arrhythmia. In the chronic setting, repetitive oxidative stress may induce ventricular remodeling predisposing to arrhythmia.[10]

5-Impaired autonomic control has been demonstrated in patients with SDB,[1,2,10] and has been proposed in arrhythmogenic mechanisms. Increased sympathetic activity occurs with the initiation of central and peripheral chemoreflexes by hypoxemia and hypercapnea,[18] where hypoxemia and apnea contribute to the imbalance of parasympathetic activity.[19] Together, this imbalance has deleterious effects on heart rate variability and coupling of cardiac and ventilatory inputs. Fluctuating autonomic activity caused by SDB can also have effects on beat-to-beat changes in ventricular repolarization, which can predispose to ventricular arrhythmia.[20] A chronic elevation of sympathetic tone has also been observed in patients with SDB,[18] representing a major disturbance linked to an increased risk of SCD.[21]

The initial clinical analyses of the relationship between SDB and ventricular arrhythmia were contradictory, with the first studies supporting an association and subsequent work refuting associations between SDB and cardiac arrhythmia.[22] Interesting findings of a substudy of the Sleep Heart Health Study have shown a significant association between SDB and ventricular arrhythmia. Mehra et al. compared a group of 228 patients with SDB to a group of 338 patients without SDB and found that over 25% of the patients with SDB experienced ventricular ectopy and 5% experienced Non-Sustained Ventricular Tachycardia (NSVT) during sleep while establishing that overall, adjusting for confounders, SDB is associated with a three-fold increase in the risk of NSVT (OR 3.40; 95 % CI 1.03-11.20, p=0.004).[23]

SDB has been linked to SCD through a study showing that CPAP decreased the incidence of SCD in patients with SDB. In a long-term study of 107 patients (mean follow-up 7.5 years), 0% of the CPAP-compliant patients experienced SCD compared to 7% of patients who were not treated with CPAP.[24] Gami et al. also demonstrated that patients with SDB who experienced SCD, were more likely to die during the night ,between 12 AM and 6 AM (RR 2.57, 95% CI 1.87-3.52, p=0.01), contrasting with a nadir in sudden death from other cardiovascular causes in the general population during the same time period. It is speculated that this peak in nocturnal SCD among SDB patients can be attributed to exposures to hypoxemia, hypertensive surges and autonomic imbalances occurring during the sleep of SDB patients.[25]

In patients with ICDs, ventricular arrhythmias

have been shown that occur significantly more often in patients with SDB compared to those without (Arrhythmia Index (AI) = 20.9 ± 18.8/h vs. non-apnea-associated Arrhythmia Index (NAI) = 4.9 ± 3.3/h).[26]

Our group recently reported on a retrospective analysis of 147 patients with ICDs to determine the impact of SDB on ICD therapy. We found that SDB was more frequently associated with appropriate ICD therapy (31% vs. 17 %; p=0.09) and that the time to first appropriate therapy was shorter (8 vs. 12 months; p= 0.12).[27] These preliminary data establish the need for further validation in a larger prospective series (Fig. 1,2).

Although information on the association between SDB and ventricular arrhythmia is limited, it is clear that they are associated and physicians need to recognize SDB in every patient to limit the risk of SCD, particularly in patients with structural heart disease. Special consideration should be given to patients receiving an ICD. Assessment of SDB is important to reduce unnecessary therapies from the ICD and

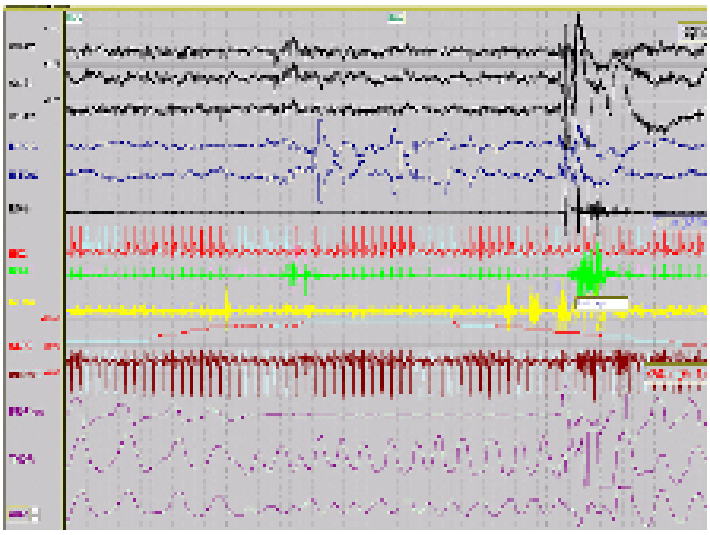

Figure 1. Snapshot of a polysomnography recording of a patient with an ICD. Note the the severe apneic episode.

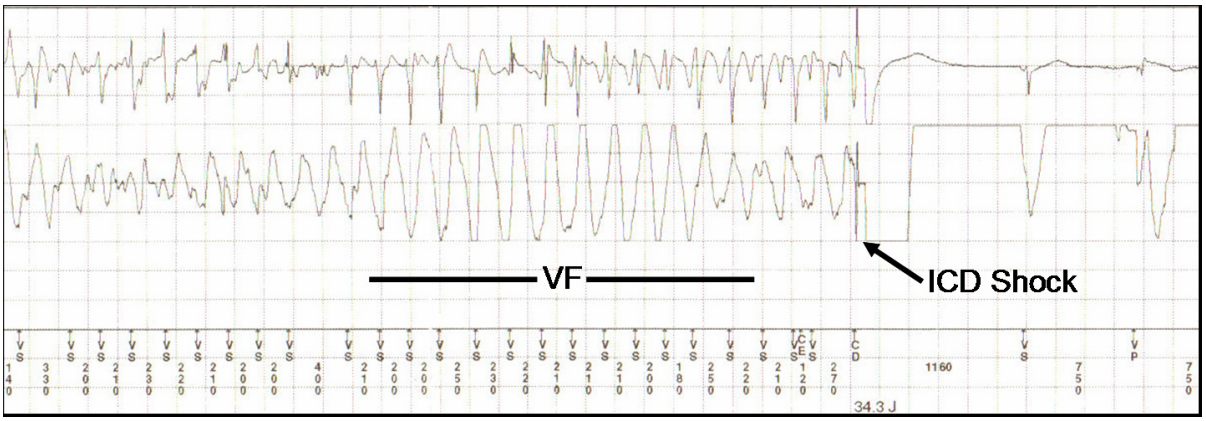

Figure 2. Intracardiac electrogram of an episode of ventricular fibrillation of a patient with severe sleep apnea, successfully treated by the ICD

to reduce triggers of ventricular arrhythmia. Research priorities in the field include further characterization of the association between SDB and ventricular arrhythmia, understanding the pathophysiological mechanisms and developing guidelines for physicians.

Conflicts of Interest no declare.

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