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Ventricular Arrhythmia and Sleep Related Breathing Disorders

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Early work described sleep as the “diastole of the cerebral beat,” a passive relaxation phase during which “brain-power is lowered.”¹ However, it is now appreciated that sleep is an active and complex process, disorders of which have downstream effects on multiple organ systems. Sleep related breathing disorders encompass various respiratory abnormalities including apnea and hypopnea. Apnea, a pause in airflow, is typically defined as greater than 10 seconds of diminished airflow at less than 20% of baseline.² Apnea may occur due to upper airway obstruction or a “central” lack of ventilatory effort. Central apnea may be idiopathic or secondary to other conditions. As cardiovascular specialists, we are most familiar with Cheyne-Stokes breathing, a secondary form of central apnea commonly associated with heart failure.^{3,4} Cheyne-Stokes breathing is characterized by a cyclic pattern of crescendo-decrescendo tidal volumes and central apnea episodes. In contrast to apnea, hypopnea is defined as a decline in airflow not meeting criteria for apnea. The typical definition for hypopnea is greater than 10 seconds of diminished airflow (at least 30% lower than baseline) and accompanied by greater than 4% de-saturation on oximetry.² Several measures have been developed to quantify the extent of sleep related breathing disorders. The most commonly utilized measure is the Apnea-Hypopnea Index, defined as the total number of apneas and hypopneas per hour of sleep.

It has been estimated that greater than half of patients with stable heart failure suffer from sleep related breathing disorders.^{5,6} The high prevalence of sleep related breathing disorders in patients with heart failure has led to extensive research on its potential association with outcomes including ventricular arrhythmia in patients with left ventricular dysfunction. It is known that ventricular ectopy tends to decrease during uninterrupted sleep. In fact, the extent of ventricular ectopy reduction during sleep has been noted to be greater than the reduction observed with quinidine, procainamide, or propranolol administration.⁷ Additionally, hypoxemia is known to associate with ventricular ectopy,⁸ and hypercapnia is associated with ventricular arrhythmia in patients with obstructive lung disease.⁹ Based upon these observations, it is biologically plausible that a group of disorders characterized by sleep loss, nocturnal hypoxemia, and hypercapnia may be associated with increased susceptibility to ventricular arrhythmia. Indeed, severe hypoxemia due to obstructive sleep apnea was shown by Shepard and colleagues to directly associate with the frequency of ventricular ectopy.¹⁰ Lanfranchi et al expanded on this finding, by showing that central sleep apnea in patients with left ventricular dysfunction is unassociated with exercise tolerance and systolic or diastolic function, but is associated with reduced heart rate variability and a higher incidence of non-sustained ventricular tachycardia.⁶ Later, Leung and colleagues demonstrated that ventricular ectopy increases during Cheyne-Stokes

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respirations in patients with heart failure and that this increase is most pronounced during the hyperpneic phase.¹¹ The association of sleep related breathing disorders with ventricular ectopy prompted investigators to investigate the association of the former with a surrogate of life-threatening ventricular arrhythmia: appropriate therapies in patients with implantable defibrillators. Two separate observational studies followed, revealing an association between sleep related breathing disorders and appropriate defibrillator therapy in patients with severe left ventricular dysfunction.^{12,13} Additionally, Serizawa and colleagues showed that the rate of total defibrillator therapies was increased at night in patients with sleep related breathing disorders, compared to other patients in whom therapies tended to occur in the morning.¹²

In this issue of the Journal, Zeidan-Shwiri, Aronson, and colleagues add to the existing evidence by presenting the results of a prospective cohort study designed to assess the association of sleep related breathing disorders with ventricular arrhythmia in 45 patients with implantable defibrillators.¹⁴ Of all patients, 60% had ischemic cardiomyopathy, and 56% received a defibrillator for secondary prevention. The authors defined sleep related breathing disorders as an Apnea-Hypopnea Index greater than 10 events per hour based on an overnight sleep study. The primary outcome measure was defined as appropriate anti-tachycardia pacing or shock for ventricular arrhythmia during 1 year of follow-up. Similar to previous studies,^{5,6} the authors found a high prevalence of sleep related breathing disorders (58%) in patients with heart failure. Patients with sleep related breathing disorders experienced 4 fold higher odds of appropriate defibrillator therapies during follow-up. The authors examined the circadian variation of appropriate therapies and confirmed that compared to other patients with heart failure, the excess of therapies experienced by patients with sleep disordered breathing occurs at night. Zeidan-Shwiri and colleagues conclude that patients with predominantly nocturnal defibrillator therapies should be screened and potentially treated for sleep related breathing disorders.

With few exceptions,¹⁵ the great majority of published studies suggest a direct association between sleep related breathing disorders and ventricular arrhythmia. Sleep related breathing disorders may associate with ventricular arrhythmia through many mediators. Such potential mediators include hypoxemia, enhanced sympathetic activation, hypertension, and vasoconstriction.¹⁶⁻¹⁹ Despite the biological plausibility and increasing weight of evidence suggesting an association between sleep related breathing disorders and ventricular arrhythmia, continuous positive airway pressure does not appear to prolong survival in patients with heart failure and sleep related breathing disorders. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial randomized 258 patients with heart failure and central sleep apnea to continuous positive airway pressure versus no therapy for sleep related breathing disorders.²⁰ During follow-up, continuous positive airway pressure was associated with a reduction in nocturnal hypoxemia, improvement in ejection fraction, lowering of nor-epinephrine levels, and six-minute walk distance. However, continuous positive airway pressure did not affect survival. In fact, the authors noted an early increased mortality in the treatment group which may have been attributable to upward titration of continuous positive airway pressure resulting in reduced cardiac output in patients with low filling pressures due to diuresis.²⁰

A causal association between sleep related breathing disorders and ventricular arrhythmia has not been established. The study by Zeidan-Shwiri and colleagues expands the evidence base suggesting an association and strongly justifies further prospective randomized studies to assess the potential for reduction of defibrillator therapies by treatment of sleep related breathing disorders in patients with heart failure. (¹⁴)

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