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OSA and Cardiac Arrhythmogenesis
Mechanistic Insights

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A surge of data has reproducibly identified strong associations of OSA with cardiac arrhythmias. As an extension of epidemiologic and clinic-based findings, experimental investigations have made strides in advancing our understanding of the putative OSA and cardiac arrhythmogenesis mechanistic underpinnings. Although most studies have focused on the links between OSA and atrial fibrillation (AF), relationships with ventricular arrhythmias have also been characterized. Key findings implicate OSA-related autonomic nervous system fluctuations typified by enhanced parasympathetic activation during respiratory events and sympathetic surges subsequent to respiratory events, which contribute to augmented arrhythmic propensity. Other more immediate pathophysiologic influences of OSA-enhancing arrhythmogenesis include intermittent hypoxia, intrathoracic pressure swings leading to atrial stretch, and hypercapnia. Intermediate pathways by which OSA may trigger arrhythmia include increased systemic inflammation, oxidative stress, enhanced prothrombotic state, and vascular dysfunction. Long-term OSA-associated sequelae such as hypertension, atrial enlargement and fibrosis, ventricular hypertrophy, and coronary artery disease also predispose to cardiac arrhythmia. These factors can lead to a reduction in atrial effective refractory period, triggered and abnormal automaticity, and promote slowed and heterogeneous conduction; all of these mechanisms increase the persistence of reentrant arrhythmias and prolong the QT interval. Cardiac electrical and structural remodeling observed in OSA animal models can progress the arrhythmogenic substrate to further enhance arrhythmia generation. Future investigations clarifying the contribution of specific OSA-related mechanistic pathways to arrhythmia generation may allow targeted preventative therapies to mitigate OSA-induced arrhythmogenicity. Furthermore, interventional studies are needed to clarify the impact of OSA pathophysiology reversal on cardiac arrhythmogenesis and related adverse outcomes. CHEST 2017; 151(1):225-241

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OSA consists of repetitive episodes of complete or partial cessation of breathing: apneas and hypopneas, respectively. OSA is a common condition with progressively rising prevalence, largely attributable to the increasingly aged population and the ongoing obesity epidemic.[1] In parallel to the increasing prevalence of OSA, atrial

ABBREVIATIONS: AF = atrial fibrillation; ERP = effective refractory period; LV = left ventricular; ROS = reactive oxygen species

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fibrillation (AF), the most common sustained cardiac arrhythmia, is projected to affect 16 million people by 2050.[2] AF is not fully explained by established risk factors, which underscores the need to definitively identify novel triggers such as OSA.[3] Although causality between OSA and arrhythmia has yet to be established, emerging data have identified a range of mechanistic pathways that may increase the propensity of cardiac arrhythmogenesis in OSA. These pathways are complex, multidirectional, and potentially synergistic. OSA and AF have shared risk factors and consequences (ie, increasing age, obesity, hypertension) that may act together to increase cardiovascular risk.

Epidemiologic studies have shown that sleep-disordered breathing approximately doubles the risk of AF; in patients with OSA and heart failure, the risk is twofold to fourfold higher compared with those without either condition.[3-12] In addition, studies of circadian rhythm and sudden cardiac death have shown a predisposition of fatal events in those with obstructive apnea to the nocturnal period, a period of relative cardioprotection for individuals without obstructive apnea.[13] Apneas and hypopneas characterizing OSA are frequently accompanied by oxygen desaturation and microarousals from sleep, the latter leading to sleep fragmentation. Autonomic nervous system imbalance characterized by vagal cardiac activation during, and unopposed sympathetic activation after, OSA events can precipitate arrhythmias.[14,15] In addition, there are prominent intrathoracic pressure fluctuations in OSA secondary to attempts to breathe against an obstructed upper airway.[16] These OSA-related pathophysiologic events lead to increased arrhythmia rates observed in patients with OSA.[4,17] Overall, we can consider a conceptual model of repeated acute physiologic insults (ie, repetitive hemodynamic, hypoxemic, and autonomic surges) resulting in cardiac structural and electrical remodeling, which operate to create an altered arrhythmogenic substrate in apnea-induced arrhythmia (Fig 1, Tables 1 and 2).

Although the present review focuses on the interrelationships of OSA and cardiac arrhythmia, it is important to recognize emerging epidemiologic data that implicate the possible role of central sleep-disordered breathing in the development of AF.[18] Furthermore, in heart failure, central sleep-disordered breathing and Cheyne-Stokes respirations entrain the ventricular response to AF by inducing rhythmic oscillations in atrioventricular node refractoriness.[19]

Cardiac arrhythmias incur heavy societal and personal burden, including lost productivity, increased health-care expenses, and raised risk of stroke.[20,21] There is an urgency to perform studies that can better elucidate causal pathways and enhance our understanding of mechanistic pathways involved in OSA and cardiac arrhythmogenesis. By understanding and acting on these immediate and intermediate time frame pathways, it may be possible for OSA-focused treatments to optimize prevention and mitigation of arrhythmia-related morbidity and mortality.

Sleep-disordered Breathing and Cardiac Electrophysiology

A variety of electrophysiologic parameters encompassing abnormal automaticity, triggered automaticity, shortening of the atrial effective refractory period (ERP), QT interval prolongation, and reentrant mechanisms may be induced by OSA pathophysiology. Abnormal cardiac impulse formation can result in abnormal automaticity (spontaneous activity in normally quiescent cardiac cells) or triggered activity. Enhanced arrhythmogenesis occurs when automaticity is either reduced (resulting in bradycardia) or increased (resulting in tachycardia). Abnormal automaticity is oftentimes generated in response to potassium dysregulation,[3,22] which is observed during the hyperpneic phase of periodic central sleep apnea as a result of hypokalemia due to transcellular ion shifts and reduced renal absorption, hypocapnia,[23,24] and beta-adrenergic stimulation.[25]

Triggered activity occurs when early or delayed afterdepolarizations reach a membrane potential threshold resulting in a spontaneous action potential (ie, triggered response). Triggered responses can result in extrasystoles that can precipitate tachyarrhythmias. Established triggered activity precipitants via early afterdepolarizations include hypoxia, acidosis, and ventricular hypertrophy,[26] all intrinsic characteristics of OSA pathophysiology. Alternatively, delayed afterdepolarizations resulting in triggered activity often occur in response to increased catecholamine levels, which are also inherent to OSA.[3,26]

The interval between the ECG T-wave peak and end has been studied as a measure of cardiac dispersion and repolarization; increases in this interval are associated with ventricular arrhythmogenesis and sudden cardiac death.[27-29] Comparisons of patients with OSA vs control subjects identified increased ECG T-wave peak

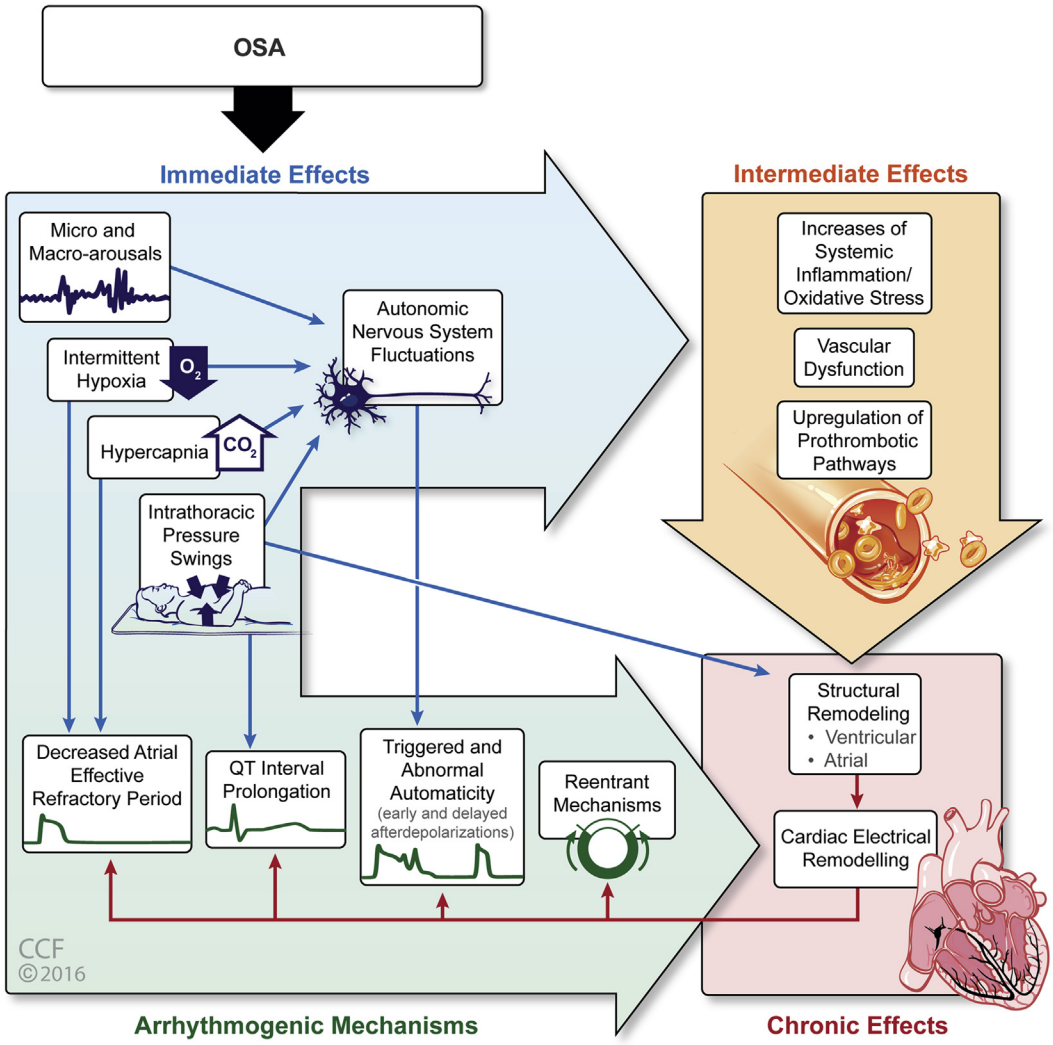

Figure 1 – *Overview of putative sleep apnea pathophysiologic pathways with varying levels of evidence potentially predisposing to cardiac arrhythmogenesis.* O_2 *= oxygen. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2016. All Rights Reserved.*

and end and QT dispersion in those with OSA[30-32] and improvement in these measures with CPAP treatment.[33,34] Because increased heterogeneity in ventricular recovery time and repolarization time are correlated with ventricular arrhythmias, these studies provide a mechanistic basis for OSA as a predisposing factor for nocturnal sudden cardiac death.[13]

After myocytes produce an action potential, there is a period of time when the activated cells are recovering and unable to produce another action potential; this interval is referred to as the ERP. The ERP typically halts further activations to prevent arrhythmias. Perturbations that shorten the atrial ERP predispose the heart to arrhythmias such as AF. Simulated by intermittent hypoxia and hypercapnia, obstructive apnea has been shown in canine models to decrease atrial ERP.[35] ERP shortens with negative tracheal pressure during simulated obstructive apnea via increased vagal tone; this effect was mitigated by administration of atropine.[36] Taken in toto, shortening of the atrial ERP during obstructive events may predispose to AF generation.

Immediate Sleep-disordered Breathing Consequences

Autonomic Nervous System Alterations

Although there are unequivocal synergies among the OSA pathophysiologic sequelae, data suggest that the OSA-related sympathovagal imbalance may be the primary trigger in cardiac arrhythmogenesis. Increasing respiratory efforts of progressive magnitude to achieve restoration of airway patency are intrinsic

TABLE 1] Overview of Clinical or Epidemiologic Studies Characterizing Sleep-disordered Breathing and Cardiac Structural and Electrophysiologic Indices

Study	Predictor (No.)	Outcome	Results
Observational			
Autonomic nervous system alterations			
Bonsignore et al[82]	OSA (29) vs OSA on CPAP after CPAP withdrawal (10) vs no OSA (11)	Baroreflex sensitivity	Lower baroreflex sensitivity in OSA improved with CPAP treatment
Electrical remodeling			
Gillis et al[34]	OSA without underlying cardiac, pulmonary, or nervous system disease (12)	RR and QT intervals before, during, and after apneas	RR and QT interval prolonged during apneas and decreased in postapnea hyperventilation, QTc shortened during apnea and postapnea periods
Roche et al[32]	OSA (30) vs no OSA (44)	QT interval related to heart rate	QT interval related to heart rate shortening at low heart rates correlated with OSA severity
Smith et al[83]	PSG ECG records of OSA participants (20)	RR, QT, and PR interval with spontaneous and respiratory-related arousals	RR and QT interval shortening during arousals, RR interval worse with respiratory-related arousals; QT and PR interval independent of arousal type
Barta et al[84]	Untreated OSA (25)	Cardiac arrhythmias, QT parameters	Increase in QT interval at night, no change in QT dispersion or arrhythmias
Dursunoglu et al[85]	Moderate to severe OSA (29) vs no OSA (20)	QT dispersion	Increased QT dispersion in OSA with positive correlation with AHI
Voigt et al[31]	OSA (101) vs no OSA (98) without structural heart disease	QT intervals, QT dispersion	Higher QT dispersion in OSA group
Kilicaslan et al[30]	Moderate to severe OSA (23) vs no OSA (23) during PSG	Tp/Te interval, Tp/Te/QT ratio, Tp/Te/QTc ratio	All measures were increased in OSA group
Cagirci et al[86]	No OSA (39) vs moderate OSA (42) vs severe OSA (45)	Atrial electromechanical coupling, intra-atrial and inter-atrial electromechanical delay, P-wave dispersion	Increased maximum P-wave duration and P-wave dispersion increased with OSA severity. Increased electromechanical delay for all indices correlating with OSA severity
Dimitri et al[87]	Paroxysmal AF ablation: OSA (20) vs no OSA (20)	Atrial ERP, conduction, corrected sinus node recovery time, complex electrograms	Prolonged conduction times; increased number, duration, and more widespread complex electrograms; longer sinus node recovery time and P-wave duration; lower atrial voltage and slower conduction velocity in OSA
Yagmur et al[79]	Moderate to severe OSA (64) vs no OSA (39)	Electromechanical delay, P-wave dispersion	Increased inter-atrial and intra-atrial electromechanical delay, and P-wave dispersion in OSA
Drager et al[63]	Control (15) vs OSA (15) vs HTN (15) vs OSA + HTN (15)	Pulse wave velocity, left atrial diameter, ventricular septal thickness, percent LV hypertrophy, LV posterior wall thickness, LV mass index	Pulse wave velocity, left atrial diameter, ventricular septal mass, LV thickness, and hypertrophy increased in OSA, further increase in LV mass index and hypertrophy in OSA + HTN group

(Continued)

TABLE 1] *(Continued)*

Study	Predictor (No.)	Outcome	Results
Cardiac structural changes			
Kim et al[88]	Mild to moderate OSA (24) vs severe OSA (20) vs no OSA (20)	Echocardiography indices of diastolic dysfunction	Decreased early diastolic velocity in severe OSA; AHI correlated with tissue Doppler imaging indexes of LV diastolic function but not conventional Doppler indices
Cioffi et al[64]	Control (20) vs mild OSA (51) vs moderate/severe OSA (86)	LV mass, relative wall thickness, concentric LV geometry	Relative wall thickness and LV concentric geometry associated with OSA
Drager et al[89]	Moderate to severe OSA (43) vs no OSA (30)	Pulse wave velocity, ejection fraction, left atrial diameter, LV mass index	Left atrial diameter, LV mass index, and pulse wave velocity increased in OSA
Arrhythmogenesis			
Matiello et al[90]	No OSA (132) vs mild to moderate OSA (17) vs severe OSA (25) after pulmonary vein ablation	AF or atrial flutter recurrence	Increased AF or atrial flutter recurrence with increasing OSA severity
Fein et al[91]	OSA with CPAP (32) vs no CPAP (32) after pulmonary vein isolation	Atrial tachyarrhythmia, antiarrhythmic drugs, need for repeat ablation	Increase AF-free survival and decreased antiarrhythmic drug use or repeat ablation in CPAP group
Naruse et al[92]	OSA no CPAP (32) vs OSA on CPAP (34) vs no OSA (37) after pulmonary vein isolation	AF recurrence	OSA, particularly without CPAP, increases risk of recurrent AF
Interventional			
Autonomic sympathetic system alterations			
Tkacova et al[93]	Before/after CPAP in patients with heart failure and OSA	Baroreflex sensitivity for heart rate	Increased baroreceptor reflex sensitivity, lower heart rate, and lower BP on CPAP
Bonsignore et al[94]	Before/after acute CPAP application in severe OSA (18)	Baroreflex sensitivity, BP	No change in mean BP or heart rate, small increase in mean baroreflex sensitivity, decreased cardiovascular variability with CPAP
Ruttanaumpawan et al[95]	RCT, 1 mo CPAP (19) vs no therapy (14) in heart failure and OSA	Baroreflex sensitivity, echocardiographic indices	Increased baroreflex sensitivity, improved ejection fraction, lower daytime heart rate and BP with CPAP
Tamisier et al[96]	Before/after CIH × 2 wk in healthy volunteers (12)	Sympathetic muscle nerve activity, BP, baroreflex control	Increases in daytime BP and sympathetic tone with decrease in baroreflex control after CIH
Tamisier et al[97]	Hypocapnic hypoxia vs hypercapnic hypoxia × 20 min in healthy volunteers (12)	Muscle sympathetic nerve activity	Increased sympathetic activity with both groups but sustained after exposure in hypercapnic hypoxia
Usui et al[98]	RCT, OSA (9) vs OSA + CPAP (8) in heart failure	Muscle sympathetic nerve activity, BP, heart rate	Decreased sympathetic nerve activity, BP, and heart rate with CPAP

(Continued)

TABLE 1] *(Continued)*

Study	Predictor (No.)	Outcome	Results
Kohler et al[99]	RCT, CPAP (20) vs sham CPAP (20) × 2 wk in previously treated OSA	BP, heart rate, urinary catecholamines	Increase in both systolic and diastolic morning BP, heart rate, and urinary catecholamines with sham CPAP
Phillips et al[100]	Before/after CPAP withdrawal × 7 d from moderate to severe OSA (20)	Sympathetic activity, inflammatory cytokine levels	Increased urinary noradrenaline but no change in measured cytokines from CPAP withdrawal
Electrical remodeling			
Roche et al[33]	OSA (38) vs OSA + CPAP treatment (same group) vs matched no OSA (38)	QT and RT intervals, ventricular ectopy	QT length related to heart rate elevated in OSA with improvement with CPAP, no change in ventricular ectopy or QT or RT intervals with CPAP
Chrysostomakis et al[101]	Before/after 2 mo of CPAP (26) vs no OSA (19)	Heart rate variability indices	Increased parasympathetic activity at night in those with OSA alleviated with CPAP
Dursunoglu et al[102]	Before/after 6 mo adherent CPAP (18) vs nonadherent (11)	QT dispersion	Positive correlation of initial QT dispersion with AHI, which decreased after CPAP therapy; no change in nonadherent CPAP group
Rossi et al[103]	RCT, patients with OSA continue on CPAP (20) vs subtherapeutic CPAP × 2 wk (21)	QT, TpTe (repolarization metrics), TpTe/QT (dispersion metric)	Increase in QT, TpTe intervals, and TpTe/QT ratio in subtherapeutic CPAP correlating with change in AHI from baseline treatment
Baranchuk et al[104]	Before/after severe OSA on CPAP × 4-6 wk (19) vs no OSA/CPAP (10)	Signal-averaged P-wave duration	Increased signal-averaged P-wave duration in OSA ameliorated with CPAP indicating reversal of atrial remodeling
Camen et al[16]	Randomized crossover study, healthy volunteers simulated obstructive apneas and hypopneas (41)	QTc and $TpTe_c$ interval	Increased premature beats, increased QTc and $TpTe_c$ interval
Maeno et al[105]	Before/after 1 mo of CPAP in moderate to severe OSA (62) vs untreated moderate to severe OSA (18)	Signal-averaged P-wave duration	Significantly shorter signal-averaged P-wave duration with CPAP therapy correlating with compliance, no change in untreated OSA
Bayır et al[106]	Before/after OSA with 6 mo of CPAP therapy (24) vs no OSA/CPAP (18)	Time 0 and 6-mo inter-atrial and intra-atrial electromechanical delay	Electromechanical delay greater in OSA group compared with control subjects with improvement after CPAP therapy
Cardiac structural remodeling			
Dursunoglu et al[107]	Before/after 6 mo of CPAP (67)	Interventricular septum and posterior wall thickness, myocardial performance index	Decreased thickness of both cardiac sites and improved myocardial performance index with CPAP

(Continued)

TABLE 1] *(Continued)*

Study	Predictor (No.)	Outcome	Results
Dursunoglu et al[108]	Before/after 6 mo of CPAP (18)	RV end-diastolic and end-systolic diameter, free wall diameter, and myocardial performance index	No change in end-diastolic or end-systolic diameters, decrease in free wall diameter, and improvement in RV myocardial performance index
Orban et al[61]	Before/after healthy adults undergoing Müller maneuver (24)	Left atrial volume index, LV end-systolic dimension, ejection fraction, cardiac output	Decreased left atrial volume index and ejection fraction, increased LV end systolic dimension and cardiac output with maneuver
Oliveira et al[109]	RCT, OSA with CPAP (15) vs sham CPAP (15)	Baseline, 12-wk, and 24-wk left atrial volume, LV diastolic performance	Improved left atrial emptying and LV diastolic function but not left atrial structural changes with CPAP
Koshino et al[62]	Before/after healthy adults undergoing Müller maneuver (24)	Echocardiographic strain and strain rate measurements	LV and RV strain and strain rate decreased (worse ventricular mechanics) during maneuver
Colish et al[110]	Before/after 1 year CPAP (47)	Echocardiographic remodeling indices	RV end-diastolic diameter, left and right atrial volume index, and pulmonary hypertension improvement with CPAP
Oliveira et al[111]	RCT, OSA with CPAP (15) vs sham CPAP (15)	Baseline, 12-wk, and 24-wk left atrial volume, RV performance	Better RV performance but not structure with CPAP
Vural et al[112]	Control (45) vs mild (22) vs moderate (27) vs severe (68) OSA; comparison vs severe OSA + CPAP for 24 wk (43)	Echocardiography indices of left atrial and LV structure and function	Worse left atrial function and LV filling pressure in severe OSA improved with CPAP
Arrhythmogenesis			
Craig et al[113]	RCT, CPAP (43) vs subtherapeutic CPAP (40) × 1 mo in moderate to severe OSA	Dysrhythmia frequency, heart rate	Decreased mean 24-h heart rate but no change in frequency of dysrhythmias with CPAP

AF = atrial fibrillation; AHI = apnea-hypoapnea index; CIH = chronic intermittent hypoxia; ERP = effective refractory period; HTN = hypertension; LV = left ventricular; PSG = polysomnography; QTc = corrected QT interval; RCT = randomized controlled trial; RV = right ventricular; Tp/Te = interval between the ECG T-wave peak and end.

to obstructive respiratory event physiology. Enhanced vagal efferent outflow to the heart leads to the bradycardia observed during the apneic event (ie, the diving reflex). These vagal influences shorten the atrial ERP and, hence, enhance vulnerability to excitatory stimuli. After upper airway patency restoration, strong sympathetic nervous system responses are elicited secondary to the interacting effects of central respiratory sympathetic coupling, hypoxia, hypercapnia, and absence of sympathoinhibition from normal lung initiation reflexes.[37] These sequential autonomic alterations lead to enhanced arrhythmia susceptibility.

Further support for the role of autonomic influences in OSA comes from a canine model in which ablation of the right ganglionated plexus resulted in inhibition of apnea-induced AF.[38] Autonomic dysfunction has been further corroborated by observations in a porcine model in response to tracheal occlusion causing increasing AF inducibility (ie, reduction of the atrial ERP) that was mitigated by renal sympathetic denervation and low-level baroreceptor stimulation, an intervention to suppress both sympathetic and parasympathetic activity.[39,40] OSA-induced intermittent hypoxemic bouts serve as recurrent instigators of sympathetic discharges, thereby favoring triggered atrial activity and abnormal automaticity,[41] a mechanism bolstered by data demonstrating the importance of the sympathetically enriched ganglionated plexus in apnea-induced AF.[38] Although shortened refractoriness may play a role in

TABLE 2] Overview of Animal Experimental Studies Characterizing Sleep-disordered Breathing and Cardiac Structural and Electrophysiologic Indices

Study	Animal Type	Groups (No.)	Intervention	Outcome
Hypoxia and hypercapnia				
De Daly and Scott[53]	Dog	Spontaneous breathing (32), artificial ventilation (20)	Normoxia vs hypoxia with or without hypocapnia	Decreased heart rate with hypoxemia that did not vary with hypocapnia
Daly and Scott[52]	Dog	Anesthetized dogs (19)	Normoxia vs hypoxia	Increase in minute ventilation, decreased BP with hypoxia
Campen et al[114]	Mouse	Acute hypoxia (6) vs CIH (8)	Acute hypoxia vs CIH × 5 wk	Decreased BP and increased RV pressure in acute hypoxia; increased BP, LV mass, and RV mass in CIH
Lesske et al[115]	Rat	Control subjects (15) vs CIH 20 d (8) vs 30 d (7) vs 25 d (7)	20 vs 30 vs 35 d of CIH	Increased LV mass and mean BP correlating with CIH duration
Lesske et al[115]	Rat	Control subjects (13) vs CIH (9) vs CIH + hypercapnia (10) vs CIH + hypocapnia (9)	CIH × 30 d with eucapnia, hypocapnia, or hypercapnia	Increase in BP and LV hypertrophy with CIH. No additional change in BP or LV hypertrophy with changes in P_{CO_2}; increase in RV hypertrophy in hypercapnia + CIH
Peng et al[45]	Rat	CIH vs normoxia control subjects	CIH for 8 h per day for 10 d vs normoxia	Increased indices of oxidative stress and mitochondrial dysfunction in CIH
Chen et al[48]	Rat	CIH (22) vs normoxia control subjects (22)	CIH for 8 h per day for 5 wk	Increased LV and heart weight, LV dilation, LV end-diastolic pressure, myocardial lipid peroxides; lower myocardial superoxide dismutase in CIH
Peng et al[44]	Mouse	Wild-type vs HIF-1α-deficient heterozygotes	10 days CIH vs 10 d normoxia	Increased carotid body response, increased ROS, augmented hypoxic ventilator response, elevated BP in wild-type but not heterozygous mice
Park and Suzuki[49]	Mouse	Normoxic control subjects (19) vs 1 wk (15) vs 2 wk (14) vs 4 wk (20) isolated heart under ischemia-reperfusion	CIH 8 h per day	Increased myocardial injury at 1 and 2 wk but not 4 wk; increased oxidative stress at 2 wk resolved by 4 wk

(Continued)

TABLE 2] *(Continued)*

Study	Animal Type	Groups (No.)	Intervention	Outcome
Chen et al[47]	Rat	CIH vs handled normoxic control subjects	CIH 8 h per day for 6 wk	Elevations in mean arterial pressure, LV end-diastolic pressure, LV cell injury markers
Souvannakitti et al[54]	Rat	Intermittent hypoxia (18) vs sustained hypoxia (12) vs control (17)	Acute hypoxia after intermittent or sustained hypoxia	Facilitation of catecholamine secretion by intermittent hypoxia and attenuation by sustained hypoxia
Stevenson et al[57]	Sheep	Control (6), hypercapnia (5), hypoxemia (6)	Control vs hypercapnia vs hypoxemia	ERP lengthening, increased conduction time with hypercapnia; increased AF vulnerability with a return to eucapnia. No changes in ERP, atrial conduction time, or AF vulnerability in hypoxia and control
Intrathoracic pressure swings				
Linz et al[36]	Pig	Intubated anesthetized pig (21)	NTP	Right atrial ERP shortening and increased AF vulnerability during maneuvers, which were completely inhibited by amiodarone followed by atropine
Linz et al[39]	Pig	Anesthetized animals (20)	NTP vs NTP + renal denervation vs NTP + atenolol	Atrial ERP shortening, increased AF inducibility, BP increases in NTP that was mitigated by renal denervation but not atenolol
Linz et al[116]	Pig	NTP (24) vs renal denervation + NTP (26) vs control (8)	NTP ± renal denervation	Increased BP and prolongation of spontaneous AF episodes with NTP; denervation inhibited BP increases, decreased plasma renin and aldosterone, reduction of occurrence and duration of AF episodes

(Continued)

TABLE 2] *(Continued)*

Study	Animal Type	Groups (No.)	Intervention	Outcome
Autonomic function				
Fletcher et al[117]	Rat	Control (13) vs CIH (13) vs denervation (11) vs CIH + denervation (8)	CIH × 40 d, sympathetic denervation	Increased BP in CIH only, all others decreased BP. Increased LV mass in all CIH groups
Lesske et al[115]	Rat	Control subjects (13) vs CIH (8) vs CIH + denervation (11) vs denervation (8)	CIH × 30 d, chemoreceptor denervation	Increased BP, LV hypertrophy in CIH, no BP change from baseline and lower catecholamines with denervation
Bao et al[118]	Rat	Hypoxia vs hypoxia + hypocapnia vs hypoxia + prazosin vs hypoxia + yohimbine vs hypoxia + atropine	Hypoxia, hypocapnia, effect of prazosin, yohimbine, atropine on hypoxia	Increased BP and decreased heart rate with CIH alone vs CIH + hypocapnia. Mitigation of BP increase after prazosin and mitigation of heart rate elevation after atropine. No effect of yohimbine
Ghias et al[38]	Dog	Atrial and pulmonary vein pacing (14) plexus ablation and cardiac pacing (16)	Ganglionated plexus ablation with induced apnea	Increased ganglionated plexus activity during apnea, autonomic blockade prevented AF; pacing-induced AF mitigated by neural ablation
Linz et al[36]	Pig	Intubated anesthetized pig (21)	NTP	Right atrial ERP shortening and increased AF vulnerability during maneuvers, which were completely inhibited by amiodarone followed by atropine
Linz et al[39]	Pig	Anesthetized animals (20)	NTP vs NTP + renal denervation vs NTP + atenolol	Atrial ERP shortening, increased AF inducibility, BP increases in NTP that were mitigated by renal denervation but not atenolol
Linz et al[116]	Pig	OSA (24) vs renal denervation + OSA (26) vs control (8)	NTP ± renal denervation	Increased BP and prolongation of spontaneous AF episodes with OSA; denervation inhibited BP increases, decreased plasma renin and aldosterone, reduction of occurrence and duration of AF episodes

(Continued)

TABLE 2] *(Continued)*

Study	Animal Type	Groups (No.)	Intervention	Outcome
Gao et al[119]	Rabbit	Simulated apnea and LLVS (6) Simulated apneas (5)	Tracheostomy clamped every 6 min over 4 h; LLVS or not	Suppression of ERP shortening and decreased AF duration mitigated with LLVS compared to apnea alone
Linz et al[40]	Pig	Low-level (n = 8) vs high-level (n = 8) baroreceptor stimulation vs control (n = 5)	NTP × 3 h + baroreceptor stimulation	Low-level stimulation: shortening atrial ERP, decreased AF inducibility; high-level stimulation: lengthening atrial ERP, no change in AF inducibility
Mixed physiology				
Revelli and Allessie[120]	Rabbit	Langendorff-perfused hearts with intra-atrial septal perforation (15)	Increasing bi-atrial pressure	Increased atrial ERP, decreased monophasic action potentials, increased AF vulnerability with increasing atrial pressure
Lu et al[35]	Dog	Experiment (10) Control (5)	10 s apnea every 30 s breathing × 1 h	Decreased heart rate variability, increased ERP; reverted after 1 h normal ventilation
Iwasaki et al[42]	Rat	OSA (no ventilation, closed airway) (11) vs no ventilation, open airway (7) vs continued ventilation (8)	Duration and inducibility of AF, atrial conduction, LV metrics	Increased AF duration and inducibility; atrial conduction slowing; and LV hypertrophy, dilation, and diastolic dysfunction in OSA
Iwasaki et al[121]	Rat	Lean (12) and obese (12) rats	No ventilation, closed airway vs no ventilation, open airway	Increased inducibility of AF in simulated OSA compared with control subjects, particularly in obese rats

HIF = hypoxia-inducible factor; LLVS = low-level vagosympathetic trunk stimulation; NTP = negative tracheal pressure; ROS = reactive oxygen species. See Table 1 legend for expansion of other abbreviations.

atrial arrhythmogenesis, conduction slowing secondary to OSA-induced cardiac structural remodeling (fibrosis and connexin dysregulation) is likely also an important mechanism contributing to arrhythmia persistence.[42]

Hypoxia and Hypercapnia

Apneas and hypopneas impair gas exchange and lead to oxygen desaturation, particularly in individuals with underlying pulmonary or cardiovascular disease.[43] Termination of upper airway obstruction subsequent to a respiratory event may lead to re-oxygenation and formation of hazardous reactive oxygen species (ROS).[44-46] Oxidative stress is implicated in myocardial hypertrophy, injury, and apoptosis leading to structural changes in animal models of the heart.[47-49] ROS generation has been linked to arrhythmogenesis both in animals and humans as a result of changes in calcium

channel activity and by promotion of microvascular ischemia.[50,51] Hypoxemia directly stimulates chemoreceptors in the carotid body, precipitating increased ventilation and sympathetic discharges.[52-54] In addition, hypoxia leads to peripheral vasoconstriction, which increases both preload and afterload, thereby causing increased cardiac workload. Oxidative stress secondary to hypoxia uncouples endothelial nitric oxide synthase, and thus increases superoxide generation and decreasing nitric oxide production. This chain of events leads to endothelial dysfunction, which has bidirectional relationships with AF.[55] Oxidative stress promotes activation of fibroblasts to myofibroblasts, leading to deposition of perivascular and interstitial fibrosis that promotes slowed and heterogeneous conduction.[56]

Although the evidence is not entirely consistent, some data support intermittent hypoxia as a potential factor enhancing arrhythmogenesis. For instance, hypoxia and hypercapnia altered measures of AF inducibility in a canine model (ie, reduced the ERP and increased the window of vulnerability).[35] In this study, 1 h of intermittent hypoxia (10 s of apnea for every 30 s of breathing) in a canine model altered heart rate variability markers of sympathovagal balance. The immediacy of the effects of intermittent hypoxia is underscored by resolution of these changes within 1 h of re-ventilation. Challenges encountered with this study and others include the limited ability to examine the isolated influences of the various facets of OSA (ie, hypoxia, hypercapnia, acidosis). Although data describing the specific relationship of hypercapnia and AF inducibility are sparse, one study was designed to examine differential effects of episodic hypercapnia relative to hypoxemia on electrophysiologic parameters in a sheep model. Hypercapnia in the setting of autonomic blockade lengthened the atrial ERP, increased right atrial conduction time and functional conduction delay, and caused a significant rise in extracellular potassium. In this study, although hypercapnia exerted a protective effect on measures of AF inducibility, return to eucapnia enhanced AF vulnerability secondary to the differential between atrial ERP shortening to below baseline levels and normalization of functional conduction delay.[57]

Intrathoracic Pressure Alterations

Upper airway occlusion generates negative intrathoracic pressures, resulting in augmented cardiac transmural pressures. These large oscillations pressure (up to –65 mm Hg) lead to increased left ventricular afterload and compromise the thin-walled, compliant atria by causing acute distension.[43] This atrial distension then leads to acute shortening of the atrial ERP via vagal activation.[36,39] In addition, these acute changes lead to increased central venous volume.[58] These mechanical cardiac influences may lead to activation of stretch-mediated ion channels and can lead to cardiac remodeling, hence enhancing arrhythmogenic propensity. Even in healthy control subjects, simulated obstructive apnea via the Müller maneuver increased premature beats and prolonged the corrected QT interval, a measure of delayed ventricular repolarization.[16] In patients with paroxysmal AF, simulated obstructive hypopneas and apneas lead to progressive increases in atrial premature beat frequency and corrected QT interval prolongation,[43] which have been implicated as precursors to AF[59] and ventricular arrhythmia/sudden cardiac death,[60] respectively.

Moreover, the large shifts in intrathoracic pressure during obstructive apneas seem to be sufficient to cause ventricular remodeling. Healthy subjects who underwent the Müller maneuver, simulating increased intrathoracic pressures, were found to have an acute increase in left ventricular afterload.[61] In addition, upper airway occlusion was found to have deleterious effects on myocardial mechanics characterized by decreased left and right ventricular deformation during systolic cardiac contraction.[62] These ventricular perturbations in response to repeated insults of negative intrathoracic pressure alterations over time can lead to fluctuations in afterload burden, left ventricular hypertrophy, and increased risk of arrhythmogenesis.[63,64] Overall, studies suggest that OSA promotes atrial and ventricular structural remodeling as well as alterations in cardiac electrophysiology predisposing to arrhythmogenesis.

Intermediate Sleep-disordered Breathing Pathways

Systemic Inflammation and Oxidative Stress

A cardinal feature of OSA is the repetitive hypoxia/re-oxygenation that causes activation of a proinflammatory cascade, cellular adenosine 5′-triphosphate depletion, and xanthine oxidase activation, all factors that drive ROS formation and reductions in nitric oxide, a key vasodilator.[65,66] Sleep fragmentation and reduced sleep associated with OSA may represent an important factor, resulting in an enhanced state of systemic inflammation and oxidative stress as exhibited by increases in myeloperoxidase and oxidized

low-density lipoprotein levels.[67] OSA induces formation of harmful ROS and activation of proinflammatory cytokines while downregulating antiinflammatory mediators; this action leads to endothelial damage and predisposes to cardiovascular disease development and possibly an increased arrhythmia propensity, although this theory is speculative.

In many studies, an array of systemic inflammatory markers has been associated with OSA. For instance, in a meta-analysis, C-reactive protein, tumor necrosis factor-α, IL-8, intercellular adhesion molecule, selectin, and vascular cellular adhesion molecule were all found to be higher with apparent monotonic relationships in those with OSA compared with control subjects.[68] Other biochemical mediators such as increasing soluble IL-6 receptor levels, considered to operate by more expansive trans-signaling pathways than IL-6, is associated with increasing severity of OSA with diurnal patterning independent of obesity.[3] In addition, recent randomized controlled trial data suggest reduction in these levels with OSA treatment. Systemic inflammation has also been implicated in AF. For instance, C-reactive protein levels are elevated in patients with AF corresponding to the AF burden level and may contribute to AF persistence.[69] Both plasma C-reactive protein and IL-6 levels are associated with left atrial dilation and endothelial dysfunction, which are recognized AF contributors.[70,71] Specific studies, however, are needed to examine upregulation of systemic inflammation and oxidative stress in those with OSA and AF.

Prothrombotic State

OSA has also been associated with increased levels of prothrombotic markers.[72] Although the identification of AF as an activator of blood coagulation markers is well recognized, emerging data implicate hypercoagulability as a potential cause or promoter of AF via induction of atrial fibrosis (ie, bidirectional pathways have been characterized).[73] The enhanced prothrombotic milieu in AF has been attributed not only to left atrial abnormalities but also to activation of coagulation factors, platelet activation, and increased fibrinolytic activity.[74] The extent of hypoxic burden and intermittent hypoxia in OSA has been associated with measures of platelet activation,[75] elevations of fibrinogen,[76] and platelet aggregation and thrombus formation response to hypobaric hypoxia in experimental models.[77] Interestingly, even at modest levels of sleep-disordered breathing, a hypercoagulable state has been observed with increases in plasminogen activator inhibitor-1 and fibrinogen independent of obesity. Subjects with an incremental rise in the apnea-hypopnea index exhibit diurnal patterning characterized by an enhanced prothrombotic state in the morning vs evening.[78] Although further study is needed, it is possible that OSA-induced hypercoagulability may result in atrial remodeling and represent a pathway contributing to AF pathogenesis.

Chronic Sleep-disordered Breathing Mechanisms

Cardiac Structural and Electrical Remodeling

Large shifts in transmural pressure, intermittent hypoxia, and upregulation of systemic inflammation and oxidative stress due to OSA over the long term can cause cardiac structural and electrical remodeling. Structural remodeling characterized by ventricular and atrial hypertrophy and increased interstitial fibrosis is a key feature of heart failure. It is unclear if increased arrhythmogenicity from heart failure and OSA is a function of a shared risk factor profile or the combined effects of these disorders causing accelerated cardiac structural change. Despite lack of difference in background risk, atrial remodeling characterized by atrial enlargement has been observed in patients with OSA compared with control subjects[3] and is significantly associated with measures of arterial stiffness.[3] Animal models of sleep apnea rapidly develop atrial remodeling.[42,57] Electrical remodeling measures captured by multipolar catheters were abnormal in patients with OSA compared with control subjects as highlighted by decreased atrial voltage, slower atrial conduction velocity, and more widespread complex electrograms.[3] Chronic apnea over 12 weeks in a canine and rat model resulted in electrical conduction prolongation, which led to increased AF inducibility.[42,57] In moderate to severe OSA, echocardiographic evidence of inter- and intra-atrial electromechanical delay in conjunction with P-wave dispersion on ECG was observed.[79] Furthermore, increased left ventricular mass and hypertrophy, the latter of which predisposes to ventricular arrhythmias and conduction delay,[80] have been observed to be particularly accentuated in individuals with both sleep apnea and hypertension.[63,64] Taken together, these studies indicate that OSA is associated with atrial remodeling and dilation as well as left ventricular hypertrophy leading to electrophysiologic alterations predisposing to arrhythmogenesis.

Future Directions

OSA results in intermittent hypoxia, hypercapnia, pronounced intrathoracic pressure swings, and autonomic nervous system dysfunction. Over time, these direct factors can cause left atrial and ventricular remodeling, exacerbate coronary artery disease, and produce metabolic dysregulation. This dysfunctional milieu sets up the substrate for increased atrial and ventricular arrhythmogenicity. This outcome has been observed most starkly in studies of AF and sudden cardiac death in those with OSA. Although increased systemic inflammation, oxidative stress, and a prothrombotic state have been identified in OSA and separately in AF, further study is needed to investigate the mediation and modulation of these pathways in the OSA and arrhythmia relationship.

To better identify preventative therapeutic targets, future research should focus on the acute compared with chronic OSA-related changes that result in cardiac structural and electrical remodeling. Scant data are focused on the investigation of hypercapnia in OSA as a culprit in arrhythmogenesis. Furthermore, evaluation of the reproducibility of existing findings in alternate experimental models is required. Specifically, organ-specific tissue and molecular experimental studies are needed to examine the direct effects of intermittent hypoxia and hypercapnia on cardiac myocyte and fibroblast voltage-gated ion channels.

Vulnerability of certain areas of the myocardium to OSA-related influences should be clarified (eg, nonpulmonary vein triggers) to inform optimal AF therapeutic approaches such as high-priority anatomical target mapping. Because phenotypic progression of paroxysmal AF to persistent AF occurs, understanding the facets of OSA pathophysiology that are responsible for this progression is important for developing effective preventative strategies. In this era of precision medicine, identifying patient subgroup susceptibilities to OSA-related consequences (eg, intermittent hypoxia or autonomic instability) that would facilitate targeted treatment approaches represents another priority area. The effect of OSA, AF, and heart failure progression as well as ischemic stroke also warrants future research.

Finally, although intriguing data seem to implicate untreated sleep-disordered breathing in the development of recurrent AF after cardioversion or ablation, our field is ripe for the conduct of rigorously performed randomized controlled trials with well-phenotyped participants followed up closely for intervention adherence to examine the effect of OSA treatment on priority AF outcomes.[81] Thus, future investigations should focus on the characterization of the OSA-specific mechanistic pathways because preferentially targeting OSA-related pathophysiologic consequences may reduce arrhythmia-associated morbidity and mortality.

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