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Connexins and Atrial Fibrillation in Obstructive Sleep Apnea

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Abstract

Purpose of the Review: To summarize the potential interactions between obstructive sleep apnea (OSA), atrial fibrillation (AF), and connexins.

Recent Findings: OSA is highly prevalent in patients with cardiovascular disease, and is associated with increased risk for end-organ substantial morbidities linked to autonomic nervous system imbalance, increased oxidative stress and inflammation, ultimately leading to reduced life expectancy. Epidemiological studies indicate that OSA is associated with increased incidence and progression of coronary heart disease, heart failure, stroke, as well as arrhythmias, particularly AF. Conversely, AF is very common among subjects referred for suspected OSA, and the prevalence of AF increases with OSA severity. The interrelationships between AF and OSA along with the well-known epidemiological links between these two conditions and obesity may reflect shared pathophysiological pathways, which may depend on the intercellular diffusion of signaling molecules into either the extracellular space or require cell-to-cell contact. Connexin signaling is accomplished via direct exchanges of cytosolic molecules between adjacent cells at gap membrane junctions for cell-to-cell coupling. The role of connexins in AF is now quite well established, but the impact of OSA on cardiac connexins has only recently begun to be investigated. Understanding the biology and regulatory mechanisms of connexins in OSA at the transcriptional, translational, and post-translational levels will undoubtedly require major efforts to decipher the breadth and complexity of connexin functions in OSA-induced AF.

Summary: The risk of end-organ morbidities has initiated the search for circulating mechanistic biomarker signatures and the implementation of biomarker-based algorithms for precision-based diagnosis and risk assessment. Here we summarize recent findings in OSA as they relate to AF risk, and also review potential mechanisms linking OSA, AF and connexins.

Keywords

Connexins; obstructive sleep apnea (OSA); atrial fibrillation (AF); obesity; cardiac connexins; exosomes

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Sleep-Disordered Breathing:

Sleep-disordered breathing (SDB) is a highly prevalent cluster of conditions that affects both genders and is frequently associated with a wide variety of co-morbid disorders affecting multiple organ systems. The major categories included in SDB consist of obstructive sleep apnea (OSA), central sleep apnea (CSA), obesity hypoventilation syndrome (OHS), and sleep-related hypoxemia such as in COPD and other lung parenchymal diseases. OSA affects at least 5-15% of the general population and possibly much more [1, 2] is characterized by recurrent collapse of the upper airway during sleep [3], and has been conclusively recognized as an independent cardiovascular disease (CVD) risk factor, as well as a major public health issue with society-wide adverse consequences involving motor vehicle accidents or work-related accidents, cognitive, mood and behavioral deficits impairing work performance, and metabolic and sexual dysfunction [4-7].

The cumulative evidence indicates that hypoxia, namely chronic intermittent hypoxia (CIH), generated during repetitive long apneic episodes is one of the major key factors linking SDB and CVD [8]. Accordingly, OSA is an independent causally-associated factor in the development of hypertension, with the risk increasing as OSA severity increases [9, 10]. Severe OSA (apnea– hypopnea index [AHI] ≥30 events/hour) has also been strongly associated with an increased risk of stroke, ischemic heart disease, atrial fibrillation (AF) and excess CVD and all-cause mortality [11-13].

To identify potential mechanisms of OSA morbidity, animal models have been developed to include not only the physiological perturbations that characterize SDB (i.e., CIH or sleep fragmentation (SF)), but also to incorporate disease aspects of human obesity and its co-morbidities that are important contributors to end-organ injury in the context of OSA. Here, we will particularly focus on the findings derived from studies in rodents who were exposed to chronic intermittent hypoxia (CIH). Most models induce environmental hypoxia using inspired oxygen concentrations in the 5–7% range, and aim to elicit nadir arterial oxyhemoglobin saturation levels of 75–80%, which closely correspond to the saturation levels seen in moderate to severe OSA in humans [14-16]. Models of CIH in mice and rats, defined as intermittent hypoxia exposures during sleep periods for 2 weeks or longer, result in phenotypic manifestations that are strikingly similar to the clinical features of human OSA. Increased oxidative stress, evidence of autonomic nervous system dysregulation with increased sympathetic tonic and reflexive activity, and activation and propagation of tissue and systemic inflammatory pathways become all apparent, usually beginning within the first few days after initiation of CIH. These alterations result in cardiovascular derangements including hypertension and increased atherogenesis, along with metabolic perturbations that include insulin resistance and dyslipidemia even in non-obese animals fed with regular diet [16-21]. These findings have been replicated in a very small number of experimental studies involving humans, usually involving relatively short 2–14 day exposures to intermittent hypoxia in young healthy volunteers, and have also resulted in measurable alterations in memory, systemic blood pressure, glucose disposition, and calculated sensitivity of peripheral tissues to insulin [22-25].

Considering that the prevalence of obesity is increasing worldwide, and that obesity represents one of the significant risk factors for OSA, as evidenced by the fact that more than 70% of patients being obese [26, 27], it is sometimes difficult to extricate the contributions of OSA and obesity to downstream morbidities. Obesity, a complex disorder, is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility. Obese individuals are susceptible to co-morbidities such as type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), asthma, cancers, cardiovascular, and neurodegenerative diseases [28-32]. The prevalence of metabolic syndrome is on the rise due to the obesity epidemic. Evidence suggests that an abnormal metabolic syndrome is associated with higher risk of diabetes and CVD [33, 34]. Obesity in turn is a well-recognized risk factor for OSA, and higher body mass index (BMI) is associated with greater severity of OSA for both genders [35].

Several attempts have been made to reproduce the pathological features of obesity-related OSA in animal models, and the more recent murine model is the New Zealand obese mouse (NZO/HlLtJ). These mice, which have anatomic and functional characteristics similar to those of obese OSA patients, also manifest obstructive respiratory events and may consequently be used as a pathophysiological model of OSA [36]. It would be beneficial to study obesity and cardiovascular risk to identify OSA patients because several cardiovascular disease mechanisms in obese people can also be attributable to occult OSA [37].

It has been demonstrated that there is an independent association between OSA, insulin resistance, and type 2 diabetes mellitus (T2DM) by a number of cross-sectional studies, observational studies, and large population-based studies [38-40]. Metabolic syndrome is a cluster of metabolic factors that increases the risk of cardiovascular disease (CVD) morbidity and mortality including AF, and also increases the risk of developing T2DM by three-fold, cardiovascular disease by two-fold, and is growing as a major public health challenge worldwide [41].

As indicated above, the physiological consequences of OSA include intermittent arterial hypoxemia, central and peripheral nervous system autonomic arousal, and large swings in intrathoracic pressures during sleep, which in turn are associated with enhanced sympathetic activation and parasympathetic withdrawal, a combination of neural inputs that clearly facilitates the induction of arrhythmias, such as AF in vulnerable individuals [42-48] Of note, these very same mechanisms have also been implicated in the pathogenesis of AF *per se* in the absence of OSA, either by triggering its initiation or by atrial remodeling so as to promote or maintain the AF arrhythmia [49-51]. However, OSA can also induce and facilitate the occurrence of hypertension, myocardial infarction, and heart failure, and, in concert with obesity, these conditions can lead to cardiac remodeling, as well as arrhythmia, particularly AF [50, 52, 53]. Therefore, as shown in Figure 1, there is strong biologic plausibility that OSA may predispose toward the development of AF [51].

OSA has not only been recognized as an independent risk factor for major postoperative cardiopulmonary complications in addition to increased consumption of economic resources and increased hospital stay duration [54], but such increased complication rates and associated

hospitalization costs are accounted in a substantial proportion by underlying strong associations between OSA and AF [55, 56]. Indeed, the prevalence of sleep apnea, particularly OSA, is 21% to 74% in patients with AF [57-59]. Similar to OSA, AF prevalence is also expected to rise given the increased percentage of the aging population segment [60, 61].

Recently, several studies have shown a favorable effect of continuous positive airway pressure (CPAP) treatment on blood pressure, but this effect exhibits great variability [62]. In fact, 25–30% of patients who use CPAP treatment for > 4 h/night do not experience a positive effect on blood pressure [63, 64]. Application of precision medicine to these patients using circulating biomarkers such as microRNAs (miRNA) was reported as a first-line intervention to avoid the prescription of ineffective treatments and excessive consumption of pharmacological drugs that do not ameliorate the cardiovascular risk [62, 65]. In parallel, Lim et al., 2017 presented a conceptual framework that provides the basis for a new P4 medicine approach to OSA, and should be considered more in depth: predict and prevent those at high risk for OSA and its morbid consequences, personalize the diagnosis and treatment of OSA, and build in patient participation to manage OSA, [66] thereby justifying its acronym of P4 (i.e., prediction, prevention, personalization, and participation). In this context, our effort to identify circulating biomarkers of personalized prediction to therapy employed identification and validation of plasma-based miRNA is the initial step in such direction [62, 65].

Atrial Fibrillation:

Atrial fibrillation (AF), is the most commonly sustained arrhythmia worldwide, is associated with significant morbidity and mortality, and impairs quality of life, while complicating the management of other chronic diseases [67-71]. AF is driven by structural and functional alterations in the atria that consequently result in complex electrophysiological perturbations. Patterns that render the atrial conductive system and the autonomic system dysfunctional, lead to a vicious cycle of exacerbated atrial and ventricular remodeling events (electrical, structural, and autonomic) that promote and maintain AF [72, 73]. Three hypotheses have been suggested that explain the mechanisms of atrial fibrillation: (i) multiple random propagating wavelets, (ii) focal electrical discharges, and (iii) localized re-entrant activity with fibrillary conduction [74].

A number of clinical conditions are associated with an increased incidence of AF. Most of these conditions contribute to a gradual and progressive process of atrial remodeling characterized by changes in (i) ion channel function, (ii) calcium homeostasis, (iii) atrial structure such as cellular hypertrophy, activation of fibroblasts, and (iv) tissue fibrosis. These alterations may favor the occurrence of “triggers” for AF that initiate the arrhythmia as well as enhance the formation of a “substrate for AF” that promotes its perpetuation [75]. The major clinical risk factors for AF incidence include age, diabetes, hypertension, heart failure, and coronary artery disease [76]. AF and the accompanying deterioration of atrial mechanical function is associated with considerable morbidity, including increased risk of cognitive impairments, a 3-fold increase in the risk of heart failure, and a 5-fold increase in the risk of stroke [77, 78]. Consequently, AF leads to substantial health care resource use and economic burden. As would be expected from the above mentioned pathophysiology, AF is a complication of many cardiopulmonary disorders that lead to increased cardiac afterload,

elevated filling pressures, and left atrial enlargement [79]. Many of the conditions associated with such cardiac effects are increasing in prevalence, including hypertension, obesity, and of course OSA [80]. Age-related declines in vascular compliance, increasing population longevity, and the increasing prevalence of cardiovascular disease in older persons has led to an expanding AF epidemic [81].

As discussed, obesity and OSA are both interactive risk factors for AF [82, 83]. Obesity is commonly clustered with metabolic syndrome, diabetes, hypertension, and OSA, all of which may contribute to the development of AF. Obesity and OSA share multiple abnormalities implicated in the pathogenesis of AF, including hypoxia, negative intrathoracic pressure leading to increased atrial wall stress, sympathovagal imbalance, left ventricular diastolic dysfunction, systemic inflammation, and increased intravascular volume [82, 84-8889, 90]. Moreover, one-third of AF patients have at least three associated comorbidities, with a low percentage of AF patients presenting with presumably no heart disease or comorbidities [91]. Figure 2 illustrates the link between obesity, OSA, and AF.

Notwithstanding the enormous advances in our understanding of the molecular pathophysiology of AF during the past decades, there are still numerous important gaps that need to be addressed. Structural remodeling seems a key for AF stabilization and therapy resistance [92]. Notwithstanding, the genomics and proteomic features of AF require further investigation and clarification. Advanced bioinformatics and computational modeling approaches have the capacity to integrate and synthesize current insights to grapple with the complexity of AF. Bioinformatic tools will undoubtedly play a key translational role in understanding and combating the mechanisms of AF *in vivo*, due to sophisticated multiscale computational modeling that can integrate the cellular and molecular processes in the second and third dimensions, providing key insights into the impact of molecular events for AF at the multicellular tissue level [92].

Pathophysiological Mechanisms of Atrial Fibrillation:

The pathophysiology of AF is complex, involving dynamic interactions among several factors, including substrate, triggers, and perpetuators, and the therapeutic approaches/ strategies are informed by the disease progression from initiation of the abnormal electrical rhythm to its maintenance [93]. It has been reported that inflammation is a key component of the pathophysiological processes that lead to the development of AF; and the amplification of inflammatory pathways triggers AF, as AF increases the inflammatory state [94]. There are a number of risk factors and comorbidities that are common to both AF and OSA including age, male sex, hypertension, congestive heart failure and coronary artery disease [95]. In addition, the intermittent hypoxia, recurrent arousals and increased negative intrathoracic pressures that characterize OSA and result in increased sympathetic nerve activity, oxidative stress, inflammation, and electrical and mechanical remodeling of both atria as well as the left ventricle are most likely to further aggravate the risk of AF or make AF more resistant to therapy while promoting recurrence [96, 97, 9899]. OSA induces deeply negative intrathoracic pressure, increases venous return, impairs LV filling, and diminishes stroke volume. Strongly negative intrathoracic pressures activate intrathoracic baroreceptors, inducing

autonomic reflex responses that promote AF [100]. AF onset tends to occur during sleep apnea episodes, suggesting that episodes of OSA acutely enhance the risk of AF [101].

Atrial Fibrillation and OSA:

There is now little doubt that the prevalence of OSA in AF is markedly higher than in the general population [95, 102], increasing the awareness of the potential relationships between AF and OSA [80, 103]. As mentioned, OSA has been documented as a comorbidity with potential interaction and impact on progression and outcome of patients with cardiovascular disease [104], and several studies have indicated the presence of OSA as a predictor of AF in specific subgroups including post-cardiac surgery, post-electrical cardioversion, post-ablation, or in association with underlying congestive heart failure [105]. It has been estimated that the risk of atrial fibrillation is four times higher in patients with OSA independent of obesity, age, hypertension, heart failure or other confounding variables. In addition, nearly 50% of patients of AF have OSA [55]. The severity of OSA has been shown to influence the prevalence of AF. Patients with an AHI of ≥10/h had an AF prevalence rate of 58% compared with 42% in those with an AHI of ≤10/h ($P<0.0001$), and the frequency of AF was even higher (70%) in patients with severe OSA (AHI ≥40/h) [102].

Mechanisms of Atrial Fibrillation in OSA:

The common mechanisms linking OSA and AF are complex and mediated by multiple mechanisms. For example, human and animal studies have demonstrated that the pathophysiologic changes brought on by OSA, including changes in intrathoracic pressure, hypoxia, and hypercapnia may cause structural and electrical changes that predispose to arrhythmia including AF [82]. It has been indicated that OSA increases atrial pressures, causing atrial stretch that could promote remodeling [106]. Furthermore, animal data evaluating the impact of apnea on atrial electrophysiology demonstrated slowed atrial conduction and increased atrial refractoriness. Temporal differences of normalization of these factors after apnea cessation enable a window for heightened AF vulnerability [107-109]. OSA induces repeated episodes of hypoxia that trigger chemoreflex and enhance sympathetic nerve activity, leading to tachycardia and blood pressure elevation, especially at the end of the apneic episodes [110]. Also, hypoxia and reoxygenation cycles in OSA cause a change in oxidative balance, leading to the formation of reactive oxygen species capable of reacting with other organic molecules impairing their functions [111]. Additionally, it has been indicated that hypoxia and hypercapnia associated with sleep apnea affect sympathetic nerve activity and cause vasoconstriction and, as a result, hypertension that is a known risk factor for AF [112, 113]. There is also increasing evidence that OSA results in atrial electrical and structural remodeling. The atria of OSA patients were shown to have extensive areas of low voltage or electrical silence and conduction abnormalities, slower atrial conduction velocity, and sinus node recovery times [114]. Very recently, it has been reported that mice exposed to CIH exhibit changes in the passive stiffness of the cardiac tissue extracellular matrix (ECM), a critical factor underlying conduction changes and predisposing to AF [115].

Understanding of AF mechanisms in the context of OSA may allow for more direct targeting of specific pathophysiological contributors. Furthermore, new insights into the molecular

pathophysiology of AF open new opportunities in risk assessment and monitoring of therapeutic responses. Novel biomarkers under investigation include noninvasive indices of atrial fibrosis and plasma biomarkers reflecting underlying biochemical mechanisms or responses [116, 117]. Genetic findings suggest that dysregulation of gene transcription and an imbalance in major regulatory pathways of cell function may contribute to the complex genesis of AF. Future challenges include the identification and investigation of the downstream components of these pathways and henceforth, the identification of therapeutic targets of AF, particularly in the context of OSA [118].

Connexins:

Connexins ubiquitous proteins that are highly expressed in the heart, brain, and liver, as well as in endothelial and smooth muscle of blood vessels [119, 120]. Connexins are critical for the development, function, and homeostasis of tissues and organs. Dysregulations of connexins are linked to many diseases such as stroke, heart attack and cancer [119]. Connexins compose of a large family of trans-membrane proteins that allow intercellular communication and the transfer of ions and small signaling molecules between cells. Their main function is to facilitate cell-cell communication by forming channels called gap junctions (GJs) that connect the cytoplasm of cells [120]. It has been reported that 20 different connexin genes have been found in mice and 21 in humans [121]. Disruption of adhesion complexes, mainly adherent junctions, tight junctions, and gap junctions, leads to interference with normal tissue function, and may eventually lead to tissue dysfunction [122]. Connexins are commonly named according to their molecular weights, and three different connexins were documented in cardiac myocytes, namely Cx40, Cx43, and Cx45. These 3 connexins were found to be expressed between cardiomyocytes, whereas Cx37 and Cx40 are present between endothelial cells [123, 124]. All connexin molecules have four membrane-spanning domains, two extracellular domains, and a cytoplasmic carboxy-terminal tail of varying length that has an important role in the regulation of the gating properties of the channel [125]. Connexin signaling can be achieved via direct exchanges of cytosolic molecules between adjacent cells at gap junctions, for cell-to-cell coupling, and possibly also can involve the formation of membrane “hemichannels,” for the extracellular release of cytosolic signals, direct interactions between connexins and other cell proteins, coordinating influence on the expression of multiple genes [126]. Among the various connexins, Cx43 is the most studied connexin protein due to its expression in a wide variety of different tissues. For example, Cx43-containing gap junctions couple cardiomyocytes with non-cardiomyocytes, which can then alter the electrophysiological properties of cardiomyocytes [127].

Connexins play a central role in the synchronized contraction of the heart muscle, as well as the essential physiological processes such as tissue inflammation and repair [128, 129]. However, the loss of connexins or mutations affecting their normal functions such as embryonic development, morphogenesis, and cell differentiation, as well as in the control of adult cell proliferation, and migration, and therefore connexins deficits have been implicated in a variety of diseases [130, 131132-135].

Cellular interaction in blood vessels is maintained by multiple communication pathways, including gap junctions and consist of intercellular channels ensuring direct interaction

between endothelial and smooth muscle Cells [125]. In general, Cx40 and Cx37 are abundantly expressed in elastic (aorta) and muscular (coronary) arteries of various species [136-138], whereas the expression of Cx43 is restricted to the endothelial cells at branch points of these arteries [137]. Furthermore, two studies reported that Cx40 plays an important role in blood-pressure regulation, and deletion of the Cx40 gene in mice results in a marked, sustained form of systemic hypertension [139, 140]. In addition, the major dysfunction in Cx40-deficient mice appeared to depend on local blood flow–induced signaling in the afferent arteriole, a concept that was elegantly confirmed in perfused kidney by using a gap-junction blocker [140]. For example, Cx43 plays a role in the looping of the ascending limb of the heart tube and the development of the right ventricle and the outflow tract, while Cx43-knockout mice die at birth of severe cardiac malformations [141].

Connexin signaling is regulated by several mechanisms at the transcriptional, posttranscriptional, translational, and posttranslational level [142, 143]. Connexin expression may be related to epigenetic mechanisms, including reversible histone modifications, DNA methylation, and microRNA-related actions [144, 145], but is predominantly controlled by the conventional *cis/trans* machinery [142]. A basal level of connexin gene transcription is maintained by general transcription factors, such as specificity protein 1 and activator protein 1. However, tissue-specific expression depends on cell type-specific repressors and activators, such as hepatocyte nuclear factor 1 alpha or Cx32 expression in the liver [146]. In addition, epigenetic mechanisms, including histone modifications, DNA methylation, and microRNA-related control, are essential determinants of connexin gene transcription [144]. In the vasculature there are several connexin (Cx) isoforms that were identified including Cx32, Cx37, Cx40, Cx43, and Cx45, which regulate the coordination of vessel contraction and relaxation. Generally, Cx32, Cx37, and Cx40 have been shown the most abundant in ECs with Cx43 and Cx45 routinely identified in the vascular SMCs [147]. However, this expression pattern varies depending on vessel size and function with Cx43 found in the endothelium at arterial branch points and in smaller resistance vessels [148].

Connexin abnormalities have now been critically implicated in the pathophysiology of AF for quite some time. Generally, either mutations that reduce the expression or function of cardiac connexins or alternatively diseases that foster declines in the expression of connexins in atrium have been shown to increase the probability of AF and the susceptibility to AF recurrence [149-155]. Initial experiments in rats indicated that induction of recurrent apneas was associated with increased probability of AF and that such susceptibility appeared to be dependent on connexins expression [109]. More recently, work from our laboratory showed that CIH down regulates the expression of cardiac connexins traditionally implicated in the pathophysiology of AF, ie., Cx40 and Cx43, and that such reductions in expression are likely mediated by increased oxidative stress, since abrogation of NADPH oxidase was protective and preserved connexins expression in atrial myocytes [156].

As discussed above, the connexin gene family undergoes extensive regulation at the transcriptional and post-transcriptional level, and also undergoes numerous modifications at the protein level, including phosphorylation, which ultimately affects their trafficking, stability, and function. Recently, it has been indicated that intercellular communication can occur directly between neighbor cells via gap junctions (GJ), or indirectly at longer

distances through soluble factors and extracellular vesicles (EVs) released into the environment [157, 158]. Furthermore, Cx43, was able to modulate the interaction and communication between exosomes and cells [157]. Extracellular vesicles (EVs) are membrane-bound, subcellular fragments that contain DNA, RNA, protein and lipids, and play an important role in intercellular communication. Currently, EVs are commonly classified based on their intracellular origin and size. Exosomes are class of EVs that were described, for the first time three decade ago, as very small vesicles of endosomal origin, and released as a result of the fusion of the multivesicular bodies (MVBs) with the plasma membrane in reticulocytes from rats and sheep [159, 160]. Exosomes transfer biological information to neighboring cells, and through this cell-to-cell communication are involved not only in physiological functions such as cell-to-cell communication, but also in the pathogenesis of some diseases, including tumors and neurodegenerative conditions. They carry the large sized molecules such as RNA and proteins that influence gene expression.

A major breakthrough was the demonstration that the cargo of EVs included both mRNA and miRNA and that EV-associated mRNAs could be translated into proteins by target cells [161]. Later studies reported on the RNA contents of EV isolates from other cell cultures and body fluids [162-166]. In both patients with OSA or in animal models using CIH or sleep fragmentation, we showed that exosomes carrying miRNAs can be internalized and transferred from one cell to another [164-169] as illustrated in Figure 3. In addition, initial work linking extracellular vesicle content and activity to AF has begun to emerge [170], suggesting that exosomes may play a contributory role in facilitating AF under specific circumstances such as OSA or obesity. Furthermore, therapeutic approaches involving exosome-based gene therapy are being explored on the ability of exosomes to cross biological barriers and their capacity to shuttle functional nucleic acids between cells [171-173]. As such, the increased propensity and prevalence of AF in OSA may be not only detectable via identification of biomarkers within exosome cargo in plasma, but may also enable development of specific therapies that are selectively delivered to atrial tissue targets via exosomes.

Summary:

OSA has now been extensively investigated as a condition influencing and adversely impacting the progression and outcomes of patients with cardiovascular disease. The awareness to the potential bidirectional interactions between AF and OSA has increased in the last decade. The mechanisms by which OSA predisposes to the development of AF, including sympathetic activation, intermittent hypoxia, transmural pressure changes, left atrial chamber enlargement, systemic inflammation, and endothelial dysfunction have been evoked, and the role of a third player, namely obesity has also emerged. It has been proposed that AF patients should be screened for OSA and therapy to alleviate OSA should be initiated as soon as it is diagnosed in patients with AF. In this context, the role of OSA in altering the expression and regulation of cardiac connexins which are mechanistically implicated in AF, and the need to identify at-risk patients with OSA or those with AF to facilitate more personalized approaches is prompting examination of circulating exosomes as both biomarkers and effectors of the OSA-AF dyad. If confirmed, exosomes may not only provide precise identification of AF risk in OSA patients, but may also constitute a precisely

targeted therapeutic approach aimed at the atrial conduction system to abrogate the risk of AF in susceptible patients.

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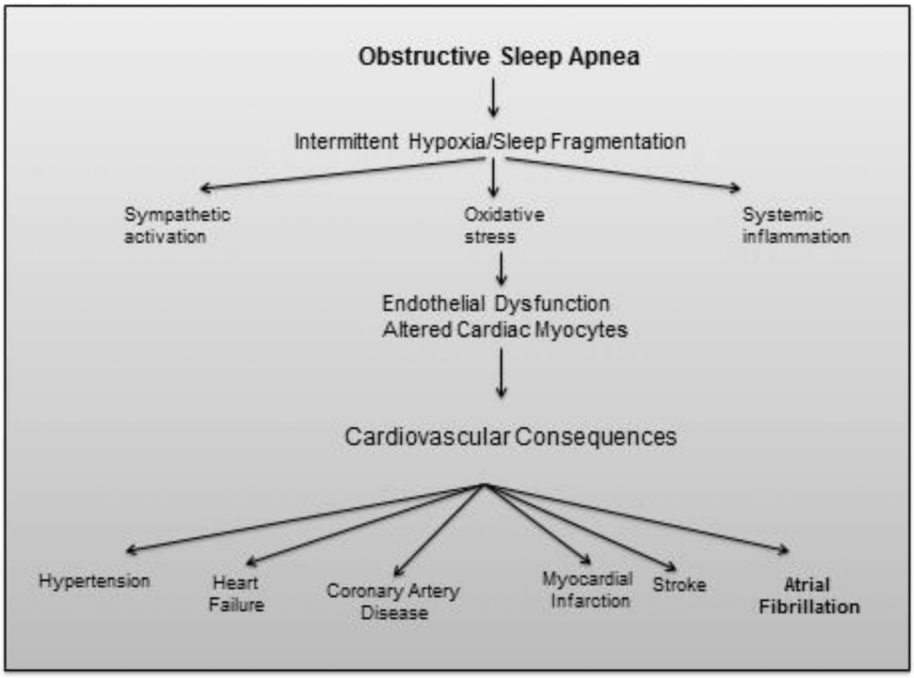

Figure 1:
Cardiovascular consequences of obstructive sleep apnea.

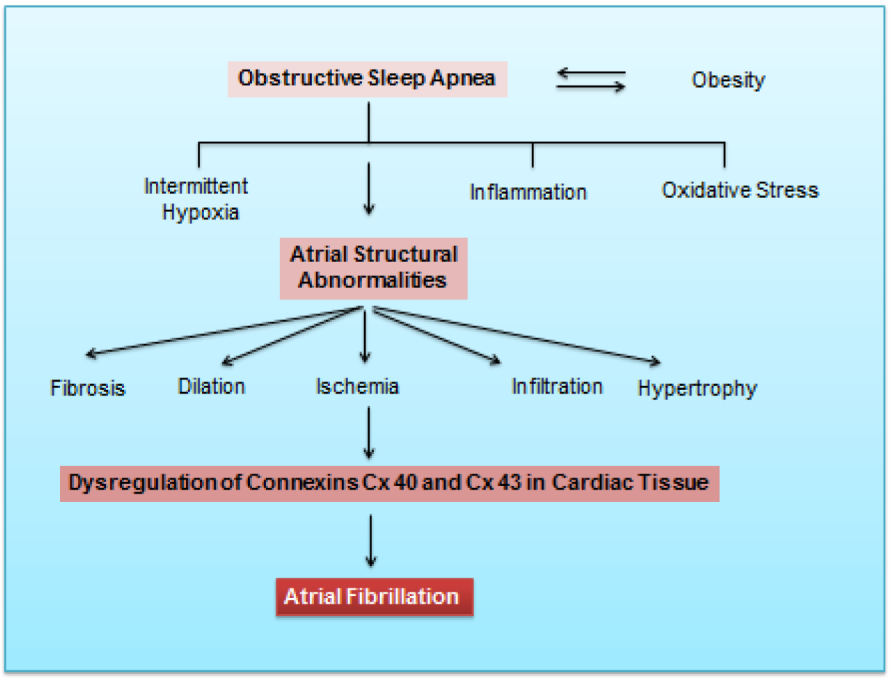

Figure 2:

Interactions between obstructive sleep apnea obesity and down-stream effects on atrial structure and function including down-regulation of connexins in atrial myocytes.

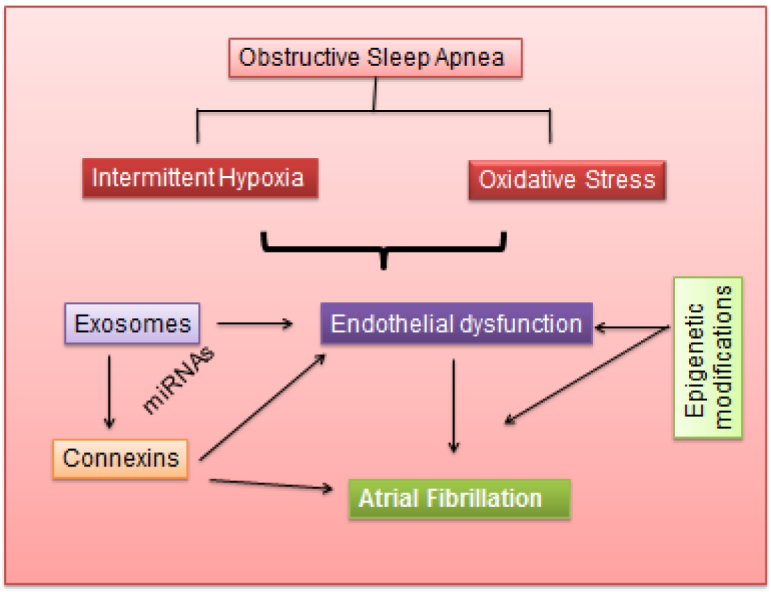

Figure 3:

Hypothetical pathways involving coordinated activities of exosomes released in patients with obstructive sleep apnea, their effects on connexins in cardiac tissues, and the potential roles of epigenetic modifications on these elements to facilitate the occurrence of atrial fibrillation.