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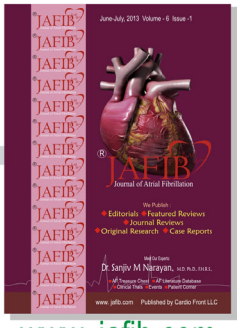

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Sleep Disordered Breathing and the Pathogenesis of Atrial Fibrillation

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Abstract

This review illustrates the importance of sleep disordered breathing in evolution and progression of atrial fibrillation. While in early years associations were mainly attributed to the impact of hypoxemia and hypertension, nowadays multiple, additional pathways have been investigated or are currently under investigation. Sleep disordered breathing has been shown to have a direct impact on mechanical and electrical remodeling. In addition hypercapnia and negative intrathoracic pressure seem to alter atrial electrophysiology. Finally, impacts on inflammation and metabolic dysregulation display the complex interplay between breathing disorders and evolution and progression of atrial fibrillation.

Introduction

Atrial fibrillation (Afib), has shown an increasing prevalence and hospitalization rate over the past decades which is expected to grow even further.[1] For the individual, existence of atrial fibrillation is not only accompanied by symptoms leading to subjective and objective exercise capacity impairment, but also means a five-fold increase in stroke risk as well as an increased mortality risk.[2,3] In recent years the impact of sleep disordered breathing (SDB) on the evolution and progression on atrial fibrillation has been extensively investigated. Within this review we aim to clarify the pathophysiological links between sleep disordered breathing and atrial fibrillation.

Pathophysiology of Atrial Fibrillation

The pathophysiology of Afib involves the interaction of a triggering event and an arrhythmogenic substrate that induces electrical instability. Profibrillatory changes of the atrial myocardium including atrial size enlargement, scarring and fibroses serve as a substrate.[4] In addition, rapid atrial rates such as those during periods of fibrillation increase myocyte calcium load. This induces adaptive mechanisms, for instance a reduction in activity or downregulation of calcium-channels which alter atrial refractory period and thereby perpetuates atrial fibrillation as well.[5;6] The most important initial trigger source for paroxysmal Afib was identified to be the muscular sleeve of the pulmonary veins.[7] With ongoing remodeling, multiple re-entrant wavelets occur that help to maintain Afib.

Sleep Disordered Breathing

Sleep disordered breathing (SDB) has been recognized as co-morbidity with potential interac tion and impact on progression and outcome of patients with cardiovascular disease.[8]

In a cardiology setting it mainly comprises two different entities: obstructive sleep apnea (OSA) on the one hand and central sleep apnea including Cheyne-Stokes respiration (CSA) on the other.[9-13] OSA is the most common form of SDB. It affects approximately 2 to 4% of the general population.[14] Due to anatomic narrowing of the upper airways, during sleep inspiratory pressure generated by pharyngeal dilator muscle tone is below pharyngeal air pressure (critical pressure), causing the airways to collapse. Occlusion of the upper airways (flattening) results in hypopneas and/or apnea with accompanying hypoxemia. Apnea is defined as a ≥90% reduction of airflow lasting for ≥10 seconds. Hypopnea is defined a ≥10 seconds lasting, ≥30% reduction of airflow accompanied by a ≥4% oxygen desaturation/arousal or a ≥10 seconds lasting, ≥50% reduction of airflow with a ≥3% desaturation or an arousal.15 "Arousal" describes a transition from sleep to a state of wakefulness for at least 3

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seconds and is caused by an increase in sympathetic drive as a result of intermittent hypoxemia in apneic or hypopneic phases of sleep disordered breathing.

Clinical Importance of Sleep Disordered Breathing in Atrial Fibrillation

Several studies propagate a prevalence of SDB of approximately 30-80% in patients with Afib, depending on the type of Afib (paroxysmal vs. persistent), underlying diseases, and the cut-off Apnea-Hypopnea-Izndex (AHI) to define SDB (between ≥5/h and ≥15/h).[13,16-19] Furthermore, SDB was shown to be an independent risk factor for incident atrial fibrillation in individuals <65 years of age.[20] However, most studies investigated the impact of SDB in the secondary prophylaxis of Afib. Focusing on electrical cardioversion, untreated OSA was found to be associated with a higher recurrence of AF compared to the general population or patients with treated OSA.[21,22] In patients undergoing ablative therapy, adequate diagnosis of SDB seems to be of major importance. In a recent study applying cardiorespiratory polygraphy, a six-channel recording system to determine type and severity of SDB, we identified moderate to severe SDB, but not SDB per se as an independent predictor for AF recurrence following cryoballoon pulmonary vein isolation.[23] Previous studies in patients who had undergone radiofrequency catheter ablation demonstrated incoherent results.[24-27] This may be traced back to assessment of SDB by clinical evaluation, only refined by questionnaires as the "Berlin Questionnaire". This method neither is validated among cardiac patients, nor does it reflect SDB severity.[28] In line with this, a recent meta-analysis on the importance of OSA as a predictor of Afib recurrence after catheter ablation showed that OSA diagnosed using polysomnography but not using the Berlin questionnaire is a strong predictor of Afib recurrence.[29]

Arterial Hypertension, Ischemia and Sleep Disordered-Breathing

The most obvious interaction between SDB and Afib is the impact of SDB on arterial hypertension and ischemia. In SDB patients recurrent nocturnal hypoxemic and hypercapnic periods are associated with an increase arousals and sympathetic activity.[30] Even though severe hypoxemias are known to have a local vasodilative effect, cycles of hypoxemia and hypercapnia are rather associated with systemic vasoconstriction, potentially leading to nocturnal arterial hypertension as well as ischemia.[30,31] In addition, an activated sympathetic nerve system is associated with increased plasma-levels of catecholamines, and a reduced α-and β2 adrenergic vascular response.[32-34] As angiotensin II induces vasoconstriction via AT1-receptor, enhanced vasoconstrictor sensitivity to angiotensin II, as seen in OSA patients, augments vasoconstriction.[35] In addition, studies confirm increased serum-level of either endothelin-1, a potent vasoconstrictive neuropeptide, or big endothelin-1 to be found in OSA patients.[36,37] On intermittent hypoxemic periods, formations of free radicals or reactive oxygen species (ROS) emerge and react with nitric oxide (NO) to produce peroxynitrite, thereby diminishing bioavailability of NO.[38,39] Consequently, OSA patients are affected by an altered vasodilatation as well as endothelial dysfunction. [40-42]

Today there is conceiving evidence that OSA is an independent risk-factor for arterial hypertension and current guidelines recommend screening procedures.[43-45] In addition, several studies demonstrate an impact on the evolution and progression of coronary artery disease as the most common cause of cardiac ischaemia.[12,46-48]

sleep disordered breathing is not only found to impact proarrhythmic structural changes of the heart indirectly via arterial hypertension and myocardial ischaemia, but also to have a direct effect on electrical and mechanical remodeling. The key-factor seems to be the renin-angiotensin-aldosterone system. Previous studies showed levels of angiotensin II and aldosterone elevated in OSA patients.[49,50] Angiotensin II promotes proliferation and growth. It increases protein synthesis in myocardial fibroblasts and myocytes, and increases coronary artery permeability with diffusion of growth factors into the myocardial interstitium.[51-53] On the other hand, angiotensin II causes oxidative stress with subsequent induction of apoptosis at the endothelial and myocyte level, as well as necrosis and fibrosis through its cytotoxic effect on cardiac myocytes.[54] Due to an increase of intracellular calcium concentration, and an increased availability of calcium contained in the sarcoplasmatic reticulum, angiotensin II also shortens the refractory period.[55,56] Increased aldosterone serum-levels stimulate collagen synthesis by myocardial fibroblasts and may also play a role in myocyte death through their effect on electrolyte balance.[57,58]

In vivo, structural and electromechanical changes of the heart have previously been linked to SDB.[59-63] In addition, SDB is a common co-morbidity among patients with structural heart disease resulting from cardiac remodeling such as systolic or diastolic heart failure or cardiomyopathies.[9-11]

Impact of Intrathoracic Pressure Alterations

Inefficient respiratory excursions, a regular occurrence in the apneic or hypopneic phases of OSA, alter transmural pressure and volume relations. This leads to increased sheer stress with subsequent mechanical remodeling.[62] In addition, this also triggers extension-sensitive ion channels.[64] A recent study demonstrates an additional mechanism by which OSA affects Afib: negative tracheal pressure shortens right atrial refractory periods and increases susceptibility to AF mainly by vagal activation.[65] Previous studies provided similar effects caused by acute hypercapnia during OSA.[66]

Inflammation and sleep disordered breathing

Another possible link between sleep disordered breathing and atrial fibrillation is chronic inflammation. Recent reports suggest that adverse atrial remodeling, which predisposes for Afib is not only linked to stimulation of myocytes and fibroblasts but also to the activation state of leukocytes.[67] An association with parameters of cell adhesion (CD15, CD11c), increased intracellular reactive oxygen species, and increased adherence to human endothelial cells on monocytes has been demonstrated for OSA patients.[68] In addition, patients with SDB face an increased expression of C – reactive protein, interleukin 6, interleukin 8, as well as functional and phenotypic changes of CD4 and CD8 t-cells, followed by an increase in tumor necrosis factor α, and interleukin 4 as well as a decrease of interleukin 10 expression.[69-71]

Metabolic Dysregulation and Sleep Disordered Breathing

Finally, metabolic syndrome was shown to be associated with Afib and to have a negative impact on primary and secondary prevention.[72-74] OSA-related factors contribute to the development of metabolic dysregulation, for instance insulin and leptin resistance.[75,76] Increased sympathetic activity due to sleep fragmentation and intermittent hypoxemia alter hypothalamic pituitary adrenocortical

axis function that in addition to the aforementioned changes in oxidative and inflammatory pathways is involved in insulin resistance and impaired pancreatic beta-cell function.[76,77]

Conclusions:

This review reveals that there are several over lapses between SDB and Afib. While in early years associations were mainly attributed to the impact of hypoxemia and arterial hypertension, nowadays multiple, additional pathways have been investigated or are currently under investigation. Direct impacts on mechanical and electrical remodeling as well as effects of negative intrathoracic pressure and hypercapnia on atrial electrophysiology, and impacts of inflammation and metabolic dysregulation allow us more detailed insights in the complex interplay between breathing disorders and the evolution and progression of atrial fibrillation.

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