Ion Channel Remodeling—A Potential Mechanism Linking Sleep Apnea and Sudden Cardiac Death

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Sudden cardiac death (SCD) claims 340 000 lives per annum, making it the leading cause of cardiovascular-related deaths in the United States. Most patients die from ischemia-driven ventricular arrhythmias (VA) secondary to myocardial infarction (MI), but other important causes of SCD include cardiomyopathy (hypertrophic, dilated, and arrhythmogenic), ion channelopathies (Brugada and long QT syndromes [LQTS]), and aortopathies.[1,2] One of the most intriguing and unsolved questions in arrhythmia research is why only some patients succumb to arrhythmia and die while others with similar underlying cardiovascular diseases (CVD) substrates do not. This, along with the abysmal survival rates of 10% following cardiac arrest, makes the search for risk factors, triggers, and maintainers of arrhythmia and SCD crucial public health priorities. Repolarization reserve and arrhythmia remodeling, due in part to long-term changes in ion channel expression, are constructs that may explain SCD susceptibility in acute MI, cardiomyopathies, and primary ion channelopathies. Obstructive sleep apnea (OSA) may be an independent risk factor for nocturnal MI, SCD, atrial fibrillation (AF), heart failure, and pulmonary and systemic hypertension.[3–10] In this issue of the *Journal*, Dudley and colleagues elegantly propose a potential mechanistic link between OSA and ion channel remodeling (ICR) by measuring circulating mRNA levels of K^+ channels in OSA patients and controls and compare changes in those treated with continuous positive airway pressure (CPAP).[11] In this accompanying editorial we provide background on arrhythmia propensity and the role of OSA in SCD.

Propensity for Arrhythmia

The negative cytosolic resting membrane potential (phase 4) of approximately -80 mV is maintained largely by the action of transmembrane cellular pumps (predominantly Na^+/K^+ ATPase and Na^+/Ca^{2+} exchanger) and closed voltage-gated ion channels (Figure 1).[12,13] The cardiac action potential (AP) is initiated in the sinoatrial node (SAN) by the slowly leaking inward "funny" current sodium channels (I_f), leading to the recruitment of Ca^{2+} channels and causing the positive depolarization current (phase 0). Gap junctions facilitate spread to adjacent cells in the atria, internodal tracts, atrioventricular node (AVN), His bundle, and both right and left bundles, the Purkinje cells, and finally, the ventricular myocardium. Phase 0 in all of the heart cells except for the SAN and AVN is caused by the opening of Na^+ channels, flooding the cytoplasm with Na^+ ions and causing the positive depolarization of the membrane. As the wave of depolarization spreads, sarcoplasmic Ca^{2+} release leads to muscular contraction (excitation-contraction coupling). Immediately after phase 0, repolarization begins with phase 1 (largely due to Cl^- ions), followed by phase 2, the plateau stage where the inner membrane potential remains relatively constant due to the influx of Ca^{2+}. Phase 3 is the latter stage of repolarization and the relative refractory period, during which a new stimulus such as a ventricular extrasystole (VE) can trigger arrhythmia. AP duration is determined largely by activation of K^+ channels. Thus, inactivation and/or down-regulation of these K^+ channels, which can be primary in genetic LQTS or secondary to other pathological states, can prolong the QTc on the surface ECG. Neurohumoral changes can modify the regionally specific AP further: increased sympathetic tone increases automaticity and conduction velocity and decreases the AP duration, leading to more rapid AP firing and recovery. Conversely, heightened parasympathetic tone decreases automaticity and prolongs the refractory periods.

Established arrhythmia mechanisms include (1) abnormal impulse initiation due to (1a) automaticity and (1b) triggered
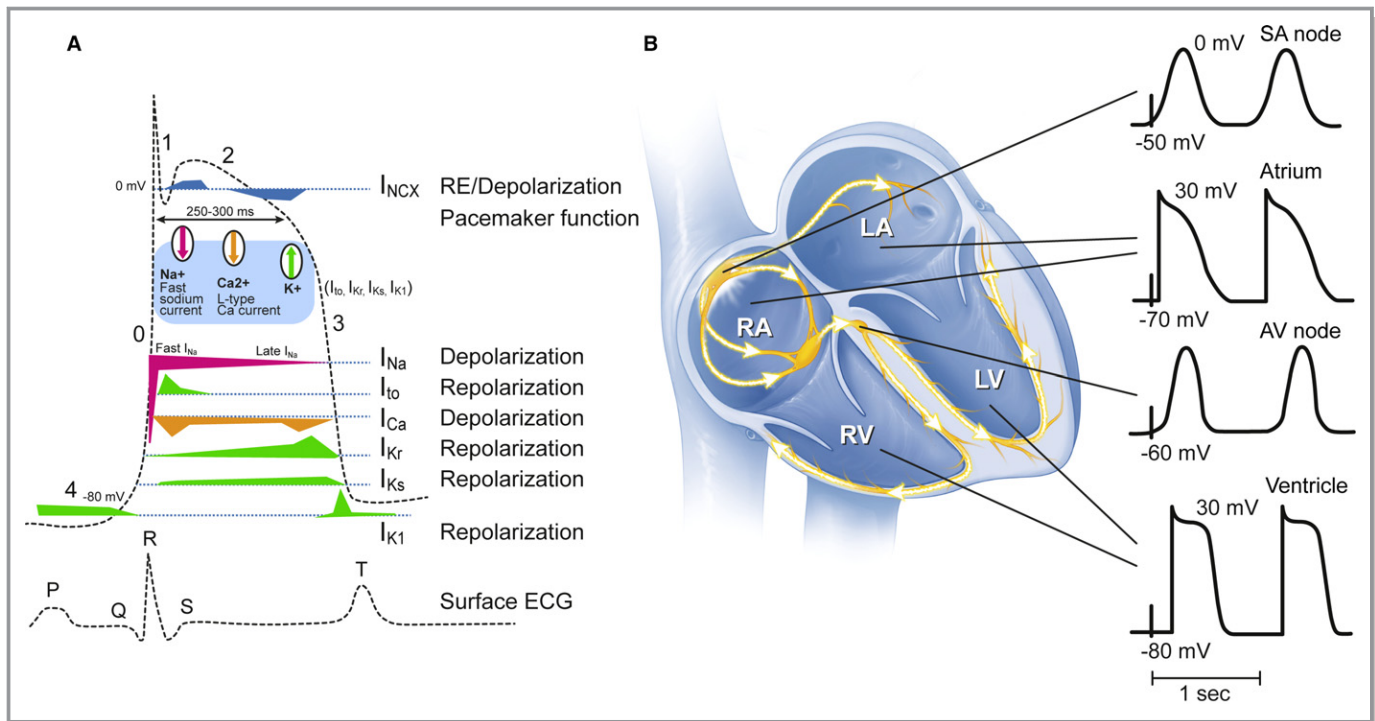
Figure 1. Schematic representation of types of action potential (AP) throughout the heart. The major differences are between the nodal tissues (sinoatrial and atrioventricular nodes) and ventricular Purkinje/myocardium. (A) on the left hand side, the ventricular AP and associated Na^+, K^+, and Ca^{2+} channels are shown. Phase 0 corresponds with the QRS wave, phase 3 with the peak of the T wave, phase 4 with the isoelectric line of the surface ECG changes. (B) action potentials from different regions within the heart. I_{Ca} indicates inward calcium current L-type; I_{Kr}, delayed inward rectifier K^+; I_{Ks}, slowly activating K^+ channel; I_{Na}, inward voltage-dependent sodium channel; I_{NCX}, sodium-calcium exchanger; I_{to}, transient outward; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Adapted from Dumotier, *Heart*[12] by permission from BMJ Publishing Group Limited, and from Nattel et al, *Physiological Reviews*,[13] with permission by the American Physiological Society.

mechanisms from early and delayed afterdepolarizations such as VEs and (2) abnormal impulse conduction due to anatomical or functional reentry and reflection. Propensity for arrhythmia is a complex interplay between the substrate (anatomical and functional) and wide-ranging modulators such as (1) autonomic tone, (2) stretch, (3) electrolyte changes, (4) ectopic beats, and (5) drugs or toxins. OSA is an important treatable and reversible modifier of arrhythmia propensity given direct and indirect effects including autonomic tone, stretch, and increased VE (described below).

Arrhythmogenic Remodeling and Repolarization Reserve

CVD modify not only the macroscopic structure of the heart but also the normally rigidly regulated ion channels, pumps, associated regulatory proteins and their expression, such that this promotes arrhythmia in a process termed "arrhythmogenic remodeling."[12–14] Many of these alterations are primarily adaptive responses for homeostasis but can result in secondary cardiac dysfunction, particularly VA. Classical models of static ion-channel structure in heathy tissue have been superseded by a dynamic model of ion-channel structure

in response to normal physiology. Recognized mechanisms of ICR include DNA transcriptional regulation, epigenetic factors, mRNA processing and translation, posttranslational modification, processing, assembly, and membrane transport of proteins, macromolecular assembly, and posttranslational regulation.[15,16] This control also has regional differences, reflecting the known differences in AP generation (see a detailed review[17]). ICR may help explain changes seen in the surface ECG, particularly QTc prolongation. Significant advances in understanding ICR in CVD have been made,[13] but ICR in noncardiac disease, such as highly prevalent OSA, are understudied.

"Repolarization reserve" is the ability of cardiac myocytes to tolerate and compensate for the loss of repolarizing currents by recruiting additional time-dependent outward (repolarizing) currents I_{Kr} and I_{ks}, which minimize repolarization deficit.[18] Minor changes to ion channel regulation can mean little loss of repolarization reserve, such that no noticeable clinical or physiological effects are seen. However, major changes to control mechanisms, and thus to repolarization reserve, can exaggerate the effects of any arrhythmic triggers that are directly relevant in prolonged QTc and the risk of VA. The presence of OSA with coexisting CVD may be

pivotal in reducing repolarization reserve, which, coupled with ICR, may help explain the higher frequency of SCD.

Obstructive Sleep Apnea

Sleep in itself is associated with changes in autonomic activity and can be considered an autonomic stressor for the heart. In healthy states, non–rapid eye movement (nonREM) sleep, composed of stages N1, N2, and N3, occupies 80% of sleep architecture and is associated with relative autonomic stability in which vagal tone dominates, baroreceptor gain is high, and sympathetic activity is both constant and low.[10] Transitions from nonREM to REM sleep can result in bursts of vagal activity causing bradycardia and asystole. During REM sleep, which occurs approximately every 90 minutes of each sleep epoch and >5 times for an average 8 hours of sleep, surges of sympathetic activity occur, which can cause tachycardia, increased VEs, and hypertension.[4,8] Vagal activity is suppressed, baroreceptor gain is reduced, and irregular breathing patterns may occur. Loss of airway muscle tone during inspiration, especially during REM, can lead to obstructive apneas, which can result in hypoxemia and hemoglobin desaturation. In patients with OSA and underlying cardiovascular and/or respiratory disease, hypoxemia can be profound and dysrhythmogenic.[10,19]

OSA can acutely elicit sympathetic activation, VA, brad-yarrhythmias, and SCD. In the longer term, OSA can result in hypertension, endothelial dysfunction, ventricular remodeling, and myocardial scarring, all of which increase the proclivity for arrhythmia. An alternative mechanism is for OSA to "trigger" an MI due to plaque rupture, de novo thrombosis, or hemodynamic disturbance leading to SCD.

OSA is also associated with increased VE activity of 60% when compared to subjects without OSA (4% to 12%), which can be decreased with the use of OSA therapies.[10] VEs initiating VA in prolonged QTc, especially during severe hypoxemia, may be key mechanisms for SCD in OSA (Figure 2). Potentiating mechanisms may include hemody-namic instability, increased platelet aggregation, plaque disruption and release of vasoactive substances, inflamma-tion, oxidative stress, endothelial dysfunction, and thrombo-sis. Direct mechanisms include the effects of a Mueller maneuver (repetitive forced inspiration against a closed upper airway) with substantial negative intrathoracic pressures, which can increase transvalvular gradients, wall stress, and afterload, which can be proarrhythmogenic. This can also increase the risk for aortic dissection and rupture, resulting in SCD. Other possible effects include altering cardiac cellular electrophysiology with prolongation of QT interval, during which the heart is susceptible to VA initiation.

In an elegant prospective observational cohort study in this issue of the Journal, Dudley and colleagues report a possible mechanistic link between OSA and prolonged QT interval and thus SCD.[11] Given the inherent procedural risks associated with endomyocardial biopsy of the different regions of the heart, the authors used mRNA in circulating white blood cells as surrogate reflectors of ion channel expression in unaf-fected controls and patients with OSA before and after 4 weeks of continuous positive airway pressure (CPAP) therapy. The authors found expression of potassium channels *KCNQ1*, *KCNH2*, *KCNE1*, *KCNJ2,* and *KCNA5* to be inversely associated with severity of OSA by the apnea-hypopnea index. *KCNQ1*, *KCNH2,* and *KCNE1* were also inversely associated with severity of hypoxemia. Loss-of-function mutations in *KCNQ1* are associated with *LQTS1*, *KCNH2* with *LQTS2*, *KCNE1* with *LQTS5*, *KCNJ2* with *LQTS7* (also known as Andersen-Tawil syndrome), and *KCNA5* with familial AF. Furthermore, the authors found just 4 weeks of CPAP therapy to be sufficient to significantly increase the mRNA levels of *KCNQ1* and *KCNJ2* in moderate OSA. The dynamic QT interval changes with ventricular rate and during normal sleep, becoming prolonged in response to stressors, including OSA. This novel study suggests a mechanistic association between OSA and altered mRNA expression of K^+ channels as a contribution to the association of OSA with SCD. However, the investigators did not assess measured QTc interval on the surface ECG during sleep and wakefulness, which would have provided important proof-of-concept insights into this poten-tial link. This study may also be relevant to genetic LQTS, as up to 20% of asymptomatic mutation carriers are phenotype negative with SCD risks comparable to the general population, implicating nongenetic modifiers. Because OSA has a high prevalence in LQTS, this could be an important modifier of phenotype.[20]

Reducing Arrhythmic Burden and Saving Lives

Although definitive randomized controlled trials remain to be completed, observational data suggest that cardiovascular effects of OSA may be mitigated with safe, established, and effective therapies (including repositioning, oxygen, mandibu-lar devices, and CPAP), making it a potentially modifiable risk factor for MI, hypertension, SCD, and cardiomyopathies.[2,3] Because these therapies have virtually no known major side effects, it is attractive and plausible that the risk of VAs and SCD could be reduced.

Summary

This study is the first to link potential mechanisms between OSA and prolonged QTc and SCD, suggesting an inverse association with mRNA expression of K^+ channels with severity of OSA. CPAP therapy diminishing OSA is able to
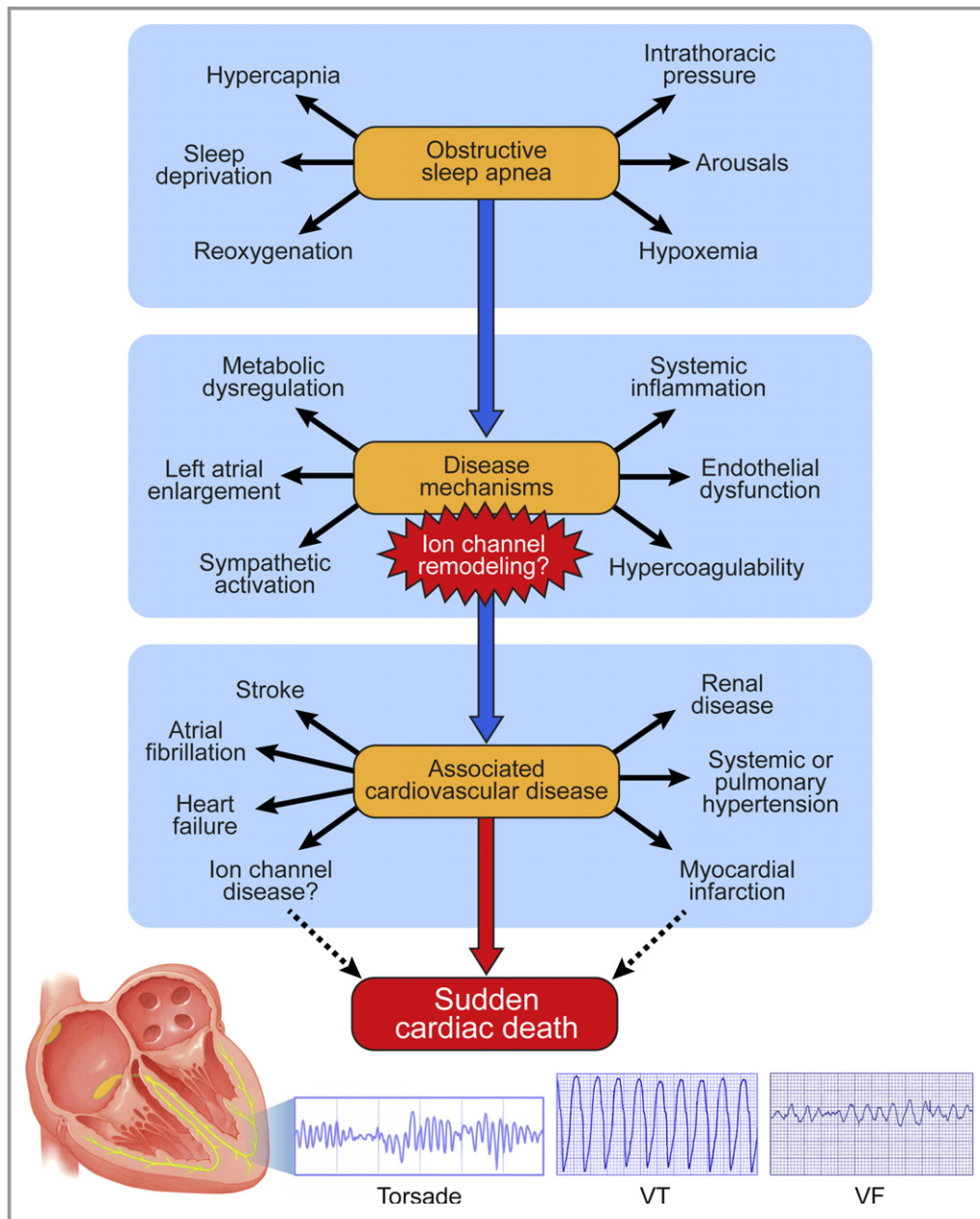
Figure 2. Schematic outlining potential pathophysiological aspects of OSA, disease mechanisms, and development of associated CVD. Ion channel remodeling may be an important mechanism in associated CVD increasing the propensity for SCD directly and indirectly. Modified from Somers et al, *Circulation,*[10] with permission from Wolters Kluwer. CVD indicates cardiovascular diseases; OSA, obstructive sleep apnea; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

reverse this relationship in 4 weeks for moderate OSA. It remains to be determined whether this effect persists in the long term and what duration of therapy is required to restore circulating levels to those in subjects without OSA. Studies showing reproducibility and an association with measured QTc levels during sleep and wakefulness will strengthen this observation. Also requiring clarification is the nature of the interaction between K^+ channel remodeling and hypoxemia and other acute effects of apnea, in the genesis of QT prolongation during apneas.

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