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Contents

Contents

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RESPONSIBLE EDITORS FOR THIS ISSUE

Do age-associated changes of voltage-gated sodium channel isoforms expressed in the mammalian heart predispose the elderly to atrial fibrillation?

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. The prevalence of the disease increases with age, strongly implying an age-related process underlying the pathology. At a time when people are living longer than ever before, an exponential increase in disease prevalence is predicted worldwide. Hence unraveling the underlying mechanics of the disease is paramount for the development of innovative treatment and prevention strategies. The role of voltage-gated sodium channels is fundamental in cardiac electrophysiology and may provide novel insights into the arrhythmogenesis of AF. $Na_v1.5$ is the predominant cardiac isoform, responsible for the action potential upstroke. Recent studies have demonstrated that $Na_v1.8$ (an isoform predominantly expressed within the peripheral nervous system) is responsible for cellular arrhythmogenesis through the enhancement of pro-arrhythmogenic currents. Animal studies have shown a decline in $Na_v1.5$ leading to a diminished action potential upstroke during phase 0. Furthermore, the study of human tissue demonstrates an inverse expression of sodium channel isoforms; reduction of $Na_v1.5$ and increase of $Na_v1.8$ in both heart failure and ventricular hypertrophy. This strongly suggests that the expression of voltage-gated sodium channels play a crucial role in the development of arrhythmias in the diseased heart. Targeting aberrant sodium currents has led to novel therapeutic approaches in tackling AF and continues to be an area of emerging research. This review will explore how voltage-gated sodium channels may predispose the elderly heart to AF through the examination of laboratory and clinical based evidence.

Key words: Voltage-gated; Sodium channels; Ageing; Atrial fibrillation; $Na_v1.5$; $Na_v1.8$; Late sodium current; Cardiac electrophysiology

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Core tip: $Na_v1.8$ has been implicated by multiple studies in producing the late sodium current, predisposing the cardiomyocyte to arrhythmogenic activity. Animal models have demonstrated an enhancement of this aberrant current in aged hearts. Human studies have identified a reduction of $Na_v1.5$ and an increase in $Na_v1.8$ in both heart failure and left ventricular hypertrophy, strongly suggesting that voltage-gated sodium channel expression plays a central role in the development of arrhythmia. Clinically, sodium channel blockade through Ranolazine has proved promising in terminating the arrhythmia. Prevention of atrial fibrillation should focus on lifestyle management, as well as targeting cardiac risk factors. Irbesartan has been demonstrated to slow atrial remodelling, prevent atrial fibrillation in animal models, as well as avert the arrhythmia in human subjects.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting an estimated 33.5 million people worldwide[1]. Prevalence of AF increases with age; 2.8% of the affected population under the age of 45, 16.6% between 45-65 and 80.5% aged 65 and over[2]. Altered expression of sodium channel isoforms associated with ageing has been demonstrated in animal models[3,4] though yet to be identified within the human heart. Furthermore, mutations in the *SCN5a* gene coding for the predominant $Na_v1.5$ isoform are strongly associated with a spectrum of cardiac arrhythmias including; Long QT syndrome, Brugada's syndrome and AF[5-8]. Unravelling the mechanistic processes that underlie rhythm disturbances in the pathogenesis of AF is a paramount strategic goal to enable the development of innovative therapies for both the prevention and treatment of the condition.

EPIDEMIOLOGY AND HEALTHCARE BURDEN OF AF

When age alone is considered as a major risk factor for developing AF[9], an ageing population will inevitably give rise to an increased prevalence of the arrhythmia. The European Union predicts the incidence of AF to more than double in it's over 55 populous by 2060[10]. More immediately worrying projections are estimated in the United States from 5.2 million cases in 2010 to 12.1 million by 2030[11]. AF carries significant morbidity with sufferers at notably higher risk of stroke[12], heart failure[13], myocardial infarction[14] and death[15]. Inpatient hospitalization specifically due to AF continues to rise by roughly 1% a year, placing a significant burden on healthcare resources[16].

Over five years, the direct cost of AF in the United Kingdom rose dramatically from £244 million to £458 million, taking into account hospitalisation and drug expenditure. Appreciating the cost of long term nursing home care as a consequence of the condition tallied an additional £111 million in the year 2000, more than double that in 1995[17]. Hospital care burden of AF continues to escalate around the globe with Korea claiming a rise of 420% between 2006-2015. The majority of these cases were due to major bleeding as a consequence of anticoagulation. The majority of patients were 70 years and older and the total cost of care for AF related hospital admissions rose from €68.4 million to €388.4 million over 9 years[18].

Further to the concerning rise in the prevalence of AF, placing a significant burden on healthcare resources worldwide; the consequences of current therapeutic strategies addressing the potentially fatal pro-thrombotic risks of AF, have inadvertently led to a sharp rise in hospital admissions due to adverse effects of said treatment. Appreciating the role of voltage-gated sodium channels (VGSCs) in the development of AF offers a fresh perspective on therapeutic approaches.

VOLTAGE-GATED SODIUM CHANNELS

VGSCs are transmembrane protein complexes that produce the depolarising influx of sodium ions at the initiation and duration of the action potential (AP)[19]. There are nine subtypes of VGSCs that are expressed within the mammalian class. Each isoform has specific features; activation/inactivation voltage threshold, amino acid sequence, and gene. VGSCs are expressed proportionately differently depending on the bodily tissues. The standardised nomenclature for these channels was first proposed by Goldin *et al*[20] in the year 2000. Na_v 1.1, 1.2, 1.3 and 1.6 are predominantly expressed in the central nervous system[21]. Na_v1.4 is dominant in skeletal muscle. Na_v 1.5 is the predominant cardiac isoform, making up nearly 90% of all sodium channel isoforms expressed in the heart; responsible for over two-thirds of the total sodium current[22]. Finally, Na_v 1.7, 1.8 and 1.9 are abundantly expressed in the peripheral nervous system[23] (Table 1).

CARDIAC SODIUM CURRENTS AND ARRYTHMOGENISIS

Fast and late sodium currents
The sodium current (I_{Na}) can be appreciated as two phases; the peak (fast) sodium current and the late (slow) sodium current (I_{NaL}). The majority of the depolarizing Na^+ current is generated by the fast I_{Na} of which Na_v1.5 the predominant channel responsible. This produces the AP upstroke and "maximum upstroke velocity" (V_{max}). The late sodium current is produced by a slow, steady influx of Na^+ which persists throughout the AP. These two currents determine not only the peak of the AP and velocity of depolarisation but also in shaping AP morphology through the length of the plateau phase, repolarisation and therefore the refractory period. As illustrated in (Figure 1) an enhanced I_{NaL} prolongs AP duration. This is directly linked to afterdepolarizations-a symptom of cellular electrical instability[24-26].

Afterdepolarizations
Afterdepolarisations describe the spontaneous, delayed depolarization of the cell due to abnormal ion flux during the AP. An abnormally enhanced influx of Na^+ underlies improper calcium handling leading to afterdepolarizations[25,27]. The depolarising sodium currents activate the influx of calcium through $Ca_{v1.2}$ channels. This triggers a calcium-induced calcium release from the sarcoplasmic reticulum via RyR2 receptors. A key process in excitation-contraction coupling. Overloaded cytosolic Ca^{2+} must be removed by the Ca^{2+}/Na^+ exchanger[27], widely accepted although still debated, three Na+ ions move into the cell for one Ca^{2+} ion out leading to an overall positive charge and therefore a further depolarising current[25]. The late sodium current (I_{NaL}) plays a pivotal role in this pathological development[24-29]. An unusually heightened late current slows repolarization of the cell due to an uncharacteristically persistent influx of Na^+ ions maintaining a positive membrane potential. Na_v1.8 has been specifically implicated in this process as blocking the channel has been shown to reduce the late sodium current, suppressing the development of afterdepolarizations in the ventricular myocytes of mice and rabbits[30].

Gene mutation of the cardiac isoform in AF
Mutations in the *SCN5a* gene encoding for the Na_v1.5 isoform aid our understanding of cardiac sodium currents as they are strongly associated with a spectrum of cardiac arrhythmias including; Long QT syndrome, Brugada's syndrome and AF[5-8]. Mutations in the *SCN5a* gene may penetrate as either gain-of-function or loss-of-function of the Na_v1.5 channel (Figure 2).

Gain-of-function describes a phenomenon where the sodium influx is enhanced due to aberrant channel gating; incomplete inactivation or late inactivation of the channel at more depolarized potentials. This enhances the late current, prolonging AP duration, leading to afterdepolarizations described above[26].

Loss-of-function mutations lead to a lower expression of Na_v1.5 or the expression of faulty channels. Mutated channels exhibit altered functionality of the voltage-sensor domain, meaning poor availability of Na^+ ions; channels are activated at more depolarized potentials and inactivated at less depolarised potentials[31,32]. This leads to a diminished AP upstroke and slowed depolarisation of the cardiomyocyte.

With regards to AF, both loss-of-function and gain of function mutations have been identified in familial forms of the disease[6,33,34]. Loss-of-function mutations increase the risk of AF due to decelerated conduction throughout the atria as a consequence of poor Na^+ availability. Gain-of-function variants lead to hyperexcitable cardiomyocytes due to prolonged I_{NaL}.

Table 1 Properties of voltage-gated sodium channel isoforms

Voltage-gated sodium channel isoform	Tissue	Gene	Amino acid length	Activated	Inactivated	Associated β-subunit
Na$_v$1.1	Brain	*SCN1A*	2009aa (human and rat)	-33 mV	-72 mV	β$_1$, β$_2$, β$_3$, β$_4$
Na$_v$1.2	Brain	*SCN2A*	2005aa (human); 2006aa (rat)	-24 mV	-53 mV	β$_1$, β$_2$, β$_3$, β$_4$
Na$_v$1.3	Brain	*SCN3A*	1951aa (human and rat)	-23 to -26 mV	-65 to -69 mV	β$_1$ and β$_3$
Na$_v$1.4	Skeletal muscle	*SCN4A*	1836aa (human); 1840aa (rat)	-26 to -30 mV	-56 mV	β$_1$
Na$_v$1.5	Heart	*SCN5A*	2016aa (human); 1951aa (rat)	-47 mV	-84 mV	β$_1$, β$_2$, β$_3$, β$_4$
Na$_v$1.6	Brain	*SCN8A*	1980aa (human); 1976aa (rat)	-37.7 mV	-98 mV	β$_1$ and β$_2$
Na$_v$1.7	PNS	*SCN9A*	1977aa (human); 1984aa (rat)	-31 mV	-61 to -78 mV	β$_1$ and β$_2$
Na$_v$1.8	PNS	*SCN10A*	1957aa (human)	-16 to -21 mV	-30 mV	Not established
Na$_v$1.9	PNS	*SCN11A*	1792aa (human); 1765aa (rat)	-47 to -54 mV	-44 to -54 mV	Not established

Illustrating the standardised nomenclature, regional tissue where the isoform predominantly located, gene, amino acid length, activation and inactivation membrane potentials and associated beta subunits. PNS: Peripheral nervous system; aa: Amino acids; mV: millivolts. Adapted from Catterall *et al*[23], 2005, with permission.

Role of non-cardiac isoforms in arrhythmogenesis

Na$_v$1.8 has been identified as responsible for producing the late sodium current and consequent arrhythmia in both mouse and human subjects[26,28,30,35]. Na$_v$1.8 is coded by the *SCN10a* gene. Unlike its neuronal counterparts Na$_v$1.8 is resistant to the neurotoxin and sodium current blocker TTX- a functional similarity to the cardiac isoform. In the human chromosome, the gene is located adjacent to *SCN5a* and shares 65% of its amino acid sequence[36]. Its close genetic and functional kinship to Na$_v$1.5, coupled with a strong association in underpinning arrhythmogenic APs has made Na$_v$1.8 a target of close study in recent years[37].

From a clinical perspective, we appreciate that patients with cardiovascular risk factors and co-morbidities are more likely to develop arrhythmia[38]. The mechanistic role of VGSCs underlying this clinical observation is of great interest. Dybkova *et al*[28] at the German Centre for Cardiovascular Research demonstrate-in human left ventricular myocytes- a significant upregulation of Na$_v$1.8 coupled with reduced expression of Na$_v$1.5 in patients with heart failure. Furthermore, they illustrate that Na$_v$1.8 contributes to AP duration and inhibition decreases the late sodium current suppressing cellular proarrhythmogenic triggers[28]. This is significant as not only does this support the literature in implicating Na$_v$1.8 to the late current and arrhythmogenesis, but it also begins to identify a deeper pathophysiological process of the diseased heart and its susceptibility to arrhythmia.

The failing heart will express greater amounts of the CNS isoform which is a less excitable channel, needing a much higher membrane potential for activation (activated at-16mV to -21mV as opposed to -41mV for Na$_v$1.5). Hence cellular depolarisation is slowed. Its inactivation is at -31mV as opposed to -84mV. This difference in gating mechanics of Na$_v$1.8 allows Na+ influx during the plateau & repolarisation phase predisposing the myocyte to afterdepolarizations. The loss of Na$_v$1.5 means the availability of Na$^+$ through open sodium channels in phase 0 of the AP is reduced. Reduced expression of Na$_v$1.5 will mimic the effect of a loss-of-function mutation; V$_{max}$ will be diminished with a delayed AP upstroke as illustrated in (Figure 3).

The same research group further published similar results with regards to the role of Na$_v$1.8 to the late current and the same inverse relationship of isoform expression in patients was also seen in patients with left ventricular hypertrophy[39]. The same observation of inversed VGSC expression in two separate-though closely related-disease entities offers a deeper appreciation of why patients suffering from cardiac illness are more susceptible to developing arrhythmia.
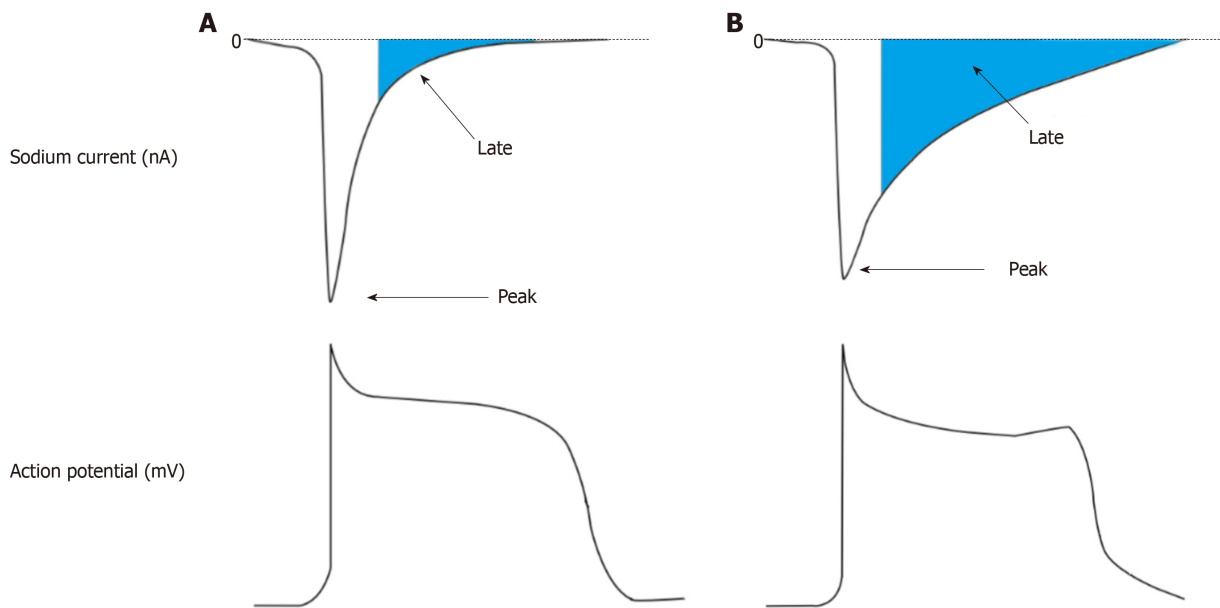
Figure 1 Peak and Late sodium currents on action potential morphology. A: Top left: An illustration of a normal sodium current within a cardiomyocyte with its rapid peak current and short late current; Bottom left: An action potential as a result of normal sodium ion influx. Plateau and repolarisation phases are not prolonged and no afterdepolarizations present; B: Top right: An Illustration of a pathologically enhanced late sodium current; Bottom right: An action potential as a consequence of enhanced late sodium current with a prolonged plateau and repolarisation period. The late upstroke between phase 2 and phase 3 represents an after depolarisation brought about due to the aberrant late sodium current. Adapted from Vadnais *et al*[74], 2010 with permission.

AGEING HEART

At a time where people are living longer than ever before, age-associated pathologies are becoming ever more commonplace in medical practice. A myriad of cardiovascular diseases are recognised to be heavily associated with the ageing heart including; AF, left ventricular hypertrophy, heart failure and ischaemic heart disease[40]. Remodelling describes the adaptation of the structure and function of the heart to allow it to meet physiological demand. During the ageing process, the heart undergoes four forms of remodelling; electrical, ionic, functional and structural[41].

AF will lead to progressive remodelling of the atria which in turn will promote abnormalities in each of these categories[42]. Functional remodelling describes the mechanical deterioration of the heart with age. This impairs the hearts central role in delivering oxygenated blood to bodily tissues. The aged heart demonstrates a decline in heart rate, reduced beat to beat variation, and significant myocardial stiffness due to fibrosis[43]. Fibrosis promotes AF due to interrupting the continuity of fibre bundles hence leading to a disruption of normal electrophysiology; impaired cell-to-cell signalling and diminished conduction velocity[44,45].

A major characteristic of electrical remodelling of the aged heart, and one central to the development of AF, is compromised pacemaker function. Sinoatrial node (SAN) loses automaticity with age due to poor excitability of SAN myocytes[46]. The loss of pacemaker function of the SAN underpins the development of ectopic focal points throughout the atria. The uncoordinated electrical firing of multiple foci means irregular contraction of the atria. Random impulses pass through the bundle of hiss to the ventricles meaning irregular ventricular contraction. This process is illustrated in the characteristic uneven baseline trace and irregularly timed QRS complexes on the electrocardiogram (ECG) of a patient with AF.

Electrophysiological remodelling leads to deviation of the normal action potential. This is ultimately underpinned through the changes of ion channel expression and function. With regards to VGSCs, Multiple sodium ion transcripts are downregulated with age leading to; shortened AP upstroke, impaired V_{max}, and prolonged AP duration[47]. Currently, there no studies comparing the expression of this channel with age in human subjects.

We know that VGSCs play a role in maintaining the plateau phase and the refractory period. The prolonged refractory period is a common feature of the elderly heart demonstrated in animal models[47,48]. A study by Baba investigating the sodium current in aged and adult canines produced contradicting results, concluding that there was no change in I_{Na} density in aged atrial cells and no structural remodelling of the fast Na^+ current with age[49]. These results stand fairly solitary contradicting a large body of evidence suggesting otherwise. Anyukhovsky *et al*[50] also carried out canine
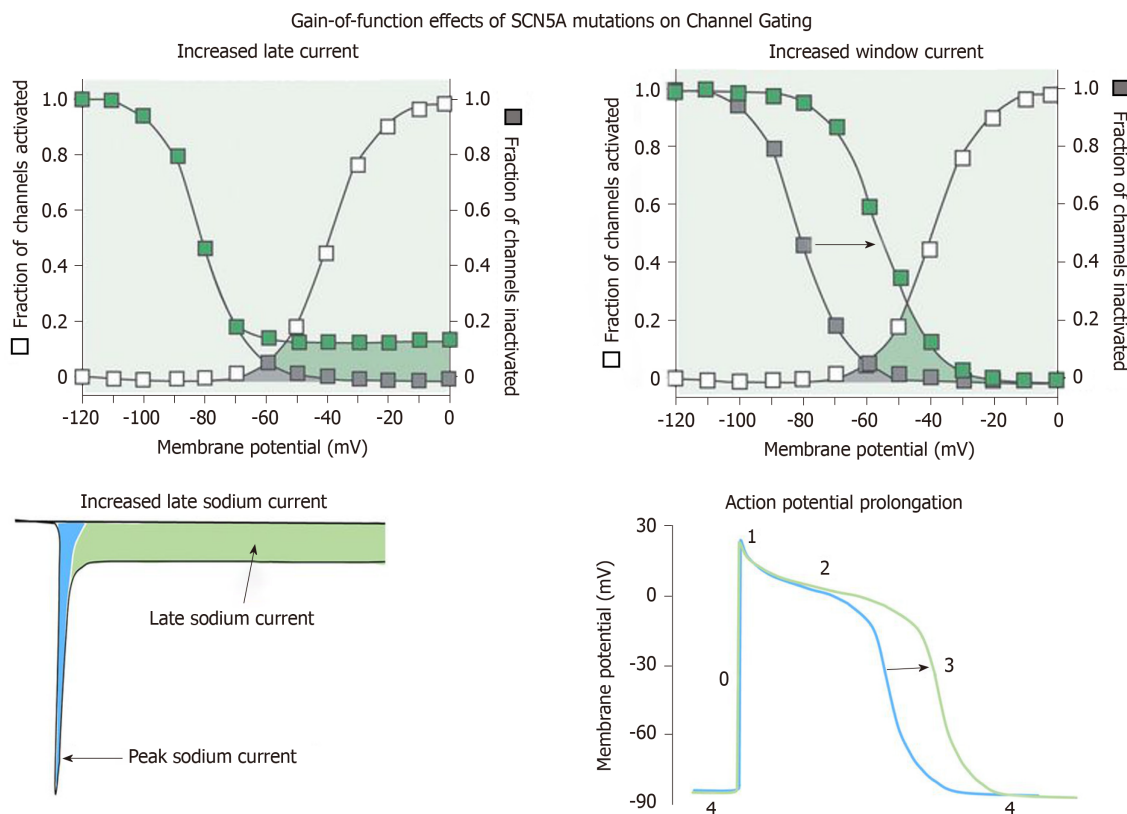
Figure 2 Gain of function effects of *SCN5a* mutations on channel gating. Top left: Curves illustrating the fraction of channels activated (white squares) and the fraction of channels inactivated (grey squares) *vs* membrane potential. Green squares demonstrate the effect of a gain of function mutation resulting in incomplete inactivation of sodium channels at higher membrane potentials. This results in a higher fraction of channels inappropriately activated for a longer period, therefore developing an enhanced late current (Bottom left); Top right: Curves illustrating the delayed inactivation of sodium channels due to gain of function mutations resulting in an increased window current where channels may reactivate, again leading to increased late current; Bottom right: A normal action potential (blue) and an action potential with a prolonged plateau and repolarisation phases (green) as a consequence of faulty sodium channel gating mechanics brought about by gain of function mutations in *SCN5a* gene leading to aberrant sodium currents. Adapted from Wilde *et al*[75], 2018, with permission.

studies investigating the effects of age and noted a significantly longer AP duration in aged dogs hence predisposing them to AF.

Currently, there is a niche within the literature for the study of the age-associated expression of cardiac sodium channels in human subjects. We would expect to see a reduction in $Na_v1.5$ and upregulation of non-cardiac isoforms, particularly Na_v18 in keeping with the literature[28,39]. Even so, the mechanisms of altered expression are poorly understood, though likely ties closely with the effect of stress age and disease places on the heart. Figure 4 shows the visual schematic representing the relative gating kinetics of $Na_v1.5$ and $Na_v1.8$.

SODIUM CHANNEL BLOCKADE AS A NOVEL THERAPUTIC TARGET FOR AF

A-803467 is a specific blocker of the $Na_v1.8$ channel. It has been successfully utilised in several studies in diminishing the I_{NaL} and restoring normal AP morphology. Furthermore, it has been demonstrated to prevent electrical remodelling and reduce the incidence and duration of paroxysmal AF in canines[51]. Blocking the 1.8 channel using this agent has also been shown to suppress ventricular arrhythmia induced via acute ischaemia[52]. Further research into the clinical use of this agent, or one of similar pharmacodynamics, is needed as results so far have only been achieved in laboratory settings.

Traditionally, pharmacological treatment for AF has mainly been focused around the use of Amiodarone (class III arrhythmic), Digoxin (cardiac glycoside), β-blockers such as Sotalol as well as calcium channel blockers Diltiazem and Verapamil. These are the drugs currently recommended for the management of AF by the National Institute for Health Care Excellence (NICE) guidelines. Sodium channel blockade is a novel therapeutic approach in the management of AF and a rapidly emerging field of research with promising clinical implications. Table 2 summarises the family of class I
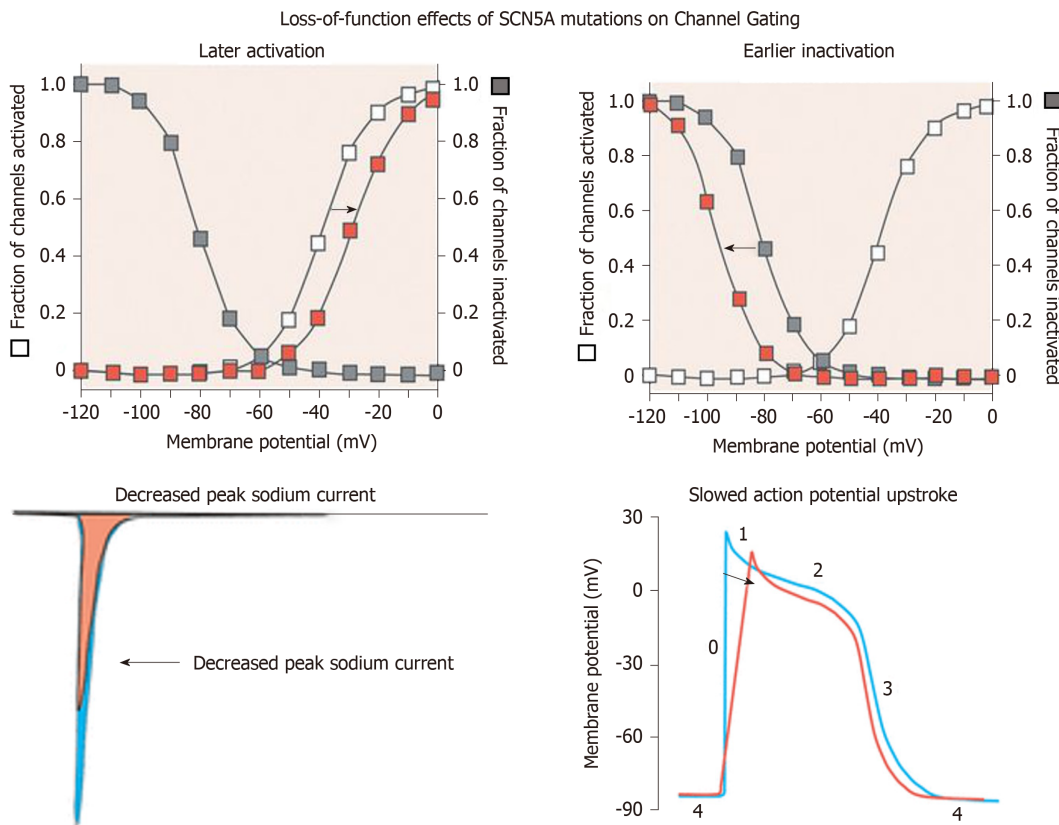
Figure 3 Loss of function effects of *SCN5a* mutations on channel gating. Top Left: Curves illustrating the fraction of channels activated (white squares) and the fraction of channels inactivated (grey squares) *vs* membrane potential. Orange squares represent the effect of loss of function mutation on channel activation, the white curve is shifted to the right demonstrating a delay; Top right: Orange squares here represent the effect of loss of function mutation on channel inactivation. The grey curve is shifted to the left demonstrating early inactivation. Both of these effects mean a reduction in Na$^+$ availability and a decreased peak sodium current (Bottom left); Bottom right: A normal action potential (blue) juxtaposed alongside an action potential due to a loss of function mutation (orange). Action potential upstroke is diminished and slowed. Adapted from Wilde *et al*[75], 2018, with permission.

antiarrhythmic drugs. Sodium channel blockers are more frequently used for the termination of ventricular arrhythmias as opposed to atrial tachycardia. Of the clinically available sodium channel blockers, Ranolazine is of particular interest. Multiple studies have illustrated its efficacy in terminating atrial tachyarrhythmia through specific blockade of the proarrhythmogenic late sodium current, reducing the risk of adverse electrophysiological effects.

Ranolazine is presently the only Vaughan-Williams class I antiarrhythmic drug of its kind. It is currently within the recommended NICE protocol for the treatment of stable angina[53]. It is a potent blocker of the late sodium current and also shown to mildly inhibit other ion currents such as $I_{kr,}$ and I_{ca}[54]. It is specific in not only for targeting $I_{NaL,}$ but also atrial myocytes compared to ventricular myocytes[55]. Its selectivity for the late sodium current is three times that of the peak current, demonstrating its superiority over Flecanide[56]. Its efficacy in native cardiomyocytes was just as potent as it was in experimental conditions[57,58]. A clinical trial in 2007 investigated the efficacy of Ranolazine as an anti-anginal medication. Total 6560 patients admitted with non-ST elevation myocardial infarction were randomised to receive either Ranolazine or a placebo. Patients had continuous ECG monitoring during their hospital stay. The Ranolazine group had a significantly reduced incidence of ventricular tachycardia ($P \leq 0.001$) and although the incidence of new-onset AF was low in both groups, the intervention arm also showed a statistically significant reduction compared to control[59].

Since its initial promising pre-clinical and clinical investigation, Ranolazine has continued to produce spectacular results including: terminating acutely induced AF in horses through cardioversion[60], found to be protective against AF in chronic ischaemic heart disease[61] and even effective in the conversion of postoperative AF in cardiac surgery[62]. The randomised control trial HARMONY tested the efficacy of Ranolazine in reducing "AF Burden" in patients with paroxysmal AF and those with implanted pacemakers over 12 wk. This was qualified through clinical laboratory tests, ECGs and symptom diaries. On its own it did not significantly reduce AF burden, however when paired with a moderate dose of dronedarone had a 59%
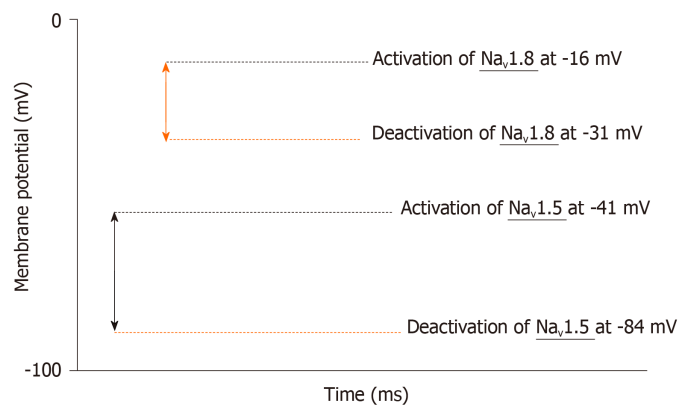
Figure 4 Visual Schematic representing the relative gating kinetics of Na$_v$1.5 and Na$_v$1.8. Na$_v$1.5 represented by the double-headed blue arrow activates at -41 mV and deactivates at -83 mV. Na$_v$1.8 represented by the double-headed orange arrow activates at -16 mV and deactivates at -31 mV.

reduction in AF burden, including fewer AF outbreaks and improved patient symptoms[63]. The clinical applications of Ranolazine continue to impress. It has been superior in and preventing and terminating post-operative AF when combined with amiodarone, compared to conventional chemical cardioversion-especially in patients undergoing coronary artery bypass grafting. In the RAFAELLO trial, 241 patients with AF who underwent electrical cardioversion received either 350 mg, 500 mg or 750 mg twice daily of Ranolazine or a placebo. Patients tolerated the drug well and the higher dose arms of the trial showed a significant reduction in AF recurrence[64].

The evidence supporting the efficacy of Ranolazine beyond that of an anti-anginal medication continues to accumulate. However, there are key questions yet to be answered regarding its clinical use. The long-term effects of the drug are still unknown due to its novelty. Also, whether it can be used as a stand-alone medication for the treatment and prevention of patients with AF-outside of a surgical context is unclear. Furthermore, the potential benefit of the drug in preventing AF in the elderly population is yet to be studied. None-the-less, Ranolazine has hugely expanded the potential for sodium channel blockade as an antiarrhythmic strategy both in pre-clinical and clinical trials.

PREVENTION OF AF

Lifestyle

Research has shed much light on the mechanics of VGSCs in arrhythmia as well as beginning to offer novel therapeutic approaches. Primary prevention strategies are much the same focusing upon common modifiable cardiac risk factors; obesity, smoking, alcohol, hypertension, hypercholesterolaemia and diabetes[65]. First and foremost, lifestyle management is the cornerstone of a healthy heart and should be the first approach to disease prevention by primary care physicians. Adherence to healthy lifestyle moderates the risk of cardiovascular disease[66] and addressing these issues early significantly reduces one's risk of AF and its consequent complications[67].

However, obesity continues to plague the western world. The United Kingdom parliament published a report in August 2019 claiming 28.7% of adults in England are obese and a further 35.6% are overweight[68]. The causes of such drastic figures are manifold and beyond the scope of this review. However, what is clear is that a concerning proportion of the population is at risk for the development of cardiac disease. Prevention should aim at tackling the root of pathology before medication becomes necessary. This holds especially true of modifiable cardiac risk factors.

In China, a recent study by Cai *et al*[69] aimed to investigate how community-based lifestyle intervention in the obese over 60 populous affected weight loss and cardiometabolic risk factors. The intervention arm of the study demonstrated significant weight loss as well as; blood pressure, waist circumference, fasting blood glucose, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol This study demonstrates that adherence to a healthy lifestyle through community-based interventions is effective at reducing cardiovascular risk factors[69].

Medication

Failing lifestyle intervention, early detection and medical management of risk factors

Table 2 Summary of sodium channel blockers (class I antiarrhythmics)

Drug	Subclass	Pharmacological targets	Electrophysiological effects	Corresponding therapeutic mechanisms	Major clinical applications
Quinidine; ajmaline; disopyramide	Ia	$Na_v1.5$ open state; intermediate dissociation kinetics; often concomitant K+ channel block	Reduction in peak I_{Na}, AP generation, increased excitation threshold; slowing of AP conduction in the atria, ventricles, and specialized conduction pathways; concomitant I_K block increasing AP duration and refractory period, increase in QT interval	(1) Reduction in ectopic ventricular/atrial automaticity; (2) Reduction in accessory pathway conduction; and (3) Increase in refractory period decreasing re-entrant tendency	SVTs, recurrent AF, VT, VF
Lidocaine; mexiletine	Ib	$Na_v1.5$ open state; rapid dissociation; window current	Reduction in peak I_{Na}, AP generation with increased excitation threshold; slowed AP conduction in the atria, ventricles and specialised ventricular conduction pathways; shortening of AP duration and refractory period in normal ventricular and Purkinje myocytes; prolongation of ERP, reduced window current in ischaemic, partially repolarised cells. Little ECG effect, slight QTc shortening	(1) Reduction in ectopic ventricular automaticity; (2) Reduction in DAD-induced triggered activity; and (3) Reduced re-entrant tendency by converting unidirectional to bidirectional block particularly In ischaemic, partially depolarised myocardium	VT and VF particularly after myocardial infarction
Propafenone; flecainide	Ic	$Na_v1.5$ inactivated state; slow dissociation	Reduction in peak I_{Na}, AP generation with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialised ventricular conduction pathways; reduced overall excitability; prolongation of APD at higher heart rates; increase in QRS duration	(1) Reduction in ectopic ventricular/atrial automaticity; (2) Reduction in DAD-induced triggered activity; and (3) Reduced re-entry tendency slowed conduction and reduced excitability particularly at rapid heart rates blocking re-entrant pathways showing depressed conduction	SVTs (atrial tachycardia, atrial flutter, AF, tachycardias involving Accessory pathways). Ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, premature ventricular contraction, catecholaminergic polymorphic VT
Ranolazine	Id	$Na_v1.5$ late current.	Reduction in the late Na+ current, affection AP recovery, refractoriness, repolarisation reserve and QT interval	(1) Decrease in AP recovery time; and (2) Reduction in EAD-induced triggered activity	Stable angina, VT. A new class of drug for the management of atrial tachyarrhythmias

Highlighting subclassification, pharmacological targets, electrophysiological effects, therapeutic mechanisms and clinical applications. AP: Action potential; SVT: Supraventricular tachycardia; DAD: Delayed afterdepolarizations; EAD: Early afterdepolarizations; ERP: Effective refractory period. Adapted from Lei *et al*[76], 2018, with permission.

is paramount. Irbesartan is a commonly prescribed angiotensin receptor blocker used to treat hypertension. Its renal safety profile allows for the drug to be administered to patients undergoing haemodialysis under NICE guidelines. As such, it warrants consideration for elderly patients in whom kidney function may be impaired due to age or polypharmacy. Interestingly, Irbesartan has been demonstrated to prevent sodium channel remodelling and improved intra-atrial conduction in canine models of AF[70]. Canine studies have also demonstrated its efficacy in reducing the progression of atrial fibrosis[71].

It's potential for AF suppression in human studies was investigated by the SILK study. The drug did not appear to have an advantage over Amlodipine in preventing AF recurrence in patients who have had ablation or electrical cardioversion for the

arrhythmia[72]. However, this relatively small-scale clinical trial of 98 patients already with the condition does not discredit the potential preventative benefits of the drug. A meta-analysis of randomized controlled trials tallying a total of 13184 patients found that recurrence of AF was significantly reduced in patients using angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers. Irbesartan was found to be particularly effective[73]. The collective evidence from laboratory and clinical studies suggests that Irbesartan certainly warrants consideration as a preventative strategy of AF, particularly in elderly patients where renal function may be compromised.

CONCLUSION

The role of VGSCs in cardiac arrhythmia is fundamental, proving to be an exciting and rapidly emerging field of research. In recent years much light has been shed on the role of Na$_v$1.8 in the arrhythmogenic process. New approaches targeting this channel in the treatment of arrhythmia have proved promising. To date, the emphasis of lifestyle management, and early medical intervention in the prevention of cardiac disease cannot be overstated. As we explore the mechanics of AF in both laboratory and clinical settings, our understanding of cardiac electrophysiology continues to evolve from the world of basic science through to the heart of clinical practice.

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