Tachycardia-bradycardia syndrome: Electrophysiological mechanisms and future therapeutic approaches (Review)

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Abstract. Sick sinus syndrome (SSS) encompasses a group of disorders whereby the heart is unable to perform its pacemaker function, due to genetic and acquired causes. Tachycardia-bradycardia syndrome (TBS) is a complication of SSS characterized by alternating tachycardia and bradycardia. Techniques such as genetic screening and molecular diagnostics together with the use of pre-clinical models have elucidated the electrophysiological mechanisms of this condition. Dysfunction of ion channels responsible for initiation or conduction of cardiac action potentials may underlie both bradycardia and tachycardia; bradycardia can also increase the risk of tachycardia, and vice versa. The mainstay treatment option for SSS is pacemaker implantation, an effective approach, but has disadvantages such as infection, limited battery life, dislodgement of leads and catheters to be permanently implanted *in situ*. Alternatives to electronic pacemakers are gene-based bio-artificial sinoatrial node and cell-based bio-artificial pacemakers, which are promising techniques whose long-term safety and efficacy need to be established. The aim of this article is to review the different ion channels involved in TBS, examine the three-way relationship between ion channel dysfunction, tachycardia and bradycardia in TBS and to consider its current and future therapies.

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Contents

1. Introduction

The association between sick sinus syndrome (SSS) and atrial fibrillation (AF) has been recognized for more than 5 decades since 1968 (1) with the first description of tachycardia-bradycardia syndrome (TBS) reported 5 years later (2). Tachycardia complicates approximately 50% of SSS cases (2-4). A related condition, Bayes syndrome, involves inter-atrial block associated with AF (5-15). Our understanding of cardiac electrophysiology has significantly advanced with the use of pre-clinical animal models, which are amenable to

pharmacological, physical or genetic manipulation for studying the consequences of ion channel abnormalities (16-19), and have provided insight for translational application (14,20-25). These studies have identified the roles of different ion channels, such as hyperpolarization-activated, cyclic nucleotide-gated (HCN), Na^+ and transient receptor potential (TRP) channels, ryanodine receptors (RyR) and gap junctions (26-28), as well as tissue-level mechanisms, in the pathogenesis of TBS. To understand the molecular basis of how ion channel dysfunction leads to bradycardia or tachycardia, and the causal relationship between bradycardia and tachycardia, the mechanisms responsible for automaticity in the sinoatrial node (SAN) and mediating action potential conduction need to be considered.

2. Ion channels underlying SAN function

Automaticity of SAN is dependent on two closely coupled clocks, voltage- and calcium-dependent mechanisms (Fig. 1) (29). The voltage-dependent mechanism involves the funny current (I_f) mediated by HCN channels located at the plasma membrane (30). I_f has several unusual properties for a transmembrane current, including activation by a hyperpolarized voltage, permeability to both Na^+ and K^+ ions, regulation by intracellular cAMP, and small single channel conductance (31). There are four recognized HCN channel isoforms (1 to 4) (32). HCN4 is the predominant subtype found in the SAN (33,34). By contrast, the Ca^{2+}-mediated mechanism involves rhythmic release of Ca^{2+} from the sarcoplasmic reticulum (SR), subsequent reuptake by the SR Ca^{2+}-ATPase and extrusion via the Na^+-Ca^{2+} exchanger (35). Together, the complex interplay of ion channels and pumps gives rise to the pacemaker action potential (AP), which is uniquely characterized by spontaneous depolarization during phase 4 (Fig. 2).

Na^+ channels are found in high numbers in the periphery of the SAN, where they are thought to play a role in exit conduction of APs to the atrium (36,37). Each Na^+ channel is formed by a pore-forming α-subunit, a modulatory β-subunit and additional regulatory proteins. The NaV1.5 α-subunit, encoded by *SCN5A* (38), has four domains (I to IV), each of which contain six transmembrane segments (S1 to S6). The positive-charged S4 segments undergo outward movement upon membrane depolarization, opening the central pore to allow Na^+ entry (39,40). The resulting I_{Na} therefore partly determines myocardial excitability and conduction velocity of the APs. Late I_{Na} results in membrane depolarization in the atrial myocardium, which produces fast inactivation, by moving the linker region between domains III and IV to occlude the central pore (41-47). This is followed by slow inactivation, where the P-segment linker sequence between S5 and S6 bends back into the plasma membrane lining the outer region of the pore (48,49). The precision of sodium channel function is vital for the maintenance of transmembrane electrochemical gradient and therefore cardiac function.

Other ion channels are also involved in SAN function, such as HCN channels, predominantly HCN4, carry the I_f current which is a combination of both sodium and potassium currents. Alterations in the highly regulated activation and inactivation of the highly regulated cycle of ion channels, such as an increase in late I_{Na} can lead to arrhythmias (47). A genetic mutation in any part of this complex pathway results in SAN dysfunction leading to arrhythmias (50).

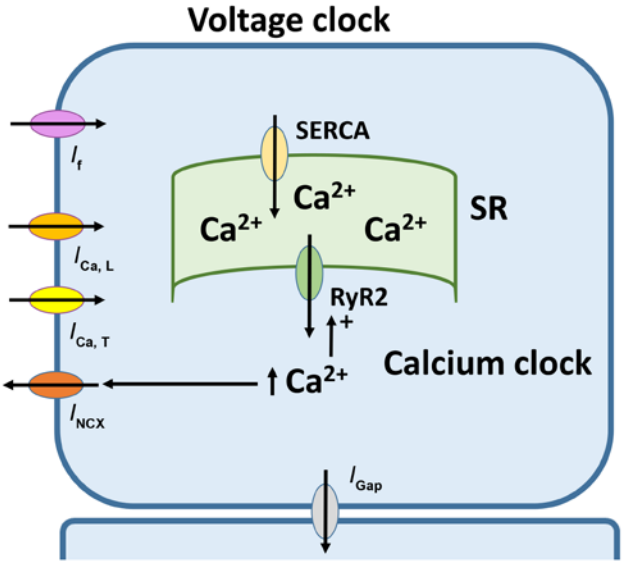

Figure 1. Sinoatrial node automaticity depends on both voltage- and calcium-dependent mechanisms. SR, sarcoplasmic reticulum.

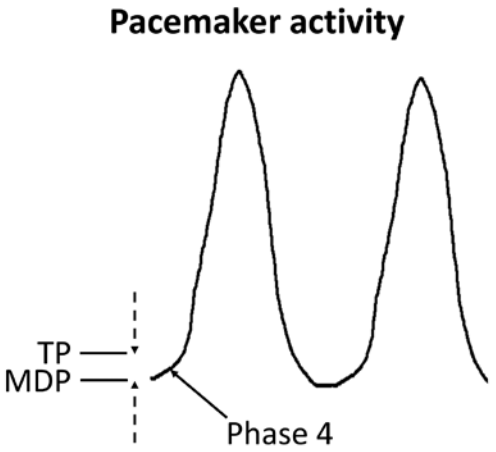

Figure 2. Pacemaker activity: from the maximum diastolic potential (MDP), spontaneous phase 4 depolarization brings the membrane to the threshold potential (TP), thereby initiating an action potential. Adapted from ref. 153 with permission.

Conduction of APs from one myocyte to the next occurs via gap junctions, each of which consists of two hexamers of connexin (Cx) subunits (51-53). Cx 30.2, 40, 43 and 45 are found in cardiac tissues (54). Cx40 is expressed only in the atria and His-Purkinje system (55,56). Cx43 is expressed throughout the atria and ventricles (57). Cx45 is the predominant isoform found in the core of SAN (58), whereas Cx43, Cx40 and Cx45 are expressed in the periphery (50). However, few gap junctions are found in the SAN core, suggesting that intercellular coupling is not required for synchronization of electrical activity within the node (59,60). The conventional membrane voltage-dependent gating, transjunctional voltage-dependent gating (61), phosphorylation (62-64), intracellular Ca^{2+} (65-68) and pH (69,70) as well as the surrounding lipid environment (71-74) all regulate gap junctional conductance.

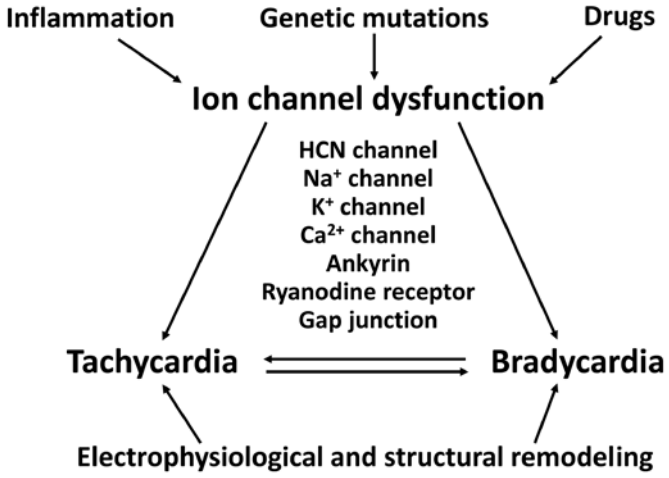

Figure 3. Molecular and electrophysiological mechanisms underlying tachycardia-bradycardia syndrome. HCN, hyperpolarization-activated, cyclic nucleotide-gated.

3. Tachycardia-bradycardia syndrome results from structural and electrophysiological remodeling

SSS can affect newborns and younger individuals, as well as elderly individuals over 65 years of age (36,75). TBS can be caused by genetic mutations, inflammation, ischaemia or drugs, involving both structural and electrophysiological remodeling (Fig. 3). Broadly, TBS can involve abnormal ion channel function, altered intercellular coupling or tissue level mechanisms.

4. Altered ionic currents

HCN4 is involved in mammalian cardiac pacemaking and is predominantly expressed in the SAN (28). Loss-of-function HCN4 mutations are known to cause atrioventricular (AV) block, long QT syndrome (LQTS), AF, familial TBS and non-compaction cardiomyopathy in addition to sinus bradycardia (76-80). The G1097W HCN4 mutation, which is a loss-of-function mutation resulting in a hyperpolarizing shift of the activation curve and reduced expression levels, demonstrates 4:1 AV block and reflex sinus tachycardia (81). A missense HCN4 mutation was found to lead to impaired trafficking of the channel to the surface membrane, resulting in SSS, long QT and *torsade de pointes* (82). Some of these phenotypes have been recapitulated in genetically modified mice, making them particularly useful for modeling TBS. For example, HCN4-knockout mice show severe sinus bradycardia complicated by AV block (83), whereas I_f-deficient mice generated by expression of a dominant-negative, non-conductive HCN4-channel subunit exhibit bradycardia, AV block and ventricular tachycardia (84). In this model, delayed afterdepolarizations in SAN, AV node and Purkinje fibres were observed, attibuted to increased SR Ca^{2+} load and increased frequency of Ca^{2+} release from the SR (84).

Mutations in the SCN5A encoding for the Na^+ channels can lead to a range of clinical phenotypes, including SSS, Brugada syndrome, LQTS type 3, AVN block, dilated cardiomyopathy, AF and overlap syndromes (85-91). In a newborn patient, a gain-of-function SCN5A mutation producing a persistent inward Na^+ current was found to cause LQTS type 3, and alternating tachycardia-bradycardia of 2:1 AV block and ventricular tachycardia have been observed (92). Individuals with loss-of-function SCN5A mutations can suffer from SSS and Brugada syndrome, which are responsible for bradycardic and tachycardic complications, respectively (93).

Upregulation of the inward rectifier current (I_{K1}) results from reduced levels of microRNA-1, observed in heart failure. This causes membrane hyperpolarization, bradycardia and shortening of APs that predisposes to atrial reentry (94). Ankyrin-B, a member of the ankyrin family, is expressed at high levels in the SAN and has functions such as cell signaling and assembly of ion channels in the plasma membrane (95,96). Humans with ANK2 gene variants suffer from SND, AF and prolonged QT intervals (96-98). Mice heterozygous for a null mutation in ankyrin-B have been generated. Cardiomyocytes isolated from these mice showed altered Ca^{2+} handling and extrasystoles that presumably arise from delayed afterdepolarizations (98,99). Ankyrin-B normally forms a complex with Na^+-K^+ ATPase, the Na^+-Ca^{2+} exchanger and the IP_3 receptor. Loss of ankyrin-B therefore leads to impaired Ca^{2+} transport across the SR and plasma membranes.

Finally, a loss-of-function mutation in the Ca^{2+} channel gene has also been shown to cause TBS (100). Normally, Ca^{2+} entry through L-type Ca^{2+} channels plays a role in pacemaker activity by contributing to diastolic depolarization. Reduction in this current can reduce the degree of spontaneous depolarization, slow pacemaker activity and increase the likelihood of spontaneous arrhythmias in SAN cells

5. Abnormal calcium handling

Ca^{2+} in myocardial cells originates from two sources: the extracellular space and intracellular store, the SR. Increased Ca^{2+} levels can arise from a number of mechanisms, such as entry via voltage-gated ion channels, receptor-operated Ca^{2+} entry (ROCE), store-operated Ca^{2+} entry (SOCE) and SR release (101,102). Alterations in any of these processes can promote the development of TBS. Ca^{2+} overload can promote apoptosis of SAN cells and stimulate fibrosis and reduce conduction velocity of APs by a calmodulin kinase II-dependent pathway (103). It is also a feature in heart failure, in which persistent activation of angiotensin II and calmodulin kinase II, higher incidence of tachyarrhythmias are also observed (103,104). Sinus node dysfunction (SND) is frequently found in heart failure patients, and it is estimated that bradycardic complications account for approximately half of the cases of sudden death (105,106).

Increased SR Ca^{2+} release, observed in catecholaminergic polymorphic ventricular tachycardia (CPVT), can arise from defective SR Ca^{2+} sensing, increased sensitivity to cytoplasmic Ca^{2+} or abnormal activation by calmodulin (107). Patients with CPVT demonstrate SND, inducible atrial arrhythmias as well as the bidirectional ventricular tachycardia traditionally observed in this condition (107,108). Experiments in mouse models indicate that SND and atrial arrhythmias are both due to abnormal Ca^{2+} handling in CPVT (109,110). In calsequestrin 2-null mice, spontaneous Ca^{2+} release led to delayed afterdepolarizations and atrial-triggered activity (109). Loss of calsequestrin 2 also produced selective interstitial fibrosis

in the atrial pacemaker complex, which disrupted SAN pacemaker activity and created conduction abnormalities that increased the tendency of atrial arrhythmias, likely by a reentrant mechanism (110).

6. Altered intercellular coupling

In the SAN, gap junctions contribute to automaticity and exit conduction of APs to the myocardium surrounding nodal tissue (111). Cx43 haploinsufficiency resulted in reduced CV in the ventricles, with tachyarrhythmias preceding bradyarrhythmias, but little effect on SAN function (112). $Cx40^{-/-}$ mice showed intra-atrial block, ectopic rhythms and abnormal conduction in the right atrium (113), inducible atrial tachycardia (114), AVN and infra-Hisian conduction delays (115).

7. Tissue level mechanisms through remodeling

If arrhythmia persists untreated, the structure of the SAN can be modified and this remodeling can lead to fibrosis and disturbance of the electrophysiology and even apoptosis of cardiac cells. This in turn increases the risk of AF and paroxysmal AF developing into permanent AF (28). The electrophysiological and structure remodeling of the SAN not only lead to arrhythmias, as discussed, but also are responsible for arrhythmias refractory to medication and recurrence following cardioversion (28).

8. Bradycardia and tachycardia in TBS: Which is the cause?

The causal relationship between bradycardia and tachycardia is bidirectional. It is unclear which precipitates which (28). Tachyarrhythmias can promote SND, resulting in sinus bradycardia (1,2). Patients with AF demonstrate structural abnormalities in the form of fibrosis in their SAN (116). Atrial tachycardia in dogs was found to lead to downregulation of HCN2, HCN4 and KCNE1 (which modulates the α-subunit of the K^+ channel), which underlies the SND observed (27). In an atrial tachycardia pacing model of TBS in rabbits, SND was associated with reduced HCN4 expression, both of which were reversible upon cessation of tachycardia pacing (26). In humans, HCN4 has been identified as a gene candidate associated with AF from a meta-analysis of genome-wide association studies (117). Adenosine is elevated in the plasma of patients, and the consequent activation of adenosine A1 receptors in the SAN is likely responsible for heart rate reduction (118). In a canine tachycardia-pacing model, A1 receptors were upregulated, which was associated with prolonged SAN conduction time, conduction block within the SAN, post-pacing pauses, shortening of atrial repolarization durations leading to a higher propensity to AF (119).

Conversely, SND can lead to the development of tachycardia (120). Genetically modified mice with an inducible deletion of cells specifically in the cardiac pacemaking and conduction system presented with degenerative fibrosis of nodal tissue, progressive bradycardia, sinus pauses, supraventricular and ventricular tachycardia and chronotropic incompetence (121). Fibrosis of the atrium was found to lead to conduction abnormalities, increased dispersion of refractoriness, thereby predisposing to the development of circus-type or spiral-wave reentry (122). Fibrosis in the setting of reduced repolarization reserve can promote early afterdepolarizations and in turn atrial and ventricular tachycardia (123,124).

9. Current and future therapeutic options for TBS

The current treatment options for TBS involve removal or correction of extrinsic causes. In acute situations where heart block is observed, the parasympathomimetic agent atropine or beta agonist isoproterenol, or temporary pacing can be used to overcome the conduction abnormalities. Tachyarrhythmias can be managed by digoxin, quinidine or propranolol. Permanent pacing using an electronic pacemaker is, at present, the only curative option however battery life and electromagnetic interference are often problematic.

Animal models have been extensively used for exploring the electrophysiological basis of complex rhythm disorders in an attempt to develop a biological pacemaker which would be free of complications such as limited battery life (125-129). These systems provide a platform for elucidating the mechanisms of arrhythmogenesis in different medical conditions (17,130-133), determining the efficacy of novel therapeutic approaches and providing insights for translational application (134-136). Generally, there are two engineering biological alternatives to electronic pacemakers. The first is a gene-based bio-artificial SAN. Ventricular cardiomyocytes normally do not possess pacemaker activity, but they can be induced to exhibit pacemaker function by genetic suppression of the inward-rectifier K^+ channels (137) or expression of HCN channels by adenoviral transfer (135-145). A second approach is cell-based bio-artificial pacemakers. This involves differentiation of human embryonic stem cells or induced pluripotent stem cells into cardiomyocytes (146,147). For example, human mesenchymal stem cells pre-transfected with HCN2 channels can be used to introduce I_f into surrounding cardiomyocytes that subsequently possess pacemaker activity (148,149). Cardiomyocytes can be converted into pacemaker cells by a cell fusion technique, where fibroblasts engineered to express HCN1 are chemically fused to the cardiomyocytes using chemicals such as polyethylene-glycol 1500 (150). Human embryonic stem cells have also been differentiated into cardiomyocytes that demonstrated intrinsic pacemaker activity, capable of pacing the ventricular myocardium *in vivo* (135,151). Experimental data do not always produce the same results when applied to animal models (152) and it would therefore be sensible not to assume that animal models will produce the same results in a human heart. Future research is needed to establish the safety of these bio-artificial pacemakers, and little is known regarding their long-term efficacy. They may provide better treatment options for debilitating complex arrhythmias such as TBS.

10. Conclusion

In this review we summarized current literature to understand the molecular and electrophysiological mechanisms and discussed the current treatment and the exciting future possibility of superior biological pacemakers which are hopefully not a too distant possibility.

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References

1. Ferrer MI: The sick sinus syndrome in atrial disease. JAMA 206: 645-646, 1968.
2. Kaplan BM, Langendorf R, Lev M and Pick A: Tachycardia-bradycardia syndrome (so-called 'sick sinus syndrome'). Pathology, mechanisms and treatment. Am J Cardiol 31: 497-508, 1973.
3. Rubenstein JJ, Schulman CL, Yurchak PM and DeSanctis RW: Clinical spectrum of the sick sinus syndrome. Circulation 46: 5-13, 1972.
4. Gomes JA, Kang PS, Matheson M, Gough WB Jr and El-Sherif N: Coexistence of sick sinus rhythm and atrial flutter-fibrillation. Circulation 63: 80-86, 1981.
5. Bayés de Luna AJ: Bloqueo a nivel auricular. Rev Esp Cardiol 32: 5-10, 1979.
6. Bayes de Luna A, Fort de Ribot R, Trilla E, Julia J, Garcia J, Sadurni J, Riba J and Sagues F: Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation. J Electrocardiol 18: 1-13, 1985.
7. Bayés de Luna A, Cladellas M, Oter R, Torner P, Guindo J, Martí V, Rivera I and Iturralde P: Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. Eur Heart J 9: 1112-1118, 1988.
8. Bayés de Luna A, Oter MC and Guindo J: Interatrial conduction block with retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmias: Influence of preventive antiarrhythmic treatment. Int J Cardiol 22: 147-150, 1989.
9. Bayés de Luna A, Guindo J, Viñolas X, Martinez-Rubio A, Oter R and Bayés-Genís A: Third-degree inter-atrial block and supraventricular tachyarrhythmias. Europace 1: 43-46, 1999.
10. Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayés-Genis A, Guindo J, Viñolas X, Garcia-Niebla J, *et al*: Interatrial blocks. A separate entity from left atrial enlargement: A consensus report. J Electrocardiol 45: 445-451, 2012.
11. Conde D, Seoane L, Gysel M, Mitrione S, Bayés de Luna A and Baranchuk A: Bayés' syndrome: The association between interatrial block and supraventricular arrhythmias. Expert Rev Cardiovasc Ther 13: 541-550, 2015.
12. Baranchuk A and Bayés de Luna A: The P-wave morphology: What does it tell us? Herzschrittmacherther Elektrophysiol 26: 192-199, 2015.
13. Baranchuk A, de Luna AB and Breithardt G: To the Editor - The role of advanced interatrial block pattern as a predictor of atrial fibrillation. Heart Rhythm 13: e87, 2016.
14. Tse G: Both transmural dispersion of repolarization and transmural dispersion of refractoriness are poor predictors of arrhythmogenicity: A role for the index of Cardiac Electrophysiological Balance (QT/QRS)? J Geriatr Cardiol (In press).
15. Zhao J, Liu T and Li G: Relationship between two arrhythmias: Sinus node dysfunction and atrial fibrillation. Arch Med Res 45: 351-355, 2014.
16. Choy L, Yeo JM, Tse V, Chan SP and Tse G: Cardiac disease and arrhythmogenesis: Mechanistic insights from mouse models. Int J Cardiol Heart Vasc 12: 1-10, 2016.
17. Tse G and Yan BP: Electrophysiological mechanisms of long and short QT syndromes: Insights from mouse models. IJC Heart & Vasculature (In press).
18. Tse G, Lai ET, Lee AP, Yan BP and Wong SH: Electrophysiological mechanisms of gastrointestinal arrhythmogenesis: Lessons from the heart. Front Physiol 7: 230, 2016.
19. Tse G, Wong ST, Tse V, Lee YT, Lin HY and Yeo JM: Cardiac dynamics: alternans and arrhythmogenesis. J Arrhythm (In press).
20. Tse G: Novel conduction-repolarization indices for the stratification of arrhythmic risk. J Geriatr Cardiol 13: 811-812, 2016.
21. Tse G: (Tpeak-Tend)/QRS and (Tpeak-Tend)/(QT x QRS): Novel markers for predicting arrhythmic risk in the Brugada syndrome. Europace (In press).
22. Tse G and Yan BP: Novel arrhythmic risk markers incorporating QRS dispersion: QRSd x (Tpeak - Tend)/QRS and QRSd x (Tpeak - Tend)/(QT x QRS). Ann Noninvasive Electrocardiol: Aug 18, 2016 (Epub ahead of print).
23. Wong J, Tan T, Chan C, Laxton V, Chan Y, Liu T, Wong J and Tse G: The role of connexins in wound healing and repair: novel therapeutic approaches. Front Physiol (In press).
24. Tse G and Yan BP: Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. Europace: Oct 4, 2016 (Epub ahead of print).
25. Tse G, Wong ST, Tse V and Yeo JM: Variability in local action potential durations, dispersion of repolarization and wavelength restitution in aged wild type and Scn5a/- mouse hearts modelling human Brugada syndrome. J Geriatr Cardiol (In press).
26. Chen Z, Sun B, Tse G, Jiang J and Xu W: Reversibility of both sinus node dysfunction and reduced HCN4 mRNA expression level in an atrial tachycardia pacing model of tachycardia-bradycardia syndrome in rabbit hearts. Int J Clin Exp Pathol 9: 8526-8531, 2016.
27. Yeh YH, Burstein B, Qi XY, Sakabe M, Chartier D, Comtois P, Wang Z, Kuo CT and Nattel S: Funny current downregulation and sinus node dysfunction associated with atrial tachyarrhythmia: A molecular basis for tachycardia-bradycardia syndrome. Circulation 119: 1576-1585, 2009.
28. Monfredi O and Boyett MR: Sick sinus syndrome and atrial fibrillation in older persons - A view from the sinoatrial nodal myocyte. J Mol Cell Cardiol 83: 88-100, 2015.
29. Lakatta EG, Vinogradova T, Lyashkov A, Sirenko S, Zhu W, Ruknudin A and Maltsev VA: The integration of spontaneous intracellular Ca2+ cycling and surface membrane ion channel activation entrains normal automaticity in cells of the heart's pacemaker. Ann N Y Acad Sci 1080: 178-206, 2006.
30. Baruscotti M, Bucchi A and Difrancesco D: Physiology and pharmacology of the cardiac pacemaker ('funny') current. Pharmacol Ther 107: 59-79, 2005.
31. DiFrancesco D: Pacemaker mechanisms in cardiac tissue. Annu Rev Physiol 55: 455-472, 1993.
32. Ludwig A, Zong X, Jeglitsch M, Hofmann F and Biel M: A family of hyperpolarization-activated mammalian cation channels. Nature 393: 587-591, 1998.
33. Shi W, Wymore R, Yu H, Wu J, Wymore RT, Pan Z, Robinson RB, Dixon JE, McKinnon D and Cohen IS: Distribution and prevalence of hyperpolarization-activated cation channel (HCN) mRNA expression in cardiac tissues. Circ Res 85: e1-e6, 1999.
34. Moroni A, Gorza L, Beltrame M, Gravante B, Vaccari T, Bianchi ME, Altomare C, Longhi R, Heurteaux C, Vitadello M, *et al*: Hyperpolarization-activated cyclic nucleotide-gated channel 1 is a molecular determinant of the cardiac pacemaker current I(f). J Biol Chem 276: 29233-29241, 2001.
35. Yaniv Y, Lakatta EG and Maltsev VA: From two competing oscillators to one coupled-clock pacemaker cell system. Front Physiol 6: 28, 2015.
36. Dobrzynski H, Boyett MR and Anderson RH: New insights into pacemaker activity: Promoting understanding of sick sinus syndrome. Circulation 115: 1921-1932, 2007.
37. Boyett MR, Honjo H and Kodama I: The sinoatrial node, a heterogeneous pacemaker structure. Cardiovasc Res 47: 658-687, 2000.
38. Gellens ME, George ALJ Jr, Chen LQ, Chahine M, Horn R, Barchi RL and Kallen RG: Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel. Proc Natl Acad Sci USA 89: 554-558, 1992.
39. Stühmer W, Conti F, Suzuki H, Wang XD, Noda M, Yahagi N, Kubo H and Numa S: Structural parts involved in activation and inactivation of the sodium channel. Nature 339: 597-603, 1989.
40. Kontis KJ, Rounaghi A and Goldin AL: Sodium channel activation gating is affected by substitutions of voltage sensor positive charges in all four domains. J Gen Physiol 110: 391-401, 1997.
41. Horn R, Patlak J and Stevens CF: Sodium channels need not open before they inactivate. Nature 291: 426-427, 1981.
42. West JW, Patton DE, Scheuer T, Wang Y, Goldin AL and Catterall WA: A cluster of hydrophobic amino acid residues required for fast Na(+)-channel inactivation. Proc Natl Acad Sci USA 89: 10910-10914, 1992.

43. Kellenberger S, Scheuer T and Catterall WA: Movement of the Na+ channel inactivation gate during inactivation. J Biol Chem 271: 30971-30979, 1996.
44. Kellenberger S, West JW, Catterall WA and Scheuer T: Molecular analysis of potential hinge residues in the inactivation gate of brain type IIA Na+ channels. J Gen Physiol 109: 607-617, 1997.
45. Kellenberger S, West JW, Scheuer T and Catterall WA: Molecular analysis of the putative inactivation particle in the inactivation gate of brain type IIA Na+ channels. J Gen Physiol 109: 589-605, 1997.
46. Smith MR and Goldin AL: Interaction between the sodium channel inactivation linker and domain III S4-S5. Biophys J 73: 1885-1895, 1997.
47. Shryock JC, Song Y, Rajamani S, Antzelevitch C and Belardinelli L: The arrhythmogenic consequences of increasing late INa in the cardiomyocyte. Cardiovasc Res 99: 600-611, 2013.
48. Balser JR, Nuss HB, Chiamvimonvat N, Pérez-García MT, Marban E and Tomaselli GF: External pore residue mediates slow inactivation in mu 1 rat skeletal muscle sodium channels. J Physiol 494: 431-442, 1996.
49. Vilin YY, Makita N, George AL Jr and Ruben PC: Structural determinants of slow inactivation in human cardiac and skeletal muscle sodium channels. Biophys J 77: 1384-1393, 1999.
50. John RM and Kumar S: Sinus Node and Atrial Arrhythmias. Circulation 133: 1892-1900, 2016.
51. Koval M, Isakson BE and Gourdie RG: Connexins, pannexins and innexins: Protein cousins with overlapping functions. FEBS Lett 588: 1185, 2014.
52. Veeraraghavan R, Gourdie RG and Poelzing S: Mechanisms of cardiac conduction: A history of revisions. Am J Physiol Heart Circ Physiol 306: H619-H627, 2014.
53. Veeraraghavan R, Poelzing S and Gourdie RG: Intercellular electrical communication in the heart: A new, active role for the intercalated disk. Cell Commun Adhes 21: 161-167, 2014.
54. Davis LM, Kanter HL, Beyer EC and Saffitz JE: Distinct gap junction protein phenotypes in cardiac tissues with disparate conduction properties. J Am Coll Cardiol 24: 1124-1132, 1994.
55. Gourdie RG, Green CR, Severs NJ, Anderson RH and Thompson RP: Evidence for a distinct gap-junctional phenotype in ventricular conduction tissues of the developing and mature avian heart. Circ Res 72: 278-289, 1993.
56. Gourdie RG, Severs NJ, Green CR, Rothery S, Germroth P and Thompson RP: The spatial distribution and relative abundance of gap-junctional connexin40 and connexin43 correlate to functional properties of components of the cardiac atrioventricular conduction system. J Cell Sci 105: 985-991, 1993.
57. Beyer EC, Paul DL and Goodenough DA: Connexin43: A protein from rat heart homologous to a gap junction protein from liver. J Cell Biol 105: 2621-2629, 1987.
58. Davis LM, Rodefeld ME, Green K, Beyer EC and Saffitz JE: Gap junction protein phenotypes of the human heart and conduction system. J Cardiovasc Electrophysiol 6: 813-822, 1995.
59. Saffitz JE, Green KG and Schuessler RB: Structural determinants of slow conduction in the canine sinus node. J Cardiovasc Electrophysiol 8: 738-744, 1997.
60. Wilders R, Verheijck EE, Kumar R, Goolsby WN, van Ginneken AC, Joyner RW and Jongsma HJ: Model clamp and its application to synchronization of rabbit sinoatrial node cells. Am J Physiol 271: H2168-H2182, 1996.
61. Bukauskas FF and Verselis VK: Gap junction channel gating. Biochim Biophys Acta 1662: 42-60, 2004.
62. Musil LS and Goodenough DA: Biochemical analysis of connexin43 intracellular transport, phosphorylation, and assembly into gap junctional plaques. J Cell Biol 115: 1357-1374, 1991.
63. Sáez JC, Nairn AC, Czernik AJ, Fishman GI, Spray DC and Hertzberg EL: Phosphorylation of connexin43 and the regulation of neonatal rat cardiac myocyte gap junctions. J Mol Cell Cardiol 29: 2131-2145, 1997.
64. Kwak BR, Hermans MM, De Jonge HR, Lohmann SM, Jongsma HJ and Chanson M: Differential regulation of distinct types of gap junction channels by similar phosphorylating conditions. Mol Biol Cell 6: 1707-1719, 1995.
65. De Mello WC: Effect of intracellular injection of calcium and strontium on cell communication in heart. J Physiol 250: 231-245, 1975.
66. Dahl G and Isenberg G: Decoupling of heart muscle cells: Correlation with increased cytoplasmic calcium activity and with changes of nexus ultrastructure. J Membr Biol 53: 63-75, 1980.
67. Burt JM: Block of intercellular communication: Interaction of intracellular H+ and Ca2+. Am J Physiol 253: C607-C612, 1987.
68. Maurer P and Weingart R: Cell pairs isolated from adult guinea pig and rat hearts: Effects of [Ca2+]i on nexal membrane resistance. Pflugers Arch 409: 394-402, 1987.
69. Hermans MM, Kortekaas P, Jongsma HJ and Rook MB: pH sensitivity of the cardiac gap junction proteins, connexin 45 and 43. Pflugers Arch 431: 138-140, 1995.
70. Morley GE, Taffet SM and Delmar M: Intramolecular interactions mediate pH regulation of connexin43 channels. Biophys J 70: 1294-1302, 1996.
71. Meyer R, Malewicz B, Baumann WJ and Johnson RG: Increased gap junction assembly between cultured cells upon cholesterol supplementation. J Cell Sci 96: 231-238, 1990.
72. Meyer RA, Lampe PD, Malewicz B, Baumann WJ and Johnson RG: Enhanced gap junction formation with LDL and apolipoprotein B. Exp Cell Res 196: 72-81, 1991.
73. Massey KD, Minnich BN and Burt JM: Arachidonic acid and lipoxygenase metabolites uncouple neonatal rat cardiac myocyte pairs. Am J Physiol 263: C494-C501, 1992.
74. Schubert AL, Schubert W, Spray DC and Lisanti MP: Connexin family members target to lipid raft domains and interact with caveolin-1. Biochemistry 41: 5754-5764, 2002.
75. Yabek SM and Jarmakani JM: Sinus node dysfunction in children, adolescents, and young adults. Pediatrics 61: 593-598, 1978.
76. Schulze-Bahr E, Neu A, Friederich P, Kaupp UB, Breithardt G, Pongs O and Isbrandt D: Pacemaker channel dysfunction in a patient with sinus node disease. J Clin Invest 111: 1537-1545, 2003.
77. Duhme N, Schweizer PA, Thomas D, Becker R, Schröter J, Barends TR, Schlichting I, Draguhn A, Bruehl C, Katus HA, *et al*: Altered HCN4 channel C-linker interaction is associated with familial tachycardia-bradycardia syndrome and atrial fibrillation. Eur Heart J 34: 2768-2775, 2013.
78. DiFrancesco D: HCN4, Sinus Bradycardia and Atrial Fibrillation. Arrhythm Electrophysiol Rev 4: 9-13, 2015.
79. Milano A, Vermeer AM, Lodder EM, Barc J, Verkerk AO, Postma AV, van der Bilt IA, Baars MJ, van Haelst PL, Caliskan K, *et al*: HCN4 mutations in multiple families with bradycardia and left ventricular noncompaction cardiomyopathy. J Am Coll Cardiol 64: 745-756, 2014.
80. Schweizer PA, Schröter J, Greiner S, Haas J, Yampolsky P, Mereles D, Buss SJ, Seyler C, Bruehl C, Draguhn A, *et al*: The symptom complex of familial sinus node dysfunction and myocardial noncompaction is associated with mutations in the HCN4 channel. J Am Coll Cardiol 64: 757-767, 2014.
81. Zhou J, Ding WG, Makiyama T, Miyamoto A, Matsumoto Y, Kimura H, Tarutani Y, Zhao J, Wu J, Zang WJ, *et al*: A novel HCN4 mutation, G1097W, is associated with atrioventricular block. Circ J 78: 938-942, 2014.
82. Ueda K, Nakamura K, Hayashi T, Inagaki N, Takahashi M, Arimura T, Morita H, Higashiuesato Y, Hirano Y, Yasunami M, *et al*: Functional characterization of a trafficking-defective HCN4 mutation, D553N, associated with cardiac arrhythmia. J Biol Chem 279: 27194-27198, 2004.
83. Baruscotti M, Bucchi A, Viscomi C, Mandelli G, Consalez G, Gnecchi-Rusconi T, Montano N, Casali KR, Micheloni S, Barbuti A, *et al*: Deep bradycardia and heart block caused by inducible cardiac-specific knockout of the pacemaker channel gene Hcn4. Proc Natl Acad Sci USA 108: 1705-1710, 2011.
84. Mesirca P, Alig J, Torrente AG, Müller JC, Marger L, Rollin A, Marquilly C, Vincent A, Dubel S, Bidaud I, *et al*: Cardiac arrhythmia induced by genetic silencing of 'funny' (f) channels is rescued by GIRK4 inactivation. Nat Commun 5: 4664-4664, 2014.
85. Makiyama T, Akao M, Shizuta S, Doi T, Nishiyama K, Oka Y, Ohno S, Nishio Y, Tsuji K, Itoh H, *et al*: A novel SCN5A gain-of-function mutation M1875T associated with familial atrial fibrillation. J Am Coll Cardiol 52: 1326-1334, 2008.
86. Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, van Langen IM, Tan-Sindhunata G, Bink-Boelkens MT, van Der Hout AH, *et al*: A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res 85: 1206-1213, 1999.
87. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, *et al*: Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet 45: 1044-1049, 2013.
88. Bezzina CR and Remme CA: Dilated cardiomyopathy due to sodium channel dysfunction: What is the connection? Circ Arrhythm Electrophysiol 1: 80-82, 2008.

89. Bezzina CR, Rook MB, Groenewegen WA, Herfst LJ, van der Wal AC, Lam J, Jongsma HJ, Wilde AA and Mannens MM: Compound heterozygosity for mutations (W156X and R225W) in SCN5A associated with severe cardiac conduction disturbances and degenerative changes in the conduction system. Circ Res 92: 159-168, 2003.
90. Remme CA, Wilde AA and Bezzina CR: Cardiac sodium channel overlap syndromes: Different faces of SCN5A mutations. Trends Cardiovasc Med 18: 78-87, 2008.
91. Tan HL, Bink-Boelkens MT, Bezzina CR, Viswanathan PC, Beaufort-Krol GC, van Tintelen PJ, van den Berg MP, Wilde AA and Balser JR: A sodium-channel mutation causes isolated cardiac conduction disease. Nature 409: 1043-1047, 2001.
92. Chang CC, Acharfi S, Wu MH, Chiang FT, Wang JK, Sung TC and Chahine M: A novel SCN5A mutation manifests as a malignant form of long QT syndrome with perinatal onset of tachycardia/bradycardia. Cardiovasc Res 64: 268-278, 2004.
93. Letsas KP, Korantzopoulos P, Efremidis M, Weber R, Lioni L, Bakosis G, Vassilikos VP, Deftereos S, Sideris A and Arentz T: Sinus node disease in subjects with type 1 ECG pattern of Brugada syndrome. J Cardiol 61: 227-231, 2013.
94. Girmatsion Z, Biliczki P, Bonauer A, Wimmer-Greinecker G, Scherer M, Moritz A, Bukowska A, Goette A, Nattel S, Hohnloser SH, *et al*: Changes in microRNA-1 expression and IK1 up-regulation in human atrial fibrillation. Heart Rhythm 6: 1802-1809, 2009.
95. Bennett V and Healy J: Organizing the fluid membrane bilayer: Diseases linked to spectrin and ankyrin. Trends Mol Med 14: 28-36, 2008.
96. Le Scouarnec S, Bhasin N, Vieyres C, Hund TJ, Cunha SR, Koval O, Marionneau C, Chen B, Wu Y, Demolombe S, *et al*: Dysfunction in ankyrin-B-dependent ion channel and transporter targeting causes human sinus node disease. Proc Natl Acad Sci USA 105: 15617-15622, 2008.
97. Mohler PJ, Splawski I, Napolitano C, Bottelli G, Sharpe L, Timothy K, Priori SG, Keating MT and Bennett V: A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. Proc Natl Acad Sci USA 101: 9137-9142, 2004.
98. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, duBell WH, Song LS, Haurogné K, Kyndt F, Ali ME, *et al*: Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 421: 634-639, 2003.
99. Mohler PJ, Le Scouarnec S, Denjoy I, *et al*: Defining the cellular phenotype of 'ankyrin-B syndrome' variants: Human ANK2 variants associated with clinical phenotypes display a spectrum of activities in cardiomyocytes. Circulation 115: 432-441, 2007.
100. Mangoni ME, Couette B, Bourinet E, Platzer J, Reimer D, Striessnig J and Nargeot J: Functional role of L-type Cav1.3 Ca2+ channels in cardiac pacemaker activity. Proc Natl Acad Sci USA 100: 5543-5548, 2003.
101. Trebak M, Zhang W, Ruhle B, Henkel MM, González-Cobos JC, Motiani RK, Stolwijk JA, Newton RL and Zhang X: What role for store-operated Ca^{2+} entry in muscle? Microcirculation 20: 330-336, 2013.
102. Ju YK, Lee BH, Trajanovska S, Hao G, Allen DG, Lei M and Cannell MB: The involvement of TRPC3 channels in sinoatrial arrhythmias. Front Physiol 6: 86, 2015.
103. Swaminathan PD, Purohit A, Soni S, Voigt N, Singh MV, Glukhov AV, Gao Z, He BJ, Luczak ED, Joiner ML, *et al*: Oxidized CaMKII causes cardiac sinus node dysfunction in mice. J Clin Invest 121: 3277-3288, 2011.
104. Erickson JR, Joiner ML, Guan X, Kutschke W, Yang J, Oddis CV, Bartlett RK, Lowe JS, O'Donnell SE, Aykin-Burns N, *et al*: A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. Cell 133: 462-474, 2008.
105. Luu M, Stevenson WG, Stevenson LW, Baron K and Walden J: Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation 80: 1675-1680, 1989.
106. Stevenson WG, Stevenson LW, Middlekauff HR and Saxon LA: Sudden death prevention in patients with advanced ventricular dysfunction. Circulation 88: 2953-2961, 1993.
107. Faggioni M, van der Werf C and Knollmann BC: Sinus node dysfunction in catecholaminergic polymorphic ventricular tachycardia: Risk factor and potential therapeutic target? Trends Cardiovasc Med 24: 273-278, 2014.
108. Sumitomo N, Sakurada H, Taniguchi K, *et al*: Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. Circ J 71: 1606-1609, 2007.
109. Faggioni M, Savio-Galimberti E, Venkataraman R, Hwang HS, Kannankeril PJ, Darbar D and Knollmann BC: Suppression of spontaneous ca elevations prevents atrial fibrillation in calsequestrin 2-null hearts. Circ Arrhythm Electrophysiol 7: 313-320, 2014.
110. Glukhov AV, Kalyanasundaram A, Lou Q, Hage LT, Hansen BJ, Belevych AE, Mohler PJ, Knollmann BC, Periasamy M, Györke S, *et al*: Calsequestrin 2 deletion causes sinoatrial node dysfunction and atrial arrhythmias associated with altered sarcoplasmic reticulum calcium cycling and degenerative fibrosis within the mouse atrial pacemaker complex1. Eur Heart J 36: 686-697, 2015.
111. Jongsma HJ: Diversity of gap junctional proteins: Does it play a role in cardiac excitation? J Cardiovasc Electrophysiol 11: 228-230, 2000.
112. Eckardt D, Theis M, Degen J, Ott T, van Rijen HV, Kirchhoff S, Kim JS, de Bakker JM and Willecke K: Functional role of connexin43 gap junction channels in adult mouse heart assessed by inducible gene deletion. J Mol Cell Cardiol 36: 101-110, 2004.
113. Bagwe S, Berenfeld O, Vaidya D, Morley GE and Jalife J: Altered right atrial excitation and propagation in connexin40 knockout mice. Circulation 112: 2245-2253, 2005.
114. Verheule S, van Batenburg CA, Coenjaerts FE, Kirchhoff S, Willecke K and Jongsma HJ: Cardiac conduction abnormalities in mice lacking the gap junction protein connexin40. J Cardiovasc Electrophysiol 10: 1380-1389, 1999.
115. VanderBrink BA, Sellitto C, Saba S, Link MS, Zhu W, Homoud MK, Estes NA III, Paul DL and Wang PJ: Connexin40-deficient mice exhibit atrioventricular nodal and infra-Hisian conduction abnormalities. J Cardiovasc Electrophysiol 11: 1270-1276, 2000.
116. Thery C, Gosselin B, Lekieffre J and Warembourg H: Pathology of sinoatrial node. Correlations with electrocardiographic findings in 111 patients. Am Heart J 93: 735-740, 1977.
117. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, *et al*: Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet 44: 670-675, 2012.
118. Funaya H, Kitakaze M, Node K, Minamino T, Komamura K and Hori M: Plasma adenosine levels increase in patients with chronic heart failure. Circulation 95: 1363-1365, 1997.
119. Lou Q, Hansen BJ, Fedorenko O, Csepe TA, Kalyanasundaram A, Li N, Hage LT, Glukhov AV, Billman GE, Weiss R, *et al*: Upregulation of adenosine A1 receptors facilitates sinoatrial node dysfunction in chronic canine heart failure by exacerbating nodal conduction abnormalities revealed by novel dual-sided intramural optical mapping. Circulation 130: 315-324, 2014.
120. Li G, Liu E, Liu T, Wang J, Dai J, Xu G, Korantzopoulos P and Yang W: Atrial electrical remodeling in a canine model of sinus node dysfunction. Int J Cardiol 146: 32-36, 2011.
121. Herrmann S, Fabritz L, Layh B, Kirchhof P and Ludwig A: Insights into sick sinus syndrome from an inducible mouse model. Cardiovasc Res 90: 38-48, 2011.
122. Tse G and Yeo JM: Conduction abnormalities and ventricular arrhythmogenesis: The roles of sodium channels and gap junctions. Int J Cardiol Heart Vasc 9: 75-82, 2015.
123. Pezhouman A, Cao H, Lee HH, Belardinelli L, Weiss JN and Karagueuzian HS: Abstract 16247: Oxidative Stress Initiates Atrial Fibrillation in Fibrotic Hearts by Early Afterdepolarization-Mediated Triggered Activity. The Key Role of Late INa. Circulation 130: A16247, 2014.
124. Morita N, Mandel WJ, Kobayashi Y and Karagueuzian HS: Cardiac fibrosis as a determinant of ventricular tachyarrhythmias. J Arrhythm 30: 389-394, 2014.
125. Tse G, Tse V and Yeo JM: Ventricular anti-arrhythmic effects of heptanol in hypokalaemic, Langendorff-perfused mouse hearts. Biomed Rep 4: 313-324, 2016.
126. Tse G, Tse V, Yeo JM and Sun B: Atrial anti-arrhythmic effects of heptanol in Langendorff-perfused mouse hearts. PLoS One 11: e0148858, 2016.
127. Tse G, Wong ST, Tse V and Yeo JM: Restitution analysis of alternans using dynamic pacing and its comparison with S1S2 restitution in heptanol-treated, hypokalaemic Langendorff-perfused mouse hearts. Biomed Rep 4: 673-680, 2016.
128. Tse G, Sun B, Wong ST, Tse V and Yeo JM: Ventricular anti-arrhythmic effects of hypercalcaemia treatment in hyperkalaemic, Langendorff-perfused mouse hearts. Biomed Rep 5: 301-310, 2016.

129. Tse G, Yeo JM, Tse V, Kwan J and Sun B: Gap junction inhibition by heptanol increases ventricular arrhythmogenicity by reducing conduction velocity without affecting repolarization properties or myocardial refractoriness in Langendorff-perfused mouse hearts. Mol Med Rep 14: 4069-4074, 2016.
130. Tse G, Lai ET, Tse V and Yeo JM: Molecular and electrophysiological mechanisms underlying cardiac arrhythmogenesis in diabetes mellitus. J Diabetes Res 2016: 2848759, 2016.
131. Tse G, Yeo JM, Chan YW, Lai ET and Yan BP: What is the arrhythmic substrate in viral myocarditis? Insights from clinical and animal studies. Front Physiol 7: 308, 2016.
132. Tse G, Yan BP, Chan YW, Tian XY and Huang Y: Reactive oxygen species, endoplasmic reticulum stress and mitochondrial dysfunction: The link with cardiac arrhythmogenesis. Front Physiol 7: 313, 2016.
133. Tse G, Lai ET, Yeo JM and Yan BP: Electrophysiological mechanisms of Bayés syndrome: Insights from clinical and mouse studies. Front Physiol 7: 188, 2016.
134. Li RA: Gene- and cell-based bio-artificial pacemaker: What basic and translational lessons have we learned? Gene Ther 19: 588-595, 2012.
135. Xue T, Cho HC, Akar FG, Tsang SY, Jones SP, Marbán E, Tomaselli GF and Li RA: Functional integration of electrically active cardiac derivatives from genetically engineered human embryonic stem cells with quiescent recipient ventricular cardiomyocytes: Insights into the development of cell-based pacemakers. Circulation 111: 11-20, 2005.
136. Nattel S: Inward rectifier-funny current balance and spontaneous automaticity: Cautionary notes for biologic pacemaker development. Heart Rhythm 5: 1318-1319, 2008.
137. Miake J, Marbán E and Nuss HB: Biological pacemaker created by gene transfer. Nature 419: 132-133, 2002.
138. Azene EM, Xue T, Marbán E, Tomaselli GF and Li RA: Non-equilibrium behavior of HCN channels: Insights into the role of HCN channels in native and engineered pacemakers. Cardiovasc Res 67: 263-273, 2005.
139. Qu J, Barbuti A, Protas L, Santoro B, Cohen IS and Robinson RB: HCN2 overexpression in newborn and adult ventricular myocytes: Distinct effects on gating and excitability. Circ Res 89: E8-E14, 2001.
140. Xue T, Siu CW, Lieu DK, Lau CP, Tse HF and Li RA: Mechanistic role of I(f) revealed by induction of ventricular automaticity by somatic gene transfer of gating-engineered pacemaker (HCN) channels. Circulation 115: 1839-1850, 2007.
141. Kass-Eisler A, Falck-Pedersen E, Alvira M, Rivera J, Buttrick PM, Wittenberg BA, Cipriani L and Leinwand LA: Quantitative determination of adenovirus-mediated gene delivery to rat cardiac myocytes in vitro and in vivo. Proc Natl Acad Sci USA 90: 11498-11502, 1993.
142. Mühlhauser J, Jones M, Yamada I, Cirielli C, Lemarchand P, Gloe TR, Bewig B, Signoretti S, Crystal RG and Capogrossi MC: Safety and efficacy of in vivo gene transfer into the porcine heart with replication-deficient, recombinant adenovirus vectors. Gene Ther 3: 145-153, 1996.
143. Chan YC, Siu CW, Lau YM, Lau CP, Li RA and Tse HF: Synergistic effects of inward rectifier (I) and pacemaker (I) currents on the induction of bioengineered cardiac automaticity. J Cardiovasc Electrophysiol 20: 1048-1054, 2009.
144. Lieu DK, Chan YC, Lau CP, Tse HF, Siu CW and Li RA: Overexpression of HCN-encoded pacemaker current silences bioartificial pacemakers. Heart Rhythm 5: 1310-1317, 2008.
145. Saito Y, Nakamura K, Yoshida M, Sugiyama H, Ohe T, Kurokawa J, Furukawa T, Takano M, Nagase S, Morita H, *et al*: Enhancement of Spontaneous Activity by HCN4 Overexpression in Mouse Embryonic Stem Cell-Derived Cardiomyocytes - A Possible Biological Pacemaker. PLoS One 10: e0138193, 2015.
146. Kong CW, Akar FG and Li RA: Translational potential of human embryonic and induced pluripotent stem cells for myocardial repair: Insights from experimental models. Thromb Haemost 104: 30-38, 2010.
147. Weng Z, Kong CW, Ren L, Karakikes I, Geng L, He J, Chow MZ, Mok CF, Keung W, Chow H, *et al*: A simple, cost-effective but highly efficient system for deriving ventricular cardiomyocytes from human pluripotent stem cells. Stem Cells Dev 23: 1704-1716, 2014.
148. Plotnikov AN, Shlapakova I, Szabolcs MJ, Danilo P Jr, Lorell BH, Potapova IA, Lu Z, Rosen AB, Mathias RT, Brink PR, *et al*: Xenografted adult human mesenchymal stem cells provide a platform for sustained biological pacemaker function in canine heart. Circulation 116: 706-713, 2007.
149. Plotnikov AN, Sosunov EA, Qu J, Shlapakova IN, Anyukhovsky EP, Liu L, Janse MJ, Brink PR, Cohen IS, Robinson RB, *et al*: Biological pacemaker implanted in canine left bundle branch provides ventricular escape rhythms that have physiologically acceptable rates. Circulation 109: 506-512, 2004.
150. Cho HC, Kashiwakura Y and Marbán E: Creation of a biological pacemaker by cell fusion. Circ Res 100: 1112-1115, 2007.
151. Kehat I, Khimovich L, Caspi O, Gepstein A, Shofti R, Arbel G, Huber I, Satin J, Itskovitz-Eldor J and Gepstein L: Electromechanical integration of cardiomyocytes derived from human embryonic stem cells. Nat Biotechnol 22: 1282-1289, 2004.
152. Verkerk AO and Wilders R: Hyperpolarization-activated current, If, in mathematical models of rabbit sinoatrial node pacemaker cells. BioMed Res Int 2013: 872454, 2013.
153. Tse G: Mechanisms of cardiac arrhythmias. J Arrhythm 32: 75-81, 2016.