Published in final edited form as:

Card Electrophysiol Clin. 2010 December 1; 2(4): 499–507. doi:10.1016/j.ccep.2010.09.001.

Genetics of sick sinus syndrome

Jeffrey B. Anderson, MD, MPH¹ and D. Woodrow Benson, MD, PhD²

¹ Instructor of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio

² Professor of Pediatrics, The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio

Keywords

sick sinus syndrome; sinus node; SCN5A; HCN; connexins

Background

Sick sinus syndrome (SSS) was first described over four decades ago as a complicating arrhythmia following cardioversion¹ and shortly thereafter its electrocardiographic features were defined.² The disorder is characterized by persistent inappropriate sinus bradycardia, episodes of sinoatrial block and/or chronotropic incompetence.³ Episodes of atrial tachycardia coexisting with sinus bradycardia (tachycardia-bradycardia syndrome) are also common in this disorder.⁴ See Figure 1. Despite extensive efforts to better understand the mechanism of SSS in terms of abnormal automaticity, sinus node exit block, or impaired intra-atrial conduction and excitability, this has remained largely an electrocardiographic diagnosis.⁴

The sinoatrial (SA) node is a complex structure and its proper function requires an intricate arrangement of cellular and molecular components. SSS, a misnomer, once thought to be simply a problem with the automaticity initiated within the SA node, can be secondary to a number of different molecular, cellular and structural abnormalities. For example, the SA node core, where automaticity arises, may be working properly with abnormal conduction from the SA node to the remainder of the atrium. As will be discussed in this review, patients diagnosed with SSS may have problems with automaticity, propagation of electrical impulses from the SA node to the remainder of the heart, abnormalities related to autonomic influences on the SA node, or a combination of these problems. SSS may occur in the absence of structural heart disease, but “atrial disease” is a recurring theme whether in the elderly with acquired heart disease or young survivors of congenital heart disease surgery.

© 2010 Elsevier Inc. All rights reserved.

Corresponding author: D. Woodrow Benson, 3333 Burnet Avenue, ML 2003, Cincinnati, OH 45229, 513-636-7716 (phone), 513-636-3952 (fax), woody.benson@cchmc.org.

Coauthor: Jeffrey B. Anderson, 3333 Burnet Avenue, ML 2003, Cincinnati, OH 45229, 513-636-3865 (phone), 513-636-3952 (fax), jeffrey.anderson@cchmc.org

The authors have no financial relationships to disclose

No external funding was utilized for this manuscript

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Patients of any age with SSS may exhibit varied symptoms including presyncope or syncope, activity intolerance and SSS may even be the cause of sudden cardiac arrest. The course of SSS can be intermittent and unpredictable, related to the severity of the underlying heart disease. While SSS is more common in the elderly and in those with structural heart disease, its true incidence is unknown as the features of SSS have not been evaluated in the general population in a standardized manner.³

Sinus node architecture and physiology

Gross and microscopic anatomy

Keith and Flack first described the SA node in 1907. Of their findings they wrote, “There is a remarkable remnant of primitive fibres persisting at the sinoauricular junction in all the mammalian hearts examined...in them the dominating rhythm of the heart is believed to normally arise.”⁵ The anatomical and histological structure of the SA node is conserved across vertebrates.⁵ The SA node is a right atrial structure that is subepicardial and can be located at the junction of the crista terminalis at the superior cavoatrial junction.⁶ It is shaped like a flattened ellipse and the prominent SA nodal artery passes through its body. Multiple autonomic nerves course to both its poles.⁷ The SA node is an extensive structure, encompassing tissue from the superior to the inferior vena cava⁸ and the size and tissue thickness of the SA node varies between species.⁶ In humans, the SA node lies beneath the epicardial surface with a layer of atrial muscle between the SA node and the endocardium.⁹ This layer of atrial muscle, along with connective tissue in the region of the SA node, are thought to protect the area against high wall stresses.¹⁰ Microscopically, the SA node is characterized by a complex pattern of cells within a fibrous stroma. Near its periphery there is an outer coat of working atrial myocytes. The function of the specialized cells of the SA node is conduction rather than contraction; therefore, they are smaller, have fewer contractile elements, and expend less energy than surrounding myocytes.⁷ See Figure 2.

Molecular architecture

The molecular organization of the SA node is complex but serves as a template to understand the characteristics that allow for its role as the primary pacemaker in the heart.^{11–12} Figure 3 shows a section cut through the SA node. SA node tissue arises from the interaval region and persists to the endocardial surface near the crista terminalis (CT) and overlaps the atrial muscle. In the atrial muscle, Cx43 is expressed and Cx45 is absent. In contrast, in the SA node core, Cx43 is absent and Cx45 is expressed while in the periphery of the SA node, both Cx43 and Cx45 are expressed. Atrial muscle expresses atrial natriuretic peptide (ANP) but not neurofilament, and the SA node core and periphery express neurofilament but not ANP. Neurofilament is a cytoskeletal protein found in nerve cells. Because it is expressed in the SA node and other cardiac pacemaker/ conducting tissues but not in the rest of the heart, it has been suggested that these tissues are neural in origin.¹³ On the basis of these markers, three cell types can be identified: *ANP-negative/ neurofilament-positive/Cx43-negative/ Cx45-positive* central cells, *ANP-negative/ neurofilament-positive/Cx43-positive/Cx45-positive* peripheral cells, and *ANP-positive/ neurofilament-negative/Cx43-positive/Cx45-negative* atrial cells. It is important to minimize electrotonic coupling.¹⁴

Gap junctions and connexins—Electron microscopy has demonstrated the presence of gap junctions in the SA node as well as in other myocardial tissue. Gap junctions are made up of serially linked channels (connexons) contributed to by two opposing cell membranes. These junctions allow for the passage of small molecules (<1 kDa) between two adjacent cells.¹⁰ Each connexon is composed of six transmembrane proteins called connexins. In cardiac tissue, three main connexin isoforms are found: Cx40, Cx43, Cx 45.¹⁴ A fourth

connexin, Cx30.2, has been identified in murine conduction tissue; its human orthologue is Cx31.9.¹⁴ There is regional and tissue specific expression of different connexin isoforms within the heart; **See** Figure 4. Cx40 is mainly expressed in the atrial myocytes, the AV node, His-bundle and in the ventricular conduction system. Cx43 is expressed in atrial and ventricular myocytes and within the distal portions of the ventricular conduction system. Cx43 is also expressed in SA node periphery but not at its core.¹⁰ There is localization of Cx45 in the SA node, the AV node, His bundle and bundle branches. Although the structures of connexin isoforms are similar, the biophysical properties of the channels they form are very different.^{15–16} For example, gap junction conductance follows the sequence of Cx40 > Cx43 > Cx45 > Cx30.2/Cx31.9 consistent with better conductance in atrial tissue compared to that at the SA node core.¹⁷ The differences in electrical properties of gap junctions help explain regional differences in electrical conduction. In addition there are regional differences in the total number of gap junctions participating in cellular communication. Gap junctions are sparsely found in the SA node and seen in great quantity in atrial tissue.¹⁸

Gap junctions in the SA node play a role in both automaticity and transfer of electrical impulses to the surrounding myocardium.¹⁹ At the SA node core Cx45 is the predominant connexin in gap junction proteins.²⁰ There are few total gap junctions found at the SA node core¹⁸, where little coupling is necessary for synchronization of electrical impulses of individual cells.²¹ In the periphery of the SA node Cx40 and Cx43 are both expressed. Studies in mice using knock-out models of Cx43 and Cx45 demonstrated no significant heart rate abnormalities but, Cx40-/- mice did display breakthrough activation of pacemaker activity at locations distant from the SA node, as seen in wild type mice.²² Haploinsufficiency or deletion of Cx43 has also been shown to have no effect on SA nodal function.²³ The fact that the SA node seems to function well, even with reduced expression or absence of apparently essential connexins, supports the thought that little coupling is needed for electrical propagation within the SA node itself.¹⁴

Connexins play an important role in electrical propagation through atrial tissue. Murine models haploinsufficient or deficient for Cx43 show no changes in electrical impulse propagation through the atria.²⁴ There have been mixed results in studies of Cx40 knock-out mice and the effect on atrial electrical impulse propagation.^{25–26} While the deficiency of Cx40 or Cx43 expression may not itself lead to decreased atrial electrical propagation, there does seem to be a relationship between impulse propagation velocity and the ratio of atrial Cx40 and Cx43 expression.^{27–28}

Ion channels, handling proteins, and receptors

Sodium and calcium current: The inward sodium current (I_{Na}) is responsible for the initial upstroke of the action potential within atrial myocardium. Within the SA node core there is an absence of I_{Na} , resulting in a slow initial upstroke of the action potential.²⁹ Blockade of I_{Na} with tetrodotoxin, in the rabbit, results in no effect on electrical activity recorded from the SA node core.³⁰ The cardiac isoform of the channel responsible for I_{Na} is most abundantly expressed in atrial muscle and has been shown to be expressed in lower amounts within the SA node and to be absent from the SA node core in a murine model.³¹

Two separate inward Ca^{2+} currents have been identified in SA node core tissue. A long lasting current (I_{CaL}) and a transient current (I_{CaT}) serve separate roles in action potential formation. I_{CaL} is the main contributor to the initial upstroke of the action potential in the SA node core and also plays a role in the plateau portion of the action potential. $Ca_v1.2$ is the principle isoform responsible for I_{CaL} in atrial myocardial tissue. In the SA node, however, $Ca_v1.3$ is the principle isoform.³² I_{CaT} contributes to the last two thirds of the

diastolic depolarization. Blockage of both calcium currents have been shown to suppress spontaneous electrical activity in the SA node core.^{30, 33}

Potassium currents: The hyperpolarization-activated cyclic nucleotide-gated (HCN) family (HCN1–4) of ion channels is responsible for I_f . These channels are directly regulated by cAMP.³⁴ This current is inward in direction and carries both Na and K ions. I_f increases when cellular cAMP levels are elevated during sympathetic stimulation and decreases when levels are reduced during vagal stimulation.³⁵ Further evidence of the contribution of I_f to automaticity has been documented in observation of a decrease in automaticity in both humans and rodents when I_f is specifically blocked with the selective I_f inhibitor ivabradine.^{36–38} Two of the four known genes encoding HCN channel subunits, HCN2 and HCN4, are pre- dominantly expressed in the heart.³⁹ The most abundant isoform of this channel within the SA node is HCN4 and HCN4 is more abundant within the SA node than in the atrial myocardium. Human genetic⁴⁰ and pharmacologic^{36, 41} studies have suggested a significant role for HCN4 subunits in SA nodal pacemaking in humans and rodents. However, targeted deletions of HCN4 in adult mice were found to cause sinus pauses but to have no effect on heart rate regulation.⁴² Similar observations were made in adult heterozygous knock-in mice expressing a cAMP binding–deficient HCN4 subunit.⁴³

Besides the HCN family, there are several potassium currents that are important in SA nodal function. The transient outward potassium current (I_{to}) activates and inactivates quickly and is responsible for the initial phase of repolarization and, in part, determines the duration of the action potential.⁸ In the rabbit, I_{to} has been shown to be present at a higher density in the SA node than in atrial myocardium.¹⁰ Delayed-rectifier potassium currents are also important in determining the duration of the action potential initiated in the SA node. During SA nodal action potential formation there are rapid and slow delayed rectifier potassium currents (I_{Kr}) and (I_{Ks}). Both help to further repolarization and determine maximum diastolic potential.⁴⁴ The inward rectifier potassium current (I_{K1}) participates in stabilization of the resting potential in myocardium. The maximum diastolic potential of the sinus node is significantly more electrically positive than that of the surrounding atrial tissue. Several isoforms of the inward rectifier potassium channel are present in myocardial tissue. $K_{V1.4}$ is primarily found in atrial myocardium and $K_{V4.2}$ is primarily found in sinus nodal tissue.³²

Calcium handling proteins: There are several proteins involved with calcium movement within SA node and atrial tissue. The arrival of the action potential leads to an increase in cytoplasmic Ca brought about by and influx of extracellular Ca. This Ca influx triggers a further release of calcium-mediated calcium release from the sarcoplasmic reticulum (SR) by way of the ryanodine receptor (RyR).⁴⁵ The cardiac ryanodine receptor (RyR2) mRNA and protein are expressed within the SA node core but is more abundant in the periphery of the SA node as well as in atrial tissue.⁴⁶ Once the membrane begins to repolarize Ca begins to be removed from the cytosol back to the SR by means of the sarcoplasmic reticulum Ca pump, SERCA2a.⁴⁵ SERCA2a is present within the SA node core but more abundantly in the periphery of the SA node as well as in atrial tissue.⁴⁶ While the majority of Ca release from the SR occurs during action potential formation (depolarization) there is some slow Ca release from the SR during diastolic repolarization. Within the SA node core this occurs as a result of high cAMP levels.⁴⁴ The release of Ca from the SR during diastolic depolarization activates a Na/Ca exchanger which results in an inward current that contributes to depolarization. Three isoforms of the Na/Ca exchanger (NCX) have been identified, NCX1–NCX3⁴⁵ but only NCX1 has been identified in pacemaking cells from several animals and is present in equal concentration within the SA node and atrial tissue.⁴⁶ If intracellular stores of Ca are depleted, the influx of extracellular Ca can be augmented by TRPC (transient

receptor potential canonical) channels. These channels have been identified in the SA node in the mouse and may be involved in pacemaking.⁴⁷

Receptors: Adenosine, adrenergic, and muscarinic receptors are all present in SA nodal tissue. Adrenergic $\alpha 1a$, $\alpha 2a$, $\alpha 2b$, and $\alpha 3$ adenosine receptors have all been identified. Alpha-1 and alpha-2 adrenergic receptors are all detectable at varying levels within the SA node. Of the muscarinic receptors, M2 are present in SA nodal tissue and M1 receptors have not been detected.⁴⁶ The presence of these receptors within the SA node gives some evidence as to the pharmacologic mechanism of action on the SA node of these classes of medications.

Physiology

The SA node is the physiological pacemaker in the human heart and is predominantly responsible for autonomous heart beat generation. The complex mechanisms underlying SA nodal automaticity remain incompletely understood. However, heart rate control is regulated through control of SA nodal automaticity by the autonomic nervous system; cholinergic stimulation slows spontaneous SA nodal activity and β -adrenergic stimulation accelerates spontaneous SA nodal activity.⁴⁸

The action potential, initiated in the SA node core, propagates first into the SA node periphery and then into the surrounding atrial tissue. The speed of action potential propagation increases as distance from the SA node core increases. Following electrical impulse propagation, there is stable resting electrical potential in the atrial myocardium. In the SA node, however, the tissue is more depolarized and there is further time-dependent depolarization, leading to initiation of the next action potential upon reaching threshold. There is minimization of electronic coupling between the SA node and the surrounding atrial tissue. While there is no distinct border between the SA node and the surrounding atrial tissue, the periphery of the SA node is surrounded by a layer of connective tissue. There is also poor electrical conduction velocity in the SA node core as compared to conduction velocity in atrial tissue. These two properties act to protect the SA node from electrical activity in the atrium that may suppress its pacemaking functions.⁴⁹

Genetic origins of sick sinus syndrome

From this discussion of the complex molecular makeup of the SA node, SSS may result from a number of genetic abnormalities leading to mutations in proteins important for its function. Family clustering of SSS has been reported and both autosomal recessive (MIM #608567) and dominant (MIM #163800) forms have been described. However, to date only a few examples have been identified.

HCN ion channels are important in the automaticity of the SA node core. HCN4 mutations have been identified in two studies of patients with SSS manifesting as marked sinus bradycardia and chronotropic incompetence.^{40, 50} Using *HCN4* as a candidate gene, both studies identified a heterozygous 1-bp deletion (1631delC) in exon 5 of the human *HCN4* gene. The mutant (HCN4-573X) is predicted to have a truncated C-terminus and lack the cyclic nucleotide-binding domain. COS-7 cells transiently transfected with HCN4-573X cDNA exhibited normal intracellular trafficking and membrane integration of HCN4-573X subunits. However, patch-clamp experiments showed that HCN4-573X channels mediated *If*-like currents that were insensitive to increased cellular cAMP levels. Co expression experiments identified a dominant-negative effect of HCN4-573X subunits on wild-type subunits. Together, these data indicate that the cardiac *If* channels are functionally expressed but with altered biophysical properties. To study the pathogenesis of HCN4-573X, Align and colleagues⁴³ generated mice with heart-specific and inducible expression of a human

HCN4-mutation (573X). They found that conditional expression of the mutation causes elimination of the cAMP sensitivity of *I_f* and decreases the maximum firing rates of SAN pacemaker cells. In conscious mice, hHCN4-573X expression leads to a marked reduction in heart rate at rest and during exercise. Despite the complete loss of cAMP sensitivity of *I_f*, the relative extent of SAN cell frequency and heart rate regulation are preserved. These results demonstrate that cAMP mediated regulation of *I_f* determines basal and maximal heart rates but does not play an indispensable role in heart rate adaptation during physical activity.

Sodium channels are essential for orderly progression of action potentials from the SA node core, through its periphery, and to the surrounding atrial tissue. Abnormalities in the genes coding for sodium channels have been examined in families with SSS. Inherited abnormalities in the alpha-subunit of *I_{Na}* are associated with three distinct channelopathies: congenital long QT syndrome⁵¹, idiopathic ventricular fibrillation^{51–52}, and progressive cardiac conduction system disease.^{53–54} Recent reports of mutational analyses have revealed more than 200 distinct mutations in *SCN5A*, of which at least 20 mutations are associated with SSS.⁵⁵ In addition to this variable expressivity, heterozygous *SCN5A* mutations have also shown incomplete penetrance. Compound heterozygous *SCN5A* mutations have also been shown to be associated with a recessive form of congenital SSS.⁴ Benson and colleagues⁴ identified individuals with SSS characterized by sinus bradycardia and loss of atrial excitability (atrial standstill). Compound heterozygous nucleotide changes in *SCN5A* were identified in five individuals from three kindreds who carried the diagnosis of SSS. Because *SCN5A* is not expressed in the SA node and SA node action potentials are not dependent on *SCN5A*, primary dysfunction of the SA node seems unlikely. However, since SA node dysfunction caused by failure of impulses to conduct into adjacent atrial myocardium (exit block) has been suggested as a cause of SSS (43, 44) it has been speculated that this is a plausible mechanism to explain this *SCN5A*-linked disorder.

In addition, certain genetic variants of *Cx40* with accompanying *SCN5A* mutations have been shown to result in the atrial standstill phenotype.⁵⁶ Groenewegen and colleagues⁵⁷ studied a large family with atrial standstill. They identified heterozygosity for a mutation in *SCN5A*, a G→A substitution in the first nucleotide of codon 1275 leading to the substitution of Asp by Asn (D1275N). Each family member affected by atrial standstill shared this haplotype; however this mutation was identified in some unaffected relatives as well. In addition, direct sequencing of the coding region of the *Cx40* gene revealed changes in the proximal promoter: a G→A change at 44 nucleotides upstream of the transcription start site, and an A→G change in exon 1 at 71 nucleotides downstream of the transcription start site. Genotyping of all relatives revealed homozygosity for these base changes in all affected individuals as well as in unaffected relatives. While mutations in both *SCN5A* and *Cx40* were seen in affected and unaffected individuals the occurrence of the *SCN5A*-D1275N mutation and the rare *Cx40* genotypes were only seen in the individuals with atrial standstill and in none of the unaffected relatives.⁵⁷ By themselves, the effect of each mutation is sufficient to result in the rare phenotype of atrial standstill. The mutation in *SCN5A* interferes with electrical impulse generation and the mutation in *Cx40* leads to impairment of propagation of any electrical activity.⁵⁷

Molecular biopacemaker

SSS can result in various clinical symptoms including presyncope or syncope, chronotropic incompetence or significant sinus bradycardia or sinus tachycardia that cause activity intolerance or even sudden death. The current treatment options for sinus node dysfunction include medical management to control tachyarrhythmias and implanted pacemakers to counter bradyarrhythmia or sinus arrest. Implanted pacemakers are well tolerated but do require invasive placement and have a limited generator life, leading to multiple invasive

procedures for replacement if needed at a young age. In the post-genomic era, there has been some interest alternative molecular therapies for individuals with SSS.

The SA node is highly adapted to its role as the primary pacemaker. Its mix of ionic currents fits it for the pacemaking function, but in addition its poor electrical coupling protects it from the inhibitory hyperpolarizing influence of the surrounding atrial tissue. Studies to date indicate the challenges to developing a biopacemaker. Several groups over the past several years have explored the possibility of a biological pacemaker which would ultimately replace implanted pacemakers. Proposed strategies include gene therapy, transplantation of donor excitable myocardium, and the delivery of modified embryonic stem cells to the heart. Fetal and neonatal cardiac cells have been shown to functionally integrate and act as an ectopic pacemaker when transplanted into the myocardium of dogs, pigs, and guinea pigs.^{58–59} Gene therapy approaches that have been discussed include overexpression of beta-adrenergic receptors, suppression of the potassium inward-rectifier current, I_{K1} , and inserting the pacemaker gene, HCN2, into the atrium using adenoviral or naked plasma vectors.⁶⁰ Another approach in the biologic treatment of SA node dysfunction is the possibility of engraftment of embryonic stem cells that have been differentiated into cardiac myocytes, into atrial tissue.⁶¹

While each of these biologic approaches have shown some promise in addressing the problem of SSS they each address specific parts of a complex system. The intricacy of the anatomic and molecular design of the sinoatrial node allows for its function as the primary pacemaker of the heart. This complex design includes not only the differences in cellular makeup compared to surrounding atrial tissue but differences in cellular makeup within the SA node itself. Each part of the SA node, at a cellular and subcellular level, plays an individual role in the initiation and propagation of electrical impulses that create normal electrical physiology within the heart. Addressing one piece of this complex puzzle is a start to creating a solution for SA node dysfunction, but a complete solution will need to include a group of interventions that create a similar configuration to the SA node.

Summary

The SA node exhibits complex cellular and molecular structure and its proper function requires an intricate arrangement of its architecture. A better understanding of the genetic and molecular makeup of the SA node has led to improved understanding of its function as primary cardiac pacemaker and the abnormalities that may lead to sick sinus syndrome, a common clinical problem. Recently, genetic studies have begun to identify the molecular underpinnings of SSS. Taken together, these findings promise improved diagnosis and alternative therapies for SSS.

References

1. Lown B. Electrical reversion of cardiac arrhythmias. *Br Heart J*. Jul; 1967 29(4):469–489. [PubMed: 6029120]
2. Ferrer MI. The sick sinus syndrome in atrial disease. *JAMA*. Oct 14; 1968 206(3):645–646. [PubMed: 5695590]
3. Brignole M. Sick sinus syndrome. *Clin Geriatr Med*. May; 2002 18(2):211–227. [PubMed: 12180244]
4. Benson DW, Wang DW, Dymont M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest*. Oct; 2003 112(7):1019–1028. [PubMed: 14523039]
5. Keith A, Flack M. The Form and Nature of the Muscular Connections between the Primary Divisions of the Vertebrate Heart. *J Anat Physiol*. Apr; 1907 41(Pt 3):172–189. [PubMed: 17232727]

6. Opthof T. The mammalian sinoatrial node. *Cardiovasc Drugs Ther.* Mar; 1988 1(6):573–597. [PubMed: 3154325]
7. Edwards, W. Cardiac anatomy and examination of cardiac specimens. In: Allen, HD.; Driscoll, DJ.; Shaddy, RE.; Feltes, TF., editors. *Moss and Adams Heart Disease in Infants, Children, and adolescents.* 7. Vol. 1. Philadelphia: Lippincott Williams and Wilkins; 2008. p. 2-33.
8. Boyett, MR.; Tellez, J.; Dobrzynski, H. The sinoatrial node: its complex structure and unique ion channel gene program. In: Zipes, Jalife J., editor. *Cardiac electrophysiology: from cell to bedside.* Vol. 5. Philadelphia: W. B. Saunders; 2009. p. 127-138.
9. Anderson, RH.; A, EB. Anatomy of the conduction tissues and accessory atrioventricular connections. In: DP, ZJJ., editor. *Cardiac electrophysiology from cell to bedside.* Philadelphia: W.B. Saunders; 1990. p. 240-248.
10. Boyett MR, Honjo H, Kodama I. The sinoatrial node, a heterogeneous pacemaker structure. *Cardiovasc Res.* Sep; 2000 47(4):658–687. [PubMed: 10974216]
11. Dobrzynski H, Li J, Tellez J, et al. Computer three-dimensional reconstruction of the sinoatrial node. *Circulation.* Feb 22; 2005 111(7):846–854. [PubMed: 15699261]
12. Wittwer M, Fluck M, Hoppeler H, Muller S, Desplanches D, Billeter R. Prolonged unloading of rat soleus muscle causes distinct adaptations of the gene profile. *FASEB J.* Jun; 2002 16(8):884–886. [PubMed: 11967225]
13. Vitadello M, Colpo P, Gorza L. Rabbit cardiac and skeletal myocytes differ in constitutive and inducible expression of the glucose-regulated protein GRP94. *Biochem J.* Jun 1; 1998 332(Pt 2): 351–359. [PubMed: 9601063]
14. Jansen JA, van Veen TA, de Bakker JM, van Rijen HV. Cardiac connexins and impulse propagation. *J Mol Cell Cardiol.* Jan; 48(1):76–82. [PubMed: 19729017]
15. Saez JC, Berthoud VM, Branes MC, Martinez AD, Beyer EC. Plasma membrane channels formed by connexins: their regulation and functions. *Physiol Rev.* Oct; 2003 83(4):1359–1400. [PubMed: 14506308]
16. van Veen AA, van Rijen HV, Opthof T. Cardiac gap junction channels: modulation of expression and channel properties. *Cardiovasc Res.* Aug 1; 2001 51(2):217–229. [PubMed: 11470461]
17. Weingart, R. Biophysical properties of gap junctions. In: Zipes, Jalife J., editor. *Cardiac electrophysiology: from cell to bedside.* Vol. 5. Philadelphia: W.B. Saunders; 2009. p. 149-155.
18. Saffitz JE, Green KG, Schuessler RB. Structural determinants of slow conduction in the canine sinus node. *J Cardiovasc Electrophysiol.* Jul; 1997 8(7):738–744. [PubMed: 9255681]
19. Jongsma HJ. Diversity of gap junctional proteins: does it play a role in cardiac excitation? *J Cardiovasc Electrophysiol.* Feb; 2000 11(2):228–230. [PubMed: 10709720]
20. Davis LM, Rodefeld ME, Green K, Beyer EC, Saffitz JE. Gap junction protein phenotypes of the human heart and conduction system. *J Cardiovasc Electrophysiol.* Oct; 1995 6(10 Pt 1):813–822. [PubMed: 8542077]
21. Wilders R, Verheijck EE, Kumar R, et al. Model clamp and its application to synchronization of rabbit sinoatrial node cells. *Am J Physiol.* Nov; 1996 271(5 Pt 2):H2168–2182. [PubMed: 8945938]
22. Bagwe S, Berenfeld O, Vaidya D, Morley GE, Jalife J. Altered right atrial excitation and propagation in connexin40 knockout mice. *Circulation.* Oct 11; 2005 112(15):2245–2253. [PubMed: 16203917]
23. Eckardt D, Theis M, Degen J, et al. Functional role of connexin43 gap junction channels in adult mouse heart assessed by inducible gene deletion. *J Mol Cell Cardiol.* Jan; 2004 36(1):101–110. [PubMed: 14734052]
24. Thomas SA, Schuessler RB, Berul CI, et al. Disparate effects of deficient expression of connexin43 on atrial and ventricular conduction: evidence for chamber-specific molecular determinants of conduction. *Circulation.* Feb 24; 1998 97(7):686–691. [PubMed: 9495305]
25. VanderBrink BA, Sellitto C, Saba S, et al. Connexin40-deficient mice exhibit atrioventricular nodal and infra-Hisian conduction abnormalities. *J Cardiovasc Electrophysiol.* Nov; 2000 11(11): 1270–1276. [PubMed: 11083248]

26. Verheule S, van Batenburg CA, Coenjaerts FE, Kirchhoff S, Willecke K, Jongsma HJ. Cardiac conduction abnormalities in mice lacking the gap junction protein connexin40. *J Cardiovasc Electrophysiol.* Oct; 1999 10(10):1380–1389. [PubMed: 10515563]
27. Beauchamp P, Yamada KA, Baertschi AJ, et al. Relative contributions of connexins 40 and 43 to atrial impulse propagation in synthetic strands of neonatal and fetal murine cardiomyocytes. *Circ Res.* Nov 24; 2006 99(11):1216–1224. [PubMed: 17053190]
28. Kanagaratnam P, Rothery S, Patel P, Severs NJ, Peters NS. Relative expression of immunolocalized connexins 40 and 43 correlates with human atrial conduction properties. *J Am Coll Cardiol.* Jan 2; 2002 39(1):116–123. [PubMed: 11755296]
29. Honjo H, Boyett MR, Kodama I, Toyama J. Correlation between electrical activity and the size of rabbit sino-atrial node cells. *J Physiol.* Nov 1; 1996 496(Pt 3):795–808. [PubMed: 8930845]
30. Kodama I, Nikmaram MR, Boyett MR, Suzuki R, Honjo H, Owen JM. Regional differences in the role of the Ca²⁺ and Na⁺ currents in pacemaker activity in the sinoatrial node. *Am J Physiol.* Jun; 1997 272(6 Pt 2):H2793–2806. [PubMed: 9227559]
31. Lei M, Jones SA, Liu J, et al. Requirement of neuronal- and cardiac-type sodium channels for murine sinoatrial node pacemaking. *J Physiol.* Sep 15; 2004 559(Pt 3):835–848. [PubMed: 15254155]
32. Tellez JO, Dobrzynski H, Greener ID, et al. Differential expression of ion channel transcripts in atrial muscle and sinoatrial node in rabbit. *Circ Res.* Dec 8; 2006 99(12):1384–1393. [PubMed: 17082478]
33. Ono K, Iijima T. Pathophysiological significance of T-type Ca²⁺ channels: properties and functional roles of T-type Ca²⁺ channels in cardiac pacemaking. *J Pharmacol Sci.* Nov; 2005 99(3):197–204. [PubMed: 16272791]
34. DiFrancesco D, Tortora P. Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. *Nature.* May 9; 1991 351(6322):145–147. [PubMed: 1709448]
35. Baruscotti M, Bucchi A, DiFrancesco D. Physiology and pharmacology of the cardiac pacemaker (“funny”) current. *Pharmacol Ther.* Jul; 2005 107(1):59–79. [PubMed: 15963351]
36. Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation.* Feb 18; 2003 107(6):817–823. [PubMed: 12591750]
37. Leoni AL, Marionneau C, Demolombe S, et al. Chronic heart rate reduction remodels ion channel transcripts in the mouse sinoatrial node but not in the ventricle. *Physiol Genomics.* Dec 14; 2005 24(1):4–12. [PubMed: 16219869]
38. Barbuti A, Baruscotti M, DiFrancesco D. The pacemaker current: from basics to the clinics. *J Cardiovasc Electrophysiol.* Mar; 2007 18(3):342–347. [PubMed: 17284289]
39. Shi W, Wymore R, Yu H, et al. Distribution and prevalence of hyperpolarization- activated cation channel (HCN) mRNA expression in cardiac tissues. *Circ Res.* Jul 9; 1999 85(1):e1–6. [PubMed: 10400919]
40. Schulze-Bahr E, Neu A, Friederich P, et al. Pacemaker channel dysfunction in a patient with sinus node disease. *J Clin Invest.* May; 2003 111(10):1537–1545. [PubMed: 12750403]
41. Mangoni ME, Nargeot J. Genesis and regulation of the heart automaticity. *Physiol Rev.* Jul; 2008 88(3):919–982. [PubMed: 18626064]
42. Herrmann S, Stieber J, Stockl G, Hofmann F, Ludwig A. HCN4 provides a ‘depolarization reserve’ and is not required for heart rate acceleration in mice. *EMBO J.* Oct 31; 2007 26(21):4423–4432. [PubMed: 17914461]
43. Alig J, Marger L, Mesirca P, Ehmke H, Mangoni ME, Isbrandt D. Control of heart rate by cAMP sensitivity of HCN channels. *Proc Natl Acad Sci U S A.* Jul 21; 2009 106(29):12189–12194. [PubMed: 19570998]
44. Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation.* Apr 10; 2007 115(14):1921–1932. [PubMed: 17420362]
45. Boyett, MR.; Tellez, J.; Dobrzynski, H. The sinoatrial node: its complex structure and unique ion channel gene program. In: Zipes, D.; Jalife, J., editors. *Cardiac electrophysiology: from cell to bedside*. 5. Philadelphia: Saunders; 2009. p. 127–138.

46. Chandler NJ, Greener ID, Tellez JO, et al. Molecular architecture of the human sinus node: insights into the function of the cardiac pacemaker. *Circulation*. Mar 31; 2009 119(12):1562–1575. [PubMed: 19289639]
47. Ju YK, Chu Y, Chaulet H, et al. Store-operated Ca^{2+} influx and expression of TRPC genes in mouse sinoatrial node. *Circ Res*. Jun 8; 2007 100(11):1605–1614. [PubMed: 17478725]
48. Schram G, Pourrier M, Melnyk P, Nattel S. Differential distribution of cardiac ion channel expression as a basis for regional specialization in electrical function. *Circ Res*. May 17; 2002 90(9):939–950. [PubMed: 12016259]
49. Joyner RW, van Capelle FJ. Propagation through electrically coupled cells. How a small SA node drives a large atrium. *Biophys J*. Dec; 1986 50(6):1157–1164. [PubMed: 3801575]
50. Nof E, Luria D, Brass D, et al. Point mutation in the HCN4 cardiac ion channel pore affecting synthesis, trafficking, and functional expression is associated with familial asymptomatic sinus bradycardia. *Circulation*. Jul 31; 2007 116(5):463–470. [PubMed: 17646576]
51. Wang Q, Shen J, Li Z, et al. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet*. Sep; 1995 4(9):1603–1607. [PubMed: 8541846]
52. Vatta M, Dumaine R, Varghese G, et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Hum Mol Genet*. Feb 1; 2002 11(3):337–345. [PubMed: 11823453]
53. Tan HL, Bink-Boelkens MT, Bezzina CR, et al. A sodium-channel mutation causes isolated cardiac conduction disease. *Nature*. Feb 22; 2001 409(6823):1043–1047. [PubMed: 11234013]
54. Schott JJ, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet*. Sep; 1999 23(1):20–21. [PubMed: 10471492]
55. Lei M, Huang CL, Zhang Y. Genetic Na^{+} channelopathies and sinus node dysfunction. *Prog Biophys Mol Biol*. Oct-Nov; 2008 98(2–3):171–178. [PubMed: 19027778]
56. Makita N, Sasaki K, Groenewegen WA, et al. Congenital atrial standstill associated with coinheritance of a novel SCN5A mutation and connexin 40 polymorphisms. *Heart Rhythm*. Oct; 2005 2(10):1128–1134. [PubMed: 16188595]
57. Groenewegen WA, Firouzi M, Bezzina CR, et al. A cardiac sodium channel mutation cosegregates with a rare connexin40 genotype in familial atrial standstill. *Circ Res*. Jan 10; 2003 92(1):14–22. [PubMed: 12522116]
58. Cai J, Lin G, Jiang H, et al. Transplanted neonatal cardiomyocytes as a potential biological pacemaker in pigs with complete atrioventricular block. *Transplantation*. Apr 15; 2006 81(7):1022–1026. [PubMed: 16612279]
59. Lin G, Cai J, Jiang H, et al. Biological pacemaker created by fetal cardiomyocyte transplantation. *J Biomed Sci*. 2005; 12(3):513–519. [PubMed: 15971007]
60. Rosen MR, Robinson RB, Brink P, Cohen IS. Recreating the biological pacemaker. *Anat Rec A Discov Mol Cell Evol Biol*. Oct; 2004 280(2):1046–1052. [PubMed: 15372435]
61. Xue T, Cho HC, Akar FG, et al. 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*. Jan 4; 2005 111(1):11–20. [PubMed: 15611367]
62. Boyett MR, Dobrzynski H, Lancaster MK, Jones SA, Honjo H, Kodama I. Sophisticated architecture is required for the sinoatrial node to perform its normal pacemaker function. *J Cardiovasc Electrophysiol*. Jan; 2003 14(1):104–106. [PubMed: 12625620]
63. Jansen JA, van Veen TA, de Bakker JM, van Rijen HV. Cardiac connexins and impulse propagation. *J Mol Cell Cardiol*. Jan; 2010 48(1):76–82. [PubMed: 19729017]

Figure 1.

Electrocardiographic findings in sick sinus syndrome.

A. Tachycardia-bradycardia. Reproduced with permission from Michael Laurent, MD, Department of Internal Medicine, University Hospital Leuven, Leuven, Belgium, <http://commons.wikimedia.org/wiki/User:Stevenfruitsmaak>.

B. Atrial fibrillation. Reproduced with permission from Michael Laurent, MD, Department of Internal Medicine, University Hospital Leuven, Leuven, Belgium, <http://commons.wikimedia.org/wiki/User:Stevenfruitsmaak>.

C. Sinoatrial block. Reproduced with permission from Frank Yanowitz, Salt Lake City, Utah, <http://library.med.utah.edu/kw/ecg>, University of Utah, 1996

Figure 2.

A. Schematic diagram of dorsal view of rabbit heart showing location and extent of central (red) and peripheral (blue) sinus node tissue. Reproduced from Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation*. Apr 10 2007;115(14):1921–1932; with permission.

B. The sinus node lies subepicardially in the terminal groove of the right atrium (right lateral view). From Edwards W. Cardiac anatomy and examination of cardiac specimens. In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, eds. *Moss and Adams Heart Disease in Infants, Children, and adolescents*. Vol 1. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2008:2–33; with permission.

C. Masson's trichrome-stained section through human sinus node. From Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation*. Apr 10 2007;115(14):1921–1932; with permission.

Figure 3.

Schematic diagram illustrating molecular architecture of the SA node. The anatomical section is through the crista terminalis (CT) and intercaval region of rabbit showing the relative relation of CT with SA node periphery and SA node core. The distribution of cell types expressing (+ve, positive) or not expressing (–ve, negative) the indicated molecular components is depicted. The section is oriented so that endocardium is up and epicardium is on the lower side. The green area depicts adipocytes and other connective tissue surrounding the SA node region. Modified from Boyett MR, Dobrzynski H, Lancaster MK, Jones SA, Honjo H, Kodama I. Sophisticated architecture is required for the sinoatrial node to perform its normal pacemaker function. *J Cardiovasc Electrophysiol.* Jan 2003;14(1):104–106; with permission..

Figure 4. Chamber specific expression of Cx40, Cx43, and Cx45 in the mouse heart. From Jansen JA, van Veen TA, de Bakker JM, van Rijen HV. Cardiac connexins and impulse propagation. *J Mol Cell Cardiol.* Jan 2010;48(1):76–82; with permission.