New Insights Into Pacemaker Activity
Promoting Understanding of Sick Sinus Syndrome

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artery (Figure 2B), although the relationship to the artery varies from individual to individual.8 The nodal cells are set in a matrix of fibrous tissue, with a relatively discrete boundary seen between the margins of the node and the adjacent atrial tissues (Figure 2B).8 The earliest reconstructions of the node9 showed it to be a small discrete collection of tissues at the crest of the right atrial appendage, at the junction of the superior caval vein with the right atrium, but this is not typical. In a small proportion of cases, the node can extend across the crest of the right atrial appendage and occupy the interatrial groove.10 More typically, however, the node is lateral and inferior to the crest. When reconstructed from serial sections, it is found to take the form of a cigar, with a tail of varying dimensions extending down the terminal crest toward the orifice of the inferior caval vein (Figure 2A).8

Structure of Sinus Node in Other Mammals

The location of the sinus node is different in the hearts of smaller mammals.11–13 Nodal cells, instead of being located at the superior cavoatrial junction, occupy the full thickness of the intercaval area adjacent to the terminal crest, as shown by our recent reconstruction of the rabbit sinus node.11 The reconstruction, shown in Figure 3, reveals the node to be extensive.11 At its margins, zones of transitional cells, shown in blue in Figure 3, form the junction with the atrial muscle of the terminal crest.11 In the rat, the node is positioned differently: The bulk of it lies in the superior caval vein, at the crest of the right atrial appendage, and tails of nodal tissue extend down both the terminal crest and the interatrial groove, as occurs in some humans (see above).12 In the developing heart, the nodal primordium is extensive (Figure 4): In the mouse, as identified by marker genes such as the T-box transcription factor, Tbx3, a continuous tract of primary myocardium, the future nodal tissue, extends from the superior caval vein down the terminal crest (Figure 4, asterisk) to become continuous with the primary myocardium of the atrioventricular (AV) canal destined to form the AV node.14,15 This is consistent with the distribution of nodal tissue in the adult rabbit (Figure 3). The continuous tract of primary myocardium in the developing heart is suggestive of an “internodal tract,” such as that proposed by James16 to provide preferential conduction from the sinus node to the AV node. With the use of standard histological techniques in

![Figure 1](http://circ.ahajournals.org/)

![Figure 2](http://circ.ahajournals.org/)
the postnatal heart, however, it is not possible to identify any insulated atrial tracts, and much of the primary myocardium loses the histological features of nodal tissue as the embryo matures. Furthermore, in the postnatal heart, preferential conduction from the sinus node to the AV node, as well as into the left atrium, can adequately be explained on the basis of the orderly longitudinal packing of atrial myocytes in prominent muscular bundles, such as the terminal crest and Bachmann’s bundle.

Leading Pacemaking Site

Whereas in smaller mammals, the sinus node extends from the superior caval vein to the inferior caval vein (Figure 3), in the human, the node, as identified by histology, is more restricted and extends only part of the way down the terminal crest (Figure 2A). Functional studies, nonetheless, have suggested that the node in the human may be as extensive as in smaller mammals. As shown in Figure 5, in the human, as in other mammals, although the leading pacemaking site can be next to the superior caval vein, it can also be at any position between the superior and inferior caval veins. In the dog, total ablation of pacemaker activity requires the destruction of a block of tissue extending from the superior caval vein along the terminal crest to the inferior caval vein. It is well known that the position of the leading pacemaking site in the node shifts depending on conditions, such as autonomic nerve stimulation. It has been suggested that there is a hierarchy of pacemakers within the node, and the more superior the position, the faster is the heart rate. Stimulation of the sympathetic nervous system, for example, leads to a superior shift of the leading pacemaking site and an increase in heart rate. The potentially widespread distribution of nodal cells may also be important pathologically because ectopic sites along the terminal crest are known to be responsible for atrial tachycardia. Ablation of the sites abolishes the tachycardias.

Pacemaking Mechanisms

In Figure 6B and 6C, we show the sequence of atrial activation as measured in an experiment and as calculated with the anatomic model of the sinus node shown in Figure 3. The action potential, initiated in the center of the node, propagates via the periphery of the node into the musculature of the terminal crest. In the center of the node, the action potential is slow and small compared with the action potential in the surrounding atrial muscle (Figure 6A). Most importantly, during diastole, whereas in the atrial muscle there is a stable resting potential, in the node the membrane is more depolarized, and there is a pacemaker potential, ie, a further time-dependent depolarization (Figure 6A). This pacemaker potential is responsible for pacemaking because, on reaching threshold, it initiates the action potential. Electric activity varies throughout the node: In the periphery, the action potential is faster and larger, and, curiously, the intrinsic pacemaker activity is faster than in the center (Figure 6D). Early attempts to understand the mechanisms underlying pacemaking were made in the 1970s, and efforts to understand it continue today. It is a controversial topic, perhaps because there is no one dominating mechanism but rather many contributory mechanisms. The depolarization during the pacemaker potential is the result of inward current, although it is facilitated by the decay of outward current (Figure 7).

Inward Currents

In the center of the node, the action potential upstroke is slow (Figure 6A) because the myocytes express little or no Na current, $I_{Na}$. It is the L-type Ca current, $I_{Ca,L}$, that is
principally responsible for the upstroke. $I_{Na}$, nonetheless, is important. In the rabbit, evidence suggests that, although $I_{Na}$ is absent in the center of the node, it is present in the periphery. Block of $I_{Na}$ by tetrodotoxin (TTX) slows pacemaking in the periphery. $I_{Na}$ may be more important in the mouse sinus node: Two components of $I_{Na}$ have been recorded, a novel $Na^+$ current that is blocked by nanomolar concentrations of TTX and the classic cardiac $Na^+$ current that is blocked by micromolar concentrations of TTX. Block of both components slows pacemaking by approximately one third (Figure 7E) and also increases the sinus node conduction time, ie, the time taken for the action potential to propagate out of the node. It is possible, therefore, that $I_{Na}$ plays 2 roles in the node: in pacemaking, especially in the mouse, and in action potential conduction (if the node is to drive the surrounding atrial muscle, it must be able to provide sufficient inward current to stimulate the atrial muscle, and this may be the function of $I_{Na}$, especially in the periphery).

Block of $I_{Ca,L}$ abolishes the action potential in the center of the node (Figure 7A) because it is responsible for the action potential upstroke. The T-type $Ca^{2+}$ current ($I_{Ca,T}$) is also involved in pacemaking; it is possibly involved in the second half of the pacemaker potential. When $I_{Ca,L}$ is blocked by Ni$^{2+}$, spontaneous rate slows by $\approx 13\%$ in rabbit nodal cells (Figure 7C). The funny current, $I_f$, is also important. When $I_t$ is blocked, spontaneous rate slows by $\approx 14\%$ in the rabbit sinus node (Figure 7B). Procoralan, or ivabradine, a blocker of $I_f$, is now being marketed as the first pure heart rate–lowering cardiac agent.

The $Na^+\cdot Ca^{2+}$ exchanger is responsible for $Ca^{2+}$ extrusion (Figure 7D). The total charge carried by inward $I_{NaCa}$ is substantial: approximately half that carried by $I_{Ca,L}$ and $I_{Ca,T}$, if the myocyte is to be in $Ca^{2+}$ balance. If the extrusion of $Ca^{2+}$ occurs in diastole, inward $I_{NaCa}$ may make an important contribution to pacemaking. The source of $Ca^{2+}$ that drives its extrusion via the exchanger is release from the sarcoplasmic reticulum (SR). All investigators agree that effective block of this release by ryanodine slows pacemaking (Figure 7F). There is disagreement, nonetheless, over detail: whether $Ca^{2+}$ release from the SR speeds pacemaking simply by activating the exchanger or by acting on other ionic currents as well; whether the $Ca^{2+}$ release from the SR, critical for pacemaking, occurs spontaneously or in response to $I_{Ca,L}$; and whether complete block of the exchanger stops pacemaking or only slows it by $\approx 20\%$. Li$^-$ cannot substitute for $Na^+$ in $Na^+\cdot Ca^{2+}$ exchange, and abolition of inward $I_{NaCa}$ by substitution of extracellular $Na^+$ by Li$^-$ also results in a slowing of pacemaking. Recently, Vinogradova et al argued that spontaneous release of $Ca^{2+}$ from the SR, which drives pacemaking, occurs because the basal level of cAMP in the node is high. A heterozygous ankyrin-B knockout mouse shows both bradycardia and sinus dysrhythmia. Ankyrin-B is a membrane adaptor protein involved in the cellular organization of the $Na^+$ pump, the $Na^+\cdot Ca^{2+}$ exchanger, and the $IP_3$ receptor. Myocytes from the heterozygous ankyrin-B knockout mouse show disturbed intracellular $Ca^{2+}$ handling. Could the bradycardia be the result of a change in $I_{NaCa}$?

**Outward Currents**

The background inward rectifier $K^+$ current, $I_{K1}$, is largely responsible for the stable resting potential in the working
myocardium. Despite the presence of $I_{K,1}$, Purkinje fibers show $I_f$-dependent pacemaking, but the pacemaking is slow and not robust. Perhaps the most important factor responsible for the rapid and robust pacemaking of the node is the absence of $I_{K,1}$ within the node. During the action potential in the node, there is an activation of the rapid and slow delayed rectifier $K^+$ currents, $I_{K,r}$ and $I_{K,s}$; this helps to bring about repolarization and determines the maximum diastolic potential. During diastole, $I_{K,r}$ and $I_{K,s}$ decay slowly, facilitating the pacemaker potential by “uncovering” inward current. This is known as the $K^+$ decay hypothesis. In *Drosophila*, a background $K^+$ channel (2-pore $K^+$ channel, ORK1) has been shown to affect cardiac pacemaking.

**Ion Channels**

Ion channel expression in the sinus node has been studied at the mRNA and protein levels and, as expected, is radically different from that in the working myocardium.

**Na$^+$ Channels**

The cardiac Na$^+$ channel, Na,1.5, encoded by the SCN5A gene, is responsible for the classic cardiac Na$^+$ current that is blocked by micromolar concentrations of TTX. Consistent with the electrophysiology, in both the human (Figure 8A) and other mammals (Figure 9), Na,1.5 is present in the atrial muscle and the periphery of the node but absent from the center. Despite this, in the mouse, knockout of Na,1.5 results in bradycardia, an increase in sinus node conduction time, and frequent sinus node conduction block. Knockout of the Na$^+$ channel $\beta_2$ subunit also results in bradycardia. Recently, various brain-type Na$^+$ channels, including Na,1.1, have also been shown to be expressed in cardiac myocytes. They are blocked by nanomolar concentrations of TTX. Na,1.1, in contrast to Na,1.5, is present in the node as well as the atrial muscle. It is likely to be responsible for the component of Na$^+$ current in mouse sinus node blocked by nanomolar concentrations of TTX.

**Ca$^{2+}$ Channels**

In the working myocardium, Ca,1.2 ($\alpha_{1C}$) is the principal isoform responsible for $I_{Ca,L}$, but in the node, Ca,1.3 ($\alpha_{1D}$) may be the principal isoform. Ca,1.3 has a more negative threshold potential and may be more appropriate for pace-
Figure 7. Pacemaking mechanisms. A, Block of $I_{Ca,L}$ by 2 μmol/L nifedipine abolishes action potential. Data from rabbit sinus node tissue. B, Block of $I_f$ by 1 mmol/L Cs$^+$ slows pacemaking. Data from isolated rabbit sinus node cell. C, Block of $I_{Ca,T}$ by 40 μmol/L Ni$^{2+}$ slows pacemaking. Data from isolated rabbit sinus node cell. D, Summary of ionic currents and ion channels involved in pacemaking. E, Block of highly TTX-sensitive $I_{Na}$ (possibly carried by Na,1.1) and poorly TTX-sensitive $I_{Na}$ (presumably carried by Na,1.5) by low and high doses of TTX slows pacemaking. Data from isolated mouse sinus node cell. F, “Block” of Ca$^{2+}$ release from the SR by ryanodine slows pacemaking. Data from isolated guinea pig sinus node cell. Rigg and Terrar.35 Panel A reproduced from Kodama et al31 with permission from the American Physiological Society. Copyright 1997. Panel B courtesy of J.C. Denyer (doctoral thesis).32 Panel C reproduced from Hagiwara et al33 with permission from Blackwell Publishing. Copyright 1988. Panel E reproduced from Lei et al34 with permission from Blackwell Publishing. Copyright 2004. Panel F reproduced from Rigg and Terrar35 with permission from Blackwell Publishing. Copyright 2004.
making. In the mouse, knockout of Cav1.3 causes bradycardia and sinus dysrhythmia, and this is linked to abolition of the major component of $I_{Ca,L}$ activating at negative voltages.51,52 Cav3.1 and Cav3.2 channels are responsible for $I_{Ca,T}$ in heart. In the mouse, Cav3.1 mRNA is $\approx 30$ times more abundant in the node than in the atrial muscle. Cav3.2 mRNA, although less abundant, is also more abundant in the node than in the atrial muscle.53 In the mouse, knockout of Cav3.1 abolishes $I_{Ca,T}$ in nodal cells, causes a bradycardia in vivo, slows the intrinsic heart rate in vivo, prolongs the sinus node recovery time, and slows pacemaking in vitro.54

**HCN Channels**

HCN channels (HCN1, HCN2, and HCN4) are responsible for $I_f$ in nodal cells.57 In vivo there is no significant bradycardia, but there is sinus dysrhythmia.57 HCN knockout mice die before birth, but the embryos exhibit a severe bradycardia and an $85\%$ decrease in cardiac $I_f$.58

**K$^+$ Channels**

In the rabbit, at least, there is a slowly recovering transient outward current, $I_{to}$, in the atrial muscle and a rapidly recovering one in the node.59 Consistent with this, there is a switch from $K_{1.4}$ in the atrial muscle to $K_{4.2}$ in the node.50 $K_{1.5}$ is responsible for ultrarapid delayed rectifier $K^+$ current, an important repolarizing current in the atrium. In the guinea pig, it is expressed in the node as well as the atrium.60 Consistent with the electrophysiology, both ERG (responsible for $I_{K_{ERG}}$) and $K_{LQT1}$ (responsible for $I_{K_{LQT}}$) mRNA are expressed in the rabbit sinus node, and expression is higher than in the atrial muscle.50 $K_{2}$ channels, responsible for $I_{K_{2}}$, are not expected to be expressed in the node. Possible evidence of such a restriction of expression comes from a study of a transgenic mouse overexpressing $K_{2.1}$ (Figure 10A).61 Figure 8C shows that, in the human, $K_{2.1}$ (this time the native channel) is indeed not expressed in the node, although it is expressed in atrial muscle. Evidence suggests that, whereas the abundance of $K_{3.1}$ and $K_{3.4}$, responsible for acetylcholine-activated $K^+$ current, $I_{K_ACh}$, is equal in the node and atrial muscle, the abundance of Kir6.2 and SUR2A, responsible for ATP-sensitive $K^+$ current, $I_{K_{ATP}}$, may be reduced in the node compared with in the atrial muscle.50,62

**Gap Junctions**

Whereas electric coupling in the working myocardium is strong, facilitating rapid conduction of the action potential, electric coupling within the sinus node is poor, and consequently conduction is slow.64 This is important functionally because it protects the pacemaking tissue from the hyperpolarizing influence of the surrounding atrial muscle.64 If electric coupling was uniformly poor throughout the node, the node would be unable to drive atrial muscle. It has been postulated, therefore, that there should be strong electric coupling at the periphery of the node.64 Gap junction channels, composed of connexins, are responsible for electric coupling between myocytes. In the atrial muscle, the strong electric coupling is the result of the abundant expression of Cx43 and perhaps Cx40, which form medium and large conductance channels.63 In the center of the node, electric coupling is weak because Cx43 and Cx40 are either absent or poorly expressed (eg, Figure 10B).63 Cx45, which forms small conductance channels, is expressed in the center of the node instead.63 Recently, Cx30.2 has been found to be expressed abundantly in the mouse conduction system, whereas it is weakly expressed in the working myocardium.65 Cx30.2 forms small conductance homomeric channels and small conductance heteromeric channels with Cx43 and Cx40.65 There is evidence that electric coupling is stronger in the periphery of the node: In the rabbit, 3 connexins (Cx40, Cx45, and Cx43) are expressed in the periphery.63 In various species, including humans, interdigitations of atrial and nodal cells in the periphery of the node have been reported.63 It has been suggested on theoretical grounds that these interdigita-
tions permit the node to drive the surrounding atrial muscle and at the same time to be protected from the hyperpolarizing influence of the atrial muscle. In Cx40 knockout mice, there is evidence of bradycardia, sinus node exit and entry block, and a prolongation of the sinus node conduction time.

New Insights

Familial Sick Sinus Syndrome

As explained above and as summarized in the Table, the knockout of various ion channel and gap junction subunits in transgenic mice has been shown to result in a sick sinus syndrome phenotype, with bradycardia, sinus dysrhythmia, and sinus node exit block. These studies raise the possibility that sick sinus syndrome as seen clinically is related to problems with ion channels and gap junctions. In the case of familial sick sinus syndrome, at least, the disease has been shown to be the result of mutations in ion channels (Table). Various families have been identified with sick sinus syndrome linked to mutations in Nav1.5 (Figure 11A). This is paradoxical because Nav1.5 is absent from the center of the node (Figure 8A). The dysfunction must be the result of impaired function of Nav1.5 at the periphery of the node (Figure 9). In addition, in patients, sinus bradycardia/sick sinus syndrome has also been linked to mutations in HCN4 and ankyrin-B.

Sick Sinus Syndrome and Aging

Because the syndrome is age dependent, it is possible that the disease can be no more than an exaggeration of the normal aging process. The function of the node is known to decline during aging in both humans and other mammals. This is manifested as a decrease in the intrinsic heart rate and an increase in the sinus node conduction time. The age-dependent changes in the node could be the result of changes in ion channels and gap junctions. It has been argued that the presence of Na1.5 (Figure 9) and INa in the periphery of the node is important for the node to be able to drive the surrounding atrial muscle. An age-dependent slowing of the action potential upstroke in the periphery of the rabbit sinus node is evidence of a loss of INa from the periphery during

References 43, 47, 48, 51, 52, 54, 57, 58, 67–75.
aging, and this could help to explain the deterioration in nodal function, ie, the increase in sinus node conduction time and sinus node exit block.78 There is an increase in action potential duration in the rabbit and cat sinus node during aging;77 is this the result of an age-dependent decrease in Kv1.5 observed in the rat sinus node?79 In the guinea pig, there is a decrease in the expression of Cx43 in the region of the node during aging, with an 14-fold increase in the area of nodal tissue without Cx43.80 Like the suggested loss of I_{Na} from the node during aging, this could help to explain the increase in the sinus node conduction time and occurrence of sinus node exit block with aging.80

**Remodeling of the Sinus Node in Heart Failure and Atrial Fibrillation**

In the United States, up to 5 million patients experience congestive heart failure, and sudden cardiac death is a significant problem in this population.81 Bradyarrhythmias account for almost half of the sudden deaths in the hospital.81 It is now known that heart failure results in significant remodeling of the node.81,82 In the human, dog, and rabbit, there is a decrease in the intrinsic heart rate during heart failure.81,83–85 Sanders et al81 demonstrated that, in patients with congestive heart failure as well as a decrease in the intrinsic heart rate, there is an increase in the corrected sinus node recovery time, a caudal shift of the leading pacemaker site, fractionated electrograms or double potentials along the terminal crest, a decrease in the amplitude of the electrograms along the terminal crest, and abnormal propagation of the action potential from the node. Changes in sensitivity of the node to acetylcholine and vagal stimulation have been observed in heart failure in the rabbit and dog.82,84 With heart failure, in the rabbit, block of I_f by zatebradine causes a

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**Figure 11.** A, B, Mutations in Na_{1.5} and HCN4 known to be responsible for sinus bradycardia/sick sinus syndrome in patients. C, Stimulus-evoked action potential in control ventricular myocyte (top) and spontaneous action potentials in Kir2.1AAA-transduced myocyte with suppressed I_{K1}, (bottom). Reproduced from Miake et al76 with permission from the Nature Publishing Group, Macmillan Publishers Ltd. Copyright 2002.
Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and in the atria is well known to result in an electrophysiological remodeling. Clinical studies have shown that sick sinus syndrome is frequently associated with AF and atrial flutter, the “bradyarrhythmia-tachyarrhythmia syndrome.”

Attractive possibility could be the transfer of an appropriate gene into the node itself to correct sick sinus syndrome. If this is the case, manipulation of the expression of the genes regulating the ion channels in the node could be an indication for pacemaker implantation. These ion channel genes in the working myocardium have been reported in the human. For example, symptomatic prolonged sinus pauses on termination of AF are an indicator for pacemaker implantation. In these patients, however, after AF ablation, there is a significant improvement in nodal function (increase in heart rate, maximal heart rate and heart rate range, and decrease in corrected sinus node recovery time). This corresponds to a recovery of the node from remodeling during AF. In patients, termination of chronic atrial flutter by ablation also leads to recovery of nodal function. In the human, rapid atrial pacing for only 10 to 15 minutes alters nodal function.

**Future Directions**

Sick sinus syndrome is a collection of conditions with multiple causes. Although degenerative fibrosis may be an important cause, it is clear that ion channels underlie the familial disease, as well as the variants related to heart failure and AF. They may also be important in the aging-related syndrome. If this is the case, manipulation of the expression of the genes regulating the ion channels in the node could be a powerful therapeutic tool. Recently, there has been much interest in generating a “biopacemaker” by manipulation of ion channel genes in the working myocardium. To date, attention has focused on either knocking out K\(_{\text{ATP}}\) or K\(_{\text{IR1}}\), because K\(_{\text{IR1}}\) is not expressed in the node (eg, Figure 8C), or expressing an HCN channel because HCNs are abundantly expressed in the node (eg, Figure 8B).

An example of the conversion of a ventricular cell into a biopacemaker (by knocking out K\(_{\text{IR1}}\)) is shown in Figure 11C. There are, however, many differences in the expression of ion channels between the sinus node and working myocardium, as we have explained above, and perhaps >1 ion channel has to be manipulated to make an effective and robust new pacemaker. An alternative and potentially more attractive possibility could be the transfer of an appropriate gene into the node itself to correct sick sinus syndrome.

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