Impaired Impulse Propagation in Scn5a-Knockout Mice
Combined Contribution of Excitability, Connexin Expression, and Tissue Architecture in Relation to Aging

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Background—The SCN5A sodium channel is a major determinant for cardiac impulse propagation. We used epicardial mapping of the atria, ventricles, and septae to investigate conduction velocity (CV) in Scn5a heterozygous young and old mice.

Methods and Results—Mice were divided into 4 groups: (1) young (3 to 4 months) wild-type littermates (WT); (2) young heterozygous Scn5a-knockout mice (HZ); (3) old (12 to 17 months) WT; and (4) old HZ. In young HZ hearts, CV in the right but not the left ventricle was reduced in agreement with a rightward rotation in the QRS axes; fibrosis was virtually absent in both ventricles, and the pattern of connexin43 (Cx43) expression was similar to that of WT mice. In old WT animals, the right ventricle transversal CV was slightly reduced and was associated with interstitial fibrosis. In old HZ hearts, right and left ventricle CVs were severely reduced both in the transversal and longitudinal direction; multiple areas of severe reactive fibrosis invaded the myocardium, accompanied by markedly altered Cx43 expression. The right and left bundle-branch CVs were comparable to those of WT animals. The atria showed only mild fibrosis, with heterogeneously disturbed Cx40 and Cx43 expression.

Conclusions—A 50% reduction in Scn5a expression alone or age-related interstitial fibrosis only slightly affects conduction. In aged HZ mice, reduced Scn5a expression is accompanied by the presence of reactive fibrosis and disarrangement of gap junctions, which results in profound conduction impairment. (Circulation. 2005;112:1927-1935.)

Key Words: fibrosis • gap junction • sodium channel • aging • conduction

The voltage-gated sodium channel is the key determinant of cardiac excitability. The amplitude of the sodium current determines the upstroke velocity of the action potential and, in conjunction with the expression/distribution of gap junction channels and the structural organization of the collagenous skeleton, the conduction velocity (CV) of the electrical impulse. The SCN5A gene encodes the pore-forming α-subunit of the cardiac sodium channel. Haplo-insufficiency in SCN5A has been associated with the inherited Lenègre disease1 (also called progressive cardiac conduction defect) and with the Brugada syndrome.2,3 In patients with inherited Lenègre disease, the conduction of the cardiac impulse is abnormally slow and becomes progressively slower with aging, ultimately leading to atroventricular block and pacemaker implantation in the elderly.1,4 A comparable conduction defect has also been associated with the SCN5A-related Brugada syndrome.5 In both situations, alteration in conduction largely predominates in the right ventricle (RV).

A mouse model with targeted disruption in Scn5a has been established.6 At the homozygous state, mice are not viable and die before birth. In contrast, heterozygous Scn5a-deficient mice live and reproduce normally. In preceding reports, we have shown that Scn5a+/− mice have ventricular conduction slowing and ventricular arrhythmias8 and that Scn5a+/− mice recapitulate many aspects of the inherited Lenègre disease, including the age-related progressive conduction slowing.9 Surprisingly, we found that the progressive alteration in conduction was associated with myocardial...
rearrangements including extensive fibrosis. In the present work, we have further characterized the conduction defect in young and old Scn5a<sup>+/-</sup> mice by making use of epicardial mapping in association with immunohistochemistry. This investigation demonstrates the following: (1) The conduction defect resides in the ventricles, whereas bundle-branch CV is unaffected; (2) conduction slowing preferentially concerns the RV, which coincides with the predominant phenotype in inherited Lenègre disease and Brugada syndrome patients; and (3) the severity of cardiac sodium channel dysfunction becomes manifest in the presence of an age-related increase in collagen deposition accompanied by a disturbed pattern of expressed gap junctions. The present study provides an experimental ground to support further evaluation of the therapeutic potential of drugs that prevent myocardial fibrosis, in the context of channelopathies related to loss-of-function SCN5A mutations.

**Methods**

**Animals**

Heterozygous Scn5a-knockout mice (HZ), generated in Cambridge, United Kingdom, were bred at l’Institut du Thorax, Faculté de Médecine, Nantes, France. All experiments were performed on adult sex- and age-matched HZ and wild-type (WT) mice from the same litter (as controls). Mice were divided in 4 groups depending on age and the electrode grid was positioned on the interventricular septum just below the atrioventricular valves. The effective refractory period (ERP), the longest coupling interval of the premature stimulus that failed to activate the entire heart, was determined for each site of stimulation separately. Every sixteenth stimulus was followed by 1 premature stimulus. Starting at 140 or 90 ms (for BCL 150 or 100 ms, respectively), the coupling interval of the premature stimulus was reduced in steps of 10 or 5 ms (for BCL 150 or 100 ms, respectively) until ERP.

**Data Analysis**

The moment of maximal negative dV/dt in the unipolar electrograms was determined with custom-written software based on Matlab (The Mathworks Inc), selected as the time of local activation and activation maps were constructed. CVs of the ventricles in longitudinal (parallel to the fiber orientation) and transversal (perpendicular to the fiber orientation) directions and of the atria in the transversal direction were determined from the paced activation maps. Activation times of at least 4 consecutive electrode terminals along lines perpendicular to intersecting isochronal lines were used to estimate CVs. Dispersion of conduction was assessed for the LV and RV.

**Preparation of Hearts for Langendorff Perfusion**

Mice were anesthetized by an intraperitoneal injection of urethane (2 g/kg body weight). The heart was excised, prepared, and connected to a Langendorff perfusion setup as described previously.

**Electrophysiological Parameters of Young and Old Scn5a<sup>+/-</sup> and Scn5a<sup>-/-</sup> Mice**

<table>
<thead>
<tr>
<th></th>
<th>Young WT</th>
<th>Young HZ</th>
<th>Old WT</th>
<th>Old HZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA CV</td>
<td>30.25±2.37 (n=8)</td>
<td>22.46±1.94 (n=5)*</td>
<td>30.4±2.81 (n=8)</td>
<td>23.6±1.19 (n=6)</td>
</tr>
<tr>
<td>LA CV</td>
<td>29.69±3.5 (n=8)</td>
<td>28.9±2.08 (n=8)</td>
<td>29.6±2.00 (n=10)</td>
<td>23.2±1.2 (n=10)</td>
</tr>
<tr>
<td>RBB CV</td>
<td>35±2.16 (n=5)</td>
<td>33.2±2.9 (n=3)</td>
<td>31.2±2.25 (n=3)</td>
<td>32.5±5.5 (n=2)</td>
</tr>
<tr>
<td>LBB CV</td>
<td>37.4±4.86 (n=6)</td>
<td>40.7±2.74 (n=3)</td>
<td>36.3±2.95 (n=5)</td>
<td>38.2±2.8 (n=5)</td>
</tr>
<tr>
<td>RV longitudinal CV</td>
<td>32.7±1.9 (n=10)</td>
<td>26.5±1.54 (n=7)*</td>
<td>30.1±1.99 (n=9)</td>
<td>21.4±1.76 (n=12)*</td>
</tr>
<tr>
<td>RV transversal CV</td>
<td>23.2±1.3 (n=10)</td>
<td>18.3±1.32 (n=7)*</td>
<td>17.5±0.59 (n=10)</td>
<td>11.2±1.07 (n=12)*†</td>
</tr>
<tr>
<td>RV AR</td>
<td>1.43±0.1 (n=10)</td>
<td>1.47±0.09 (n=7)</td>
<td>1.76±0.11 (n=9)</td>
<td>2.02±0.20 (n=12)†</td>
</tr>
<tr>
<td>LV longitudinal CV</td>
<td>36.2±2.77 (n=9)</td>
<td>30.1±3.58 (n=6)</td>
<td>34.6±2.06 (n=9)</td>
<td>23.1±1.59 (n=12)*</td>
</tr>
<tr>
<td>LV transversal CV</td>
<td>20.3±1.22 (n=10)</td>
<td>19.7±1.22 (n=6)</td>
<td>18.6±1.42 (n=9)</td>
<td>13.2±1.09 (n=12)*†</td>
</tr>
<tr>
<td>LV AR</td>
<td>1.81±0.1 (n=8)</td>
<td>1.5±0.12 (n=6)</td>
<td>1.92±0.14 (n=9)</td>
<td>1.89±0.21 (n=12)</td>
</tr>
<tr>
<td>RA ERP</td>
<td>40.8±6.45 (n=12)</td>
<td>55.7±3.69 (n=7)</td>
<td>46.7±4.71 (n=9)</td>
<td>60.4±4.47 (n=11)</td>
</tr>
<tr>
<td>LA ERP</td>
<td>43.8±7.16 (n=12)</td>
<td>62.5±7.26 (n=6)</td>
<td>71±5.86 (n=10)†</td>
<td>69.1±6.67 (n=11)</td>
</tr>
<tr>
<td>RV ERP</td>
<td>54.6±1.9 (n=12)</td>
<td>68.1±3.77 (n=8)*</td>
<td>68.3±2.04 (n=9)†</td>
<td>78.5±3.27 (n=13)*†</td>
</tr>
<tr>
<td>LV ERP</td>
<td>71.4±4.04 (n=7)</td>
<td>70±4.47 (n=6)</td>
<td>80.5±3.2 (n=10)</td>
<td>94.7±4.96 (n=15)*†</td>
</tr>
</tbody>
</table>
ANOVA, with Holm-Sidak post hoc test with SigmaStat 3.11 (Systat). RV and LV ERPs and right and left bundle-branch CVs were compared by a Mann-Whitney rank sum test. All data are expressed as mean±SEM, and probability values <0.05 were considered statistically significant.

ECG Recording and QRS Axis Measurement
Our method to record mouse ECG (leads I, II, and III) can be found elsewhere.7 The QRS axis was calculated for 12 young Scn5a+/− mice and 19 WT littermates. For each lead, the QRS complex surface area of an average beat was measured and plotted as a vector on an Einthoven triangle. The electrical axis of the QRS complex was then determined as the resultant of the 3 vectors.

Immunohistochemistry and Histology
After excision, hearts were rapidly frozen in liquid nitrogen and stored at −80°C. For each of the 4 groups, 6 hearts were sectioned serially to generate sections of 10 μm thickness. Sections taken from different levels were incubated with antibodies as reported previously.9 After immunolabeling, sections were mounted in Vectashield (Vector Laboratories) and examined with a classic light microscope with epifluorescence equipment (Nikon Optiphot-2). To evaluate the presence of fibrosis, sections serial to the ones used for antibody labeling were fixed with 4% paraformaldehyde (in PBS, 30 minutes at room temperature) and stained with Pico Sirius red.13

Antibodies
We used mouse monoclonal antibodies raised against connexin (Cx) 43 (Transduction Laboratories) and rabbit polyclonal antibodies raised against Cx40 (Alpha Diagnostics). Secondary antibodies (Texas Red and FITC conjugated whole IgG) were purchased from Jackson Laboratories.

Results
Ventricular Conduction and Refractoriness
Typical activation maps of the LV and RV are illustrated in Figure 1. Crowding of isochronal lines in both LV and RV activation maps was most prominent in old HZ animals. The Table shows the average values for CV and ERP of the atria, bundle branches, and ventricles. Significant differences for separate groups are indicated, whereas the 2 rightmost columns indicate the overall effects of age and genotype. In young mice, longitudinal and transversal CVs of the RV were significantly reduced in HZ mice, whereas the anisotropic ratio (longitudinal CV divided by the transversal CV) was unchanged. In the LV of young mice, both longitudinal and transversal CVs were unaltered. Predominant alteration of the RV CV was in agreement with the rightward shift of the QRS axes as measured in surface ECG recordings (Figure 2). QRS axes of WT mice clustered in the left inferior quadrant, with an average value of 75±6°. In contrast, most HZ mice had a rightward deviation of their QRS axis, with an average value of 121±25°. The QRS axis of old HZ mice was much more...
atrial CV was not significantly different between the 4 groups except for RA, where a reduction in CV due to genotype was found (Table). ERP in the LA of old WT mice was increased significantly compared with young mice (Table). In the RA, there was an overall increase in ERP due to genotype, but for the separate groups (young HZ versus young WT and old HZ versus old WT), statistical significance was not reached.

**Ventricular Distribution of Fibrosis and Expression of Gap Junction Proteins**

Histochemical analysis was performed to reveal the presence of fibrosis in relation to the expression pattern of Cx43, which constituted the main conductive gap junction channels in the ventricles. In young mice, either WT or HZ, ventricular fibrosis (red staining) was virtually absent (Figure 4A). As shown in Figure 4B, old WT hearts demonstrated interstitial fibrosis as tiny strands between the muscle fibers. In contrast, fibrosis in old HZ hearts was largely increased as compared with either young HZ or old WT hearts. In addition to increased interstitial fibrosis (arrowhead), Sirius red staining showed a different pattern of reactive fibrosis (asterisk), which was heterogeneously present throughout the LV free wall, RV free wall, and interventricular septum. This pattern was found in 6 of 6 old HZ hearts. In contrast, small spots of reactive fibrosis could be detected in only 1 of 6 old WT hearts.

Immunolabeling of sections serial to the ones used for evaluation of fibrosis revealed a regular and comparable pattern of Cx43 in young WT and HZ hearts (Figure 4A). In old WT hearts with mild interstitial fibrosis (Figure 4B, upper left), Cx43 expression was gathered in large plaques in a regular distribution (Figure 4B, upper right) comparable to the patterns observed in young WT and HZ hearts. In old HZ hearts, fibrosis was heterogeneous and locally massive (Figure 4B, lower left). In areas with severe deposition of fibrosis, Cx43 was downregulated, whereas the remaining Cx43 showed an irregular pattern (Figure 4B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 in young WT and HZ hearts (Figure 4A). In addition to Cx43, the deposition of fibrosis aligned with the expression pattern of Cx43, which was heterogeneously present throughout the LV free wall, RV free wall, and interventricular septum. This pattern was found in 6 of 6 old HZ hearts. In contrast, small spots of reactive fibrosis could be detected in only 1 of 6 old WT hearts. This pattern clearly differed from that found in tissue forming the borderzone between nonfibrotic and fibrotic tissue. Here, labeling was more diffuse (Figure 5C) and not gathered in distinct gap junction plaques that might be indicative for redistribution (arrow). Central in a fibrotic spot, the remaining viable myocytes still expressed low amounts of Cx43, whereas the remaining Cx43 showed an irregular pattern (Figure 5B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 that was close to normal (Figure 5B), comparable to the expression pattern found in old WT hearts. This pattern clearly differed from that found in tissue forming the borderzone between nonfibrotic and fibrotic tissue. Here, labeling was more diffuse (Figure 5C) and not gathered in distinct gap junction plaques that might be indicative for redistribution (arrow). Central in a fibrotic spot, the remaining viable myocytes still expressed low amounts of Cx43, whereas the remaining Cx43 showed an irregular pattern (Figure 5B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 that was close to normal (Figure 5B), comparable to the expression pattern found in old WT hearts. This pattern clearly differed from that found in tissue forming the borderzone between nonfibrotic and fibrotic tissue. Here, labeling was more diffuse (Figure 5C) and not gathered in distinct gap junction plaques that might be indicative for redistribution (arrow). Central in a fibrotic spot, the remaining viable myocytes still expressed low amounts of Cx43, whereas the remaining Cx43 showed an irregular pattern (Figure 5B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 that was close to normal (Figure 5B), comparable to the expression pattern found in old WT hearts. This pattern clearly differed from that found in tissue forming the borderzone between nonfibrotic and fibrotic tissue. Here, labeling was more diffuse (Figure 5C) and not gathered in distinct gap junction plaques that might be indicative for redistribution (arrow). Central in a fibrotic spot, the remaining viable myocytes still expressed low amounts of Cx43, whereas the remaining Cx43 showed an irregular pattern (Figure 5B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 that was close to normal (Figure 5B), comparable to the expression pattern found in old WT hearts. This pattern clearly differed from that found in tissue forming the borderzone between nonfibrotic and fibrotic tissue. Here, labeling was more diffuse (Figure 5C) and not gathered in distinct gap junction plaques that might be indicative for redistribution (arrow). Central in a fibrotic spot, the remaining viable myocytes still expressed low amounts of Cx43, whereas the remaining Cx43 showed an irregular pattern (Figure 5B, lower right). Because of the heterogeneous character of fibrotic deposition in the old HZ hearts (Figure 5A), areas existed with an expression pattern of Cx43 that was close to normal (Figure 5B), comparable to the expression pattern found in old WT hearts.
in adult working ventricular cardiomyocytes. Figures 6A and 6B show the results obtained in young and old hearts, respectively. In young mice (Figure 6A), a low amount of fibrosis was present in both bundle branches, which were positively labeled with Cx40 staining. With regard to the degree of fibrosis, no differences were observed between WT and HZ hearts or between the left and right bundles. Similar results were obtained with analysis of old HZ and WT hearts (Figure 6B). However, the overall degree of fibrosis that surrounded the myocytes composing the Cx40-positive bundle branches was increased compared with young hearts.

Atrial Distribution of Fibrosis and Expression of Gap Junction Proteins

Atrial expression patterns of the gap junction proteins Cx40 and Cx43 were analyzed in young (Figure 7A) and old hearts (Figure 7B) of both genotypes. In young WT and HZ atria, the expression of Cx40 and of Cx43 was highly comparable. In old HZ mice, however, atrial expression of both Cx40 and Cx43 differed from that in old WT hearts. Both isoforms were regionally downregulated, and the pattern of expression was more diffuse for HZ than for WT atria. In young mice, atrial fibrosis was absent in both genotypes (Figure 7A, right; fibrosis in red). Although the general degree of atrial fibrosis in old mice was increased compared with young mice, no difference in degree of fibrosis was found between old WT and old HZ atria (Figure 7B, right panels) or between the LA and RA. In addition, reactive fibrosis such as that observed in old HZ ventricles was not found in the atria of all groups.

Discussion

Our mouse model, in which expression of Scn5a in the heart is genetically reduced by 50%, has been shown to have slowed ventricular conduction. Here, we report that al-
though there is slightly impaired conduction of the electrical impulse (mainly in the RV) in young heterozygous animals, it is only in older heterozygous animals that conduction becomes markedly impaired at the ventricular level. In those hearts, reduced expression of Scn5a was associated with increased fibrosis and a reorganized expression pattern of gap junction channels. Our observations indicate that only the synergism between reduced Scn5a expression, increased fibrosis, and impaired intercellular coupling leads to markedly decreased CV of the electrical impulse in the ventricles.

Determinants of Impulse Propagation

Intercellular coupling, sodium channel expression, and tissue architecture mediate propagation of the electrical impulse in cardiac tissue. Disturbances in one of these determinants may affect propagation of the electrical impulse and vulnerability for arrhythmias. However, a 50% reduction in expression of Cx43 per se does not affect impulse propagation in the mouse heart.11,16 Supported by a theoretical study,17 it has been shown that to induce electrical disturbances, the reduction has to be very robust11,18 or highly heterogeneous.19 Our recordings in Scn5a young heterozygous mice in the present study show that CV is only mildly affected by a 50% reduction in sodium channel expression, in agreement with previous observations.6 Finally, an increase of interstitial fibrosis by a factor of 4, as observed in old WT mice, also has only a mild effect on conduction. This indicates that CV integrity is preserved over a wide range of alterations in the determinants of conduction if only 1 of them is affected.

Location of Conduction Slowing

Widening of the QRS complex in the surface ECG of the heterozygous mice, as previously observed,6,7 could be due to impaired conduction in the bundle branches or ventricular myocardium. The present study shows that CV in the bundle branches of heterozygous mice is normal, whereas it is reduced in the ventricular myocardium. In addition, the study
affected. A 50% reduction in sodium channel expression alone only affects conduction in the RV significantly, albeit slightly (15%). Aging in the WT mice in the present study increased fibrosis by a factor of 4. This slightly reduced CV in the RV, but only in the transverse direction. This is compatible with other studies that show that the major effect of fibrosis on conduction is in the transverse direction. Normal transversal CV in the LV, as mentioned before, might be related to its greater wall thickness and the transmural rotation of the fiber direction.

The synergistic effects on conduction of decreased excitability and cell-cell coupling, in concert with increased collagen deposition, may be due to the following factors. Reactive fibrosis has been shown to give rise to tissue discontinuities, which may result in conduction delay due to a mismatch between current supply and demand. If demand surpasses supply, less current for excitation is available at the discontinuity, which delays conduction. Delay at the discontinuity will be further increased if less sodium current is available because of reduced Scn5a expression. Finally, the reduced cell-cell coupling caused by disturbed connexin expression reduces conduction even further.

Conduction Slowing in the Atria

In the atria of old heterozygous animals, a mild increase in fibrosis was observed similar to that found in old WT hearts. Atrial expression patterns of Cx40 and Cx43 in old WT hearts were comparable to those found in young WT animals, although expression of both isoforms in old Scn5a heterozygous atria was slightly aberrant. Both Cx40 and Cx43 were regionally reduced and irregularly distributed. Electrophysiological measurements showed a reduction of CV due to genotype in RA only. In both atria, there was no effect of age on conduction. The lack of dramatic effects of age on impulse propagation is likely related to the modest morphological alterations of the atria from old heterozygous hearts.

Comparison With Lenègre Disease and Brugada Syndrome

The heterozygous mouse model reveals some characteristics of Lenègre disease but differs in other aspects. The mouse model mimics Lenègre disease because the severity of conduction defects in the heterozygous mouse increases with age, as in Lenègre disease. In patients with inherited Lenègre disease, conduction slowing predominates in the RV, as in the mouse. Among a group of 25 Lenègre gene carriers, 9 had right bundle-branch block and 8 had parietal block, whereas only 2 had left bundle-branch block. The high incidence of parietal block (33%) suggests that in many patients, CV in the bundles remains close to normal. The mouse model differs from Lenègre disease, however, because in young and old heterozygous mice, CV in the bundle branches remains normal. In the mouse, fibrosis around the bundle branches increases with age, but there was no increased deposition of collagen within the bundle branches that could affect conduction. This opposes pathological observations made by Lenègre and Moreau. This difference might be related to the difference in size between mouse and human hearts. In the mouse, CV in the bundles is only slightly faster than in the ventricles (see the
Table, and the role of the bundles in propagating the impulse is less prominent than in humans. In the Brugada syndrome, alterations in conduction also predominate in the RV, and an aspect of right bundle-branch block in the right precordial leads is a common finding that leads to delayed contraction of the RV. Extensive fibrosis has been observed in an explanted heart of a patient with Brugada syndrome. Whether fibrosis participates in the pathophysiology of the Brugada syndrome remains to be established. Recently, several loss-of-function mutations in the \( \text{Scn5a} \) channel have been linked to triggering the onset of dilated cardiomyopathy in patients at middle age. In the mouse, the mechanisms that lead to structural changes are still unclear. We previously reported upregulation of \( \text{Atf3} \) in heterozygous mice. \( \text{Atf3} \), a member of the CREB/ATF family of transcription factors expressed at very low levels in the normal heart, has been shown to induce fibrosis and conduction abnormalities when overexpressed.

In conclusion, the present data show that CV is slightly reduced in young heterozygous \( \text{SCN5A} \)-knockout mice, in which only sodium channel expression is affected. In old HZ mice, reduced expression of cardiac sodium channels is accompanied by the presence of an age-related increase in collagen deposition and a disturbed pattern of expressed gap junctions, which results in pronounced conduction slowing at the ventricular level. The present study provides experimental grounds to support further evaluation of the therapeutic potential of drugs that prevent myocardial fibrosis in the context of channelopathies related to loss-of-function \( \text{SCN5A} \) mutations.

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References
Conduction Velocity in *Scn5a*-Knockout Mice

The cardiac electrical system is characterized by redundancy and substantial safety margins. A 50% reduction in sodium channel expression in ventricular myocardium slows conduction only marginally. Similarly, a reduction in connexin expression alone has limited effect on conduction. Thus, the heart has solid conduction reserve. A disease process that affects only 1 factor may not necessarily compromise conduction of the electrical impulse. However, cardiac diseases that produce electrical remodeling usually alter not only ion channels but also expression and distribution of gap junction channels that affect cell-to-cell coupling. In addition, aging is accompanied by reduced cellular coupling. These principles are well demonstrated in mice that are genetically engineered to have reduced cardiac sodium channels. The young animals have reduced sodium channels and relatively preserved conduction. With aging, the animals develop fibrosis and diminished cellular coupling, which is accompanied by a marked slowing of conduction. This model demonstrates how a cardiac ion channel abnormality can have little effect during youth but can become significant as fibrosis and cellular uncoupling develop with age or additional electrical remodeling. These findings imply that the clinical effect of a genetic or pathological process may be reduced by therapies that prevent or reduce structural remodeling and fibrosis.
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