Conduction Disturbances and Increased Atrial Vulnerability in Connexin40-Deficient Mice Analyzed by Transesophageal Stimulation

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Background—Recently, it has been reported that connexin40 (Cx40) deficiency in targeted mouse mutants is associated with a prolongation of P-wave and QRS complex duration on surface electrograms. The specific effects of Cx40 deficiency on sinus node function, sinoatrial, and atrioventricular conduction properties as well as on atrial vulnerability have not yet been investigated systematically by electrophysiological analysis.

Methods and Results—Fifty-two mice (18 Cx40+/+, 15 Cx40+/−, and 19 Cx40−/−) were subjected to rapid atrial transesophageal stimulation after anesthesia with avertin. A significant prolongation of sinus node recovery time was noticed in Cx40−/− mice compared with Cx40+/− and Cx40+/+ mice (287.8±109.0 vs 211.1±61.8 vs 204.4±60.9 ms; P<0.05). In addition, Wenckebach periodicity occurred at significantly longer atrial pacing cycle lengths in Cx40−/− mice than in Cx40+/− or Cx40+/+ mice (93.3±11.8 vs 83.9±9.7 vs 82.8±8.0 ms, P<0.05). Analysis of 27 Cx40−/− mice showed a significant increase in intra-atrial conduction time and atrioventricular conduction time compared with 52 Cx40−/− and 31 wild-type (Cx40+/+) mice. Furthermore, in Cx40−/− mice, atrial tachyarrhythmias could be induced frequently by atrial burst pacing, whereas no atrial arrhythmias were inducible in heterozygous or wild-type mice.

Conclusions—This study demonstrates that Cx40 deficiency is associated with sinoatrial, intra-atrial, and atrioventricular conduction disturbances. In atrial myocardium of the mouse, Cx40 deficiency results in increased atrial vulnerability and might contribute to arrhythmogenesis. (Circulation. 1999;99:1508-1515.)

Key Words: atrium ■ proteins ■ conduction ■ electrophysiology ■ arrhythmia

Adjacent cardiomyocytes are connected by gap junctions, which are clusters of intercellular channels consisting of a hexameric assembly of proteins known as connexins (Cx). These gap junctional channels are responsible for the electrical coupling of cardiac myocytes. The gap junctional permeability depends on the constituent connexin. In the mammalian heart, expression of Cx37, Cx40, Cx43, Cx45, Cx46, and Cx50 mRNAs was observed and Cx40, Cx43, and Cx45 protein was detected in cardiac myocytes. There are interspecies differences in expression of Cx40 and Cx43. In mammalian heart, Cx43 is highly expressed in myocytes but absent from sinus nodal and atrioventricular (AV) nodal tissue as well as from the proximal part of the ventricular conductive myocardium in adult mouse and rat. Cx40 is expressed in atrial myocytes and in the His-Purkinje system of the mouse heart. So far, expression of Cx40 in the mouse sinus node and the compact AV node has not been reported, but Cx40 was shown to be present in the canine sinus node. It was found that absence of gap junctions resulted in disturbances of pulse propagation in the heart. In heterozygous Cx43 mice, a reduced cardiac conduction velocity was reported. Recently we demonstrated that P-wave duration, PQ interval, and QRS duration were significantly prolonged in Cx40-deficient mice. These findings were supported by Simon and coworkers, who reported a high prevalence of PQ prolongation and the pattern of bundle-branch block during normal sinus rhythm in Cx40-deficient mice. However, the effects of Cx40 deficiency on cardiac pulse propagation under conditions other than sinus rhythm remain unclear.

Aside from disturbances of pulse propagation, abnormalities in connexin distribution, content, and phenotype may increase anisotropy and facilitate the occurrence of unidirectional conduction blocks and heterogeneous conduction delays. Unidirectional conduction blocks and conduction delays are well-known pathophysiological conditions for the development of tachyarrhythmias, based on reentrant phenomena. Accordingly, it has been hypothesized that molecular and structural alterations of gap junctions resulted in an increased myocardial vulnerability and are involved in the
pathophysiology of arrhythmias. This hypothesis was supported by findings from animal studies and by observations in humans with underlying heart disease. In human ventricular myocardium from hearts subject to chronic ischemia from coronary artery disease and to chronic pressure overload from aortic valve stenosis, the amount of Cx43 gap junctions was significantly reduced compared with normal ventricular myocardium.\(^{18}\) Both patients with coronary artery disease and patients with valvular heart disease are prone to the development of ventricular tachyarrhythmias. In the canine model, it was demonstrated that the distribution of Cx43 gap junctions was markedly altered throughout early remodeling of ventricular myocardium after infarction. In these studies, gap junctional disorganization correlated with the localization of the common central pathway of inducible ventricular reentrant tachycardias.\(^{19,20}\) In our study on 31 Cx40-deficient mice, 1 mouse showed a spontaneous atrial tachycardia.\(^{15}\) Aside from this observation, no data are available about the effects of Cx40 deficiency on atrial or ventricular vulnerability.

To evaluate cardiac pulse generation and propagation as well as susceptibility for atrial arrhythmias, electrophysiological testing by atrial stimulation is an established method. The electrophysiological effects of Cx40 deficiency have not yet been investigated. In the present study, Cx40-deficient mice were investigated by surface ECG recordings as well as by transesophageal atrial stimulation. The aim of the present study was to further analyze the impact of Cx40 deficiency on sinoatrial, intra-atrial, and atrioventricular conduction capabilities as well as on susceptibility for atrial reentrant arrhythmias in mice.

### Methods

**Cx40 Mutant Mice**

Cx40-deficient mice were generated by gene targeting as described previously.\(^{14}\) The genotypes of the mice were determined by polymerase chain reaction. All analysis was done on littermates generated by interbreeding mice heterozygous for Cx40.

**Animals, Anesthesia, and Preparation**

Male and female 8- to 16-week-old mice, weighing 25 to 35 g, were anesthetized by intraperitoneal injection of avertin (Sigma-Chemie; 1.25%, 0.02 mL per gram body weight). A surface 6-lead ECG was obtained by cutaneous clips at each of the 4 limbs of the spontaneously breathing mice. The ECG channels were amplified, filtered between 10 and 100 Hz, and sampled with a rate of 4 kHz (Bard Stamp amplifier; Bard LabSystem). The data were stored on optical disk. A warming light was used to stabilize body temperature.

**Surface Electrocardiographic Study**

Surface ECG recordings were obtained within a time frame of 5 minutes. The determination of time intervals was performed at the end of each registration period. Spontaneous cycle length was determined by averaging 10 consecutive R-R intervals. P-wave duration, PQ interval, QR duration, QRS duration, QT\(_{\text{max}}\), and QT interval were measured by determining the earliest onset and latest offset of atrial and ventricular deflection from 3 simultaneously recorded surface leads. As displayed schematically in Figure 1, QRS duration and QT\(_{\text{max}}\) interval were calculated from ECG tracings by measuring the duration between the onset of the QRS complex and the maximum/minimum of the S, R, and T waves regarding the most distinguishable tracing.

**Transesophageal Electrophysiological Study**

For the transesophageal electrophysiological study, a 2F pacing catheter with four 1-mm ring electrodes and an interelectrode distance of 2 mm (Arrow) was used. Bipolar recordings were obtained from the distal and the proximal electrode pairs. Unipolar recordings were obtained from each ring electrode. Unipolar pacing was performed at electrode 1 or 2. Rapid atrial pacing was performed with twice the diastolic threshold (Biotronik, UHS 20). The following pacing protocol was used: Initially, a constant atrial capture was documented. Subsequently, pacing was performed for 30 seconds with a pacing cycle length 10 ms shorter than the spontaneous cycle length. After a period of normal sinus rhythm, pacing was repeated with a pacing cycle length 10 ms shorter than the initial pacing cycle length. This was repeated with a consecutive reduction of the pacing cycle length until the minimum cycle length was reached that was required to maintain 1:1 AV conduction. For each pacing cycle length, sinus node recovery time was determined by measuring the interval between the last stimulus spike and the first spontaneous atrial depolarization after termination of pacing. In addition, the first spontaneous cycle length after sinus node recovery time was determined. In a subgroup of mice, atrial vulnerability was tested by high frequency atrial burst stimulation for 10 to 12 seconds, with a pacing cycle length of 25 ms. Burst pacing was repeated 10 times in each animal. Occurrence and duration of inducible arrhythmias were documented.

**Statistical Analysis**

Data are presented as mean±SD. A 1-way ANOVA and post hoc Tukey B tests were used for the comparison of ECG parameters. Probability values of <0.05 were considered statistically significant.

**Results**

**Surface ECG**

A total of 116 mice were anesthetized for surface ECG recordings. Two mice died shortly after intraperitoneal injection of avertin probably as the result of inadvertent intravascular injection. In 4 additional mice, ECG recordings were obtained, but these animals died during the waking-up period. These 6 mice were excluded from the study. Thus 110 mice were used for analysis. Among these, 31 were wild-type for...
Ca40 (Ca40+/−), 52 mice were heterozygous for Ca40 (Ca40+/−), and 27 were homozygous Ca40-deficient mice (Ca40−/−).

The results of the surface ECG recordings are summarized in Table 1. Individual data are displayed as scattergram in Figure 2. In Ca40−/− mice, the spontaneous cycle length was significantly longer compared with that observed in Ca40+/− mice. Though a tendency was found toward longer spontaneous cycle lengths, spontaneous cycle length was not statistically different between Ca40+/− and Ca40−/− mice. In 2 Ca40−/− mice, a spontaneous intermittent second-degree sinoatrial block was documented (Figure 3). Sinoatrial block was not found in Ca40+/− or Ca40+/− mice. The P-wave duration was shorter in both Ca40+/− and Ca40+/− mice than in Ca40−/− mice. The PQ interval was significantly longer in Ca40+/− mice compared with the PQ interval in Ca40+/− and Ca40+/− mice. In addition, 4 Ca40−/− mice showed a spontaneous second- or third-degree AV block (Figure 4). The QRS duration was significantly longer in Ca40−/− mice than in Ca40+/− and Ca40+/− mice. In summary, surface ECG recordings revealed prolonged atrial, AV, and ventricular conduction parameters in Ca40−/− mice compared with both Ca40+/− mice and Ca40+/− mice (Figure 5). In comparison to Ca40+/− mice, P-wave duration lengthened by 56% in Ca40+/− mice, PQ interval by 15%, and QRS duration by 30%. No significant differences were found between Ca40+/− and Ca40+/− mice.

In none of the wild-type Ca40 mice were spontaneous supraventricular or ventricular arrhythmias documented. One Ca40+/− mouse showed spontaneous isolated atrial premature beats. Ventricular arrhythmias were not found. In Ca40+/− mice, spontaneous arrhythmias were documented in 4 animals. Three Ca40+/− mice exhibited isolated atrial or ventricular premature beats, and 1 Ca40+/− mouse exhibited spontaneous atrial tachycardia with constant tachycardia cycle length (Figure 6).

Transesophageal Stimulation
Transesophageal atrial pacing was performed in 55 mice. Three mice were excluded from analysis because of anesthesia problems (1 mouse) or a sudden drop in heart rate caused by accidental endotracheal catheterization (2 mice). No further complications were noticed throughout or after the investigation. Thus 18 Ca40+/+, 15 Ca40+/−, and 19 Ca40−/− mice were studied.

The results of the transesophageal stimulation are summarized in Table 2. The individual results for 1:1 AV conduction time and sinus node recovery time are displayed as scattergrams in Figure 7. Transesophageal stimulation revealed that the 1:1 AV conduction time was significantly shorter in Ca40+/+ and Ca40+/− mice (Figure 8) compared with that observed in Ca40-deficient mice (Figure 9). Loss of 1:1 AV conduction was always associated with a Wenckebach periodicity. Relative to Ca40+/+ mice, the 1:1 AV conduction time was extended by 13% in Ca40−/− mice. No significant differences were detected in Ca40+/+ compared with Ca40+/− mice.

Strong evidence was found for a sinus node entry block resulting in an unaltered sinus nodal pulse generation despite an adequate atrial capture in 5 Ca40−/− mice during atrial stimulation for determination of sinus node recovery time. These mice had to be excluded from analysis. This phenomenon was not observed in Ca40+/+ or Ca40+/− mice. In the
remaining Cx40-deficient mice, the sinus node recovery time was found to be significantly longer than in Cx40$^{1/1}$ and Cx40$^{1/2}$ mice (Figure 10). Results in Cx40$^{1/1}$ mice and in Cx40$^{1/2}$ mice did not differ significantly.

Arrhythmia Detection

Atrial vulnerability was tested by atrial burst stimulation in 8 Cx40$^{1/1}$ mice, 8 Cx40$^{1/2}$ mice, and 8 Cx40$^{2/2}$ mice. In Cx40$^{1/1}$ and Cx40$^{1/2}$ mice, no evidence of inducible arrhythmias was found. In contrast, burst pacing resulted in atrial arrhythmias in 5 of 8 Cx40-deficient mice. One mouse showed a sustained, regular supraventricular tachycardia (Figure 11). This tachycardia was terminated by overdrive pacing and reinducible. Thus reentry had to be considered as the underlying pathophysiological mechanism. In 4 Cx40$^{2/2}$ mice, atrial burst pacing resulted in a nonsustained or sustained atrial arrhythmia with irregular R-R intervals and without distinct P waves (Figure 12). The heart rate was similar or lower during this arrhythmia than during normal sinus rhythm. All episodes spontaneously converted to normal sinus rhythm.

Discussion

In the present study, the effects of Cx40 deficiency on sinoatrial, intra-atrial, and AV nodal pulse propagation were studied with surface ECG recordings and transesophageal atrial stimulation. Five sets of results can be distinguished. First, Cx40 deficiency was associated with a spontaneous occurrence of sinoatrial blocks and with a prolongation of sinus node recovery time, all indicating a disturbance of sinoatrial electrophysiology. Second, Cx40 deficiency was associated with a disturbance of intra-atrial pulse propagation. Third, Cx40 deficiency was associated with a prolongation of PQ interval, with spontaneous second- or third-degree AV blocks, and with a prolongation of 1:1 AV conduction time, all indicating a decreased AV conduction capacity. Fourth, the QRS duration was significantly lengthened in Cx40-deficient mice. And finally, Cx40 deficiency was associated with an increased atrial vulnerability.

Sinoatrial Conduction Disturbances

Density of gap junctions is very low in the mammalian central sinus node.21–23 Expression of Cx40 was reported in the mammalian central sinus node.24–26 Table 2 shows the measurements of transesophageal ECG parameters: spontaneous cycle length, 1:1 AV conduction time, sinus node recovery time, and first spontaneous cycle length after SNRT in 18 C$^{+/-}$ wild-type mice, 15 C$^{1/1}$ mice heterozygous for C$^{x40}$, and 19 C$^{x40}$-deficient mice.

Table 2. Measurements of Transesophageal ECG Parameters: Spontaneous Cycle Length, 1:1 AV Conduction Time, Sinus Node Recovery Time, and First Spontaneous Cycle Length After SNRT in 18 C$^{+/-}$ Wild-Type Mice, 15 Mice Heterozygous for C$^{x40}$, and 19 C$^{x40}$-Deficient Mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C$^{+/-}$</th>
<th>C$^{1/1}$</th>
<th>C$^{x40}$</th>
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<tbody>
<tr>
<td>SCL, ms</td>
<td>125.6±15.3</td>
<td>123.2±15.1</td>
<td>139.6±22.3*</td>
</tr>
<tr>
<td>WP, ms</td>
<td>82.8±8.0</td>
<td>83.9±9.7</td>
<td>93.3±11.8*</td>
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<tr>
<td>SNRT, ms</td>
<td>204.4±60.9</td>
<td>211.1±61.8</td>
<td>287.8±109.0*</td>
</tr>
<tr>
<td>PESP, ms</td>
<td>142.1±20.3</td>
<td>140.5±18.1</td>
<td>164.2±38.2</td>
</tr>
</tbody>
</table>

SCL indicates spontaneous cycle length; WP, 1:1 AV conduction time; SNRT, sinus node recovery time; and PESP, first SCL after SNRT. *P<0.05 C$^{x40}$ vs C$^{+/-}$ and C$^{1/1}$. 

Figure 4. Typical surface ECG recordings of total AV block with stable ventricular escape rhythm in a Cx40$^{-/-}$ mouse. P indicates P wave; V, QRS complex. All intervals are expressed in milliseconds.

Figure 5. Representative ECG tracing of Cx40$^{1/1}$ (A) and Cx40$^{1/2}$ mice (B). All intervals are expressed in milliseconds. Note that P-wave duration, PQ interval, and QRS duration were prolonged in Cx40$^{-/-}$ mice.

Figure 6. Surface ECG recording of sustained supraventricular tachycardia with spontaneous onset (top) and termination (bottom) observed in a Cx40$^{-/-}$ mouse. Before onset and after termination of tachycardia, P waves (P) can be identified. Whereas QRS duration is identical during sinus rhythm and at the beginning of tachycardia, it exhibits a progressive prolongation throughout the course of the tachycardia.

Figure 7. Typical surface ECG recordings of total AV block with stable ventricular escape rhythm in a Cx40$^{-/-}$ mouse. P indicates P wave; V, QRS complex. All intervals are expressed in milliseconds.
the canine sinus node, but there are no data on the mouse sinus node. In this transesophageal electrophysiological study, strong evidence was found for a "communication boundary" between the central sinus node and the perinodal atrial myocardium. This conduction disturbance affected pulse propagation in either direction: from the sinus node to the atrium, as can be assumed from the occurrence of spontaneous sinoatrial blocks as well as from the atrial myocardium into the sinus node, as can be concluded from the high incidence of sinus node entry block during atrial stimulation. In addition, sinus node recovery time was significantly prolonged in Cx40-deficient mice.

Figure 7. Scattergram of 1:1 AV conduction time and maximum sinus node recovery time (SNRT) in Cx40+/+, Cx40−/−, and Cx40−−/− mice.

Figure 8. Determination of 1:1 AV conduction time by transesophageal atrial pacing in wild-type Cx40+/+ mouse. Recordings obtained during transesophageal atrial pacing in sinus rhythm with pacing cycle length of 105 ms (A), 95 ms (B), and 85 ms (C) in a Cx40+/+ mouse. S indicates stimulus artifact; V, ventricular deflection. During atrial pacing with pacing cycle length of 105 ms, 1:1 AV conduction with constant AV interval (SV interval) of 50 ms (A) is present. During atrial pacing with pacing cycle length of 95 ms, AV interval increases to 65 ms (B). Pacing with cycle length of 85 ms resulted in a Wenckebach periodicity with continuous prolongation of AV conduction time (75 ms, 82 ms) until atrial stimulation failed to result in ventricular deflection (*). Consequently, AV conduction properties have been recovered and AV conduction time is short again (60 ms, 63 ms).

Figure 9. Determination of 1:1 AV conduction time by transesophageal atrial pacing in a Cx40-deficient mouse. Recordings obtained during transesophageal atrial pacing in sinus rhythm with pacing cycle length of 100 ms. Abbreviations as in Figure 8. Atrial pacing with pacing cycle of 100 ms resulted in a Wenckebach periodicity with continuous prolongation of AV conduction time (90 to 140 ms) until atrial stimulation failed to result in ventricular deflection (*). Consequently, AV conduction properties have been recovered and AV conduction time is short again (80 ms). Note that pacing cycle length of 1:1 AV conduction time is longer in this Cx40−−/− mouse than that observed in Cx40−/− mice (see Figure 8).

Figure 10. Determination of sinus node recovery time (SNRT) after transesophageal atrial pacing in Cx40+/+ mouse (A) and Cx40−−/− mouse (B). Recordings obtained during transesophageal atrial pacing in sinus rhythm with pacing cycle length of 75 ms (A) and 105 ms (B). S indicates stimulus artifact; P, atrial deflection; V, ventricular deflection. In this example, termination of atrial pacing with pacing cycle length of 75 ms resulted in sinus node recovery time of 140 ms in Cx40−−/− mouse. In contrast, sinus node recovery time was markedly prolonged in Cx40−/− mice.

A. Cx40+/+

B. Cx40−−/−
Atrial Conduction Disturbances
Cx40 deficiency alters the passive electrical properties and electrophysiological characteristics of the cardiac tissue. In contrast to mice with normal Cx40 abundance and distribution, pulse propagation is decelerated in Cx40−/− mice. In this study, the P-wave duration was significantly prolonged in Cx40-deficient mice. This corresponds to the abundance of Cx40 in atrial myocardium. However, several details of the underlying pathophysiology remain unclear. A prolongation of the P wave could be the result of various mechanisms. One explanation would be a decrease of intra-atrial conduction velocity in terms of a delayed depolarization of consecutive cells without changing the vector of pulse propagation. This must be distinguished from a prolongation of conduction time caused by a conduction block with a consecutive prolongation of the length of activation way. Furthermore, it remains unclear whether P-wave prolongation accounts for effects of Cx40 deficiency in all atrial components or whether only specific, anatomically defined conduction pathways are affected.

Decreased AV Conduction Capacity
In Cx40−/− mice, the mean PQ interval was significantly longer than in Cx40+/− and Cx40+/+ mice. According to its definition, the PQ interval reflects conduction through the AV node as well as conduction from the high right atrium to the AV node and from the AV node through the His bundle to the proximal Purkinje system. Because the prolongation of PQ interval extended that of P-wave duration in most of the Cx40−/− mice, the PQ prolongation cannot be exclusively accounted for intra-atrial conduction delay. Thus a decreased AV nodal conduction velocity might be assumed. However, without an intracardiac recording of His bundle potentials, an additive effect of an intrahisian conduction delay cannot be ruled out. In addition to the conduction delay, a decreased 1:1 AV conduction capacity was found in Cx40-deficient mice. The 1:1 AV conduction time is a parameter of the effective refractory periods of the specific conducting tissue and independent of the AV conduction velocity. Loss of 1:1 AV conduction was associated with a typical Wenckebach periodicity. A Wenckebach periodicity occurs most commonly at the AV nodal level, whereas conduction disturbances at the His bundle mainly result in a 2:1 or 3:1 block. Though it cannot be proven without simultaneous His bundle recordings, this finding provides evidence that the AV node is involved in the electrophysiological effects of Cx40 deficiency. Since it is well known that the electrophysiological properties of the AV node rely on modulating influences of the so-called transitional AV nodal fibers, it might be hypothesized that the effects of Cx40 deficiency on the AV nodal conduction properties are mediated by a profound alteration of the input from perinodal tissue.

Delayed Conduction in His-Purkinje System or Ventricles
In Cx40−/−-deficient mice, the QR and QRS duration as well as QTmax and QT interval were significantly prolonged com-
pared with Cx40+/− and Cx40+/− mice. Because no evidence was found for the existence of Cx40 gap junctions in the ventricular working myocardium, it can be hypothesized that the observed prolongation of conduction time is due to a conduction delay in the bundle branches of the His-Purkinje system. However, to rule out the possibility of intraventricular conduction delay, determination of intraventricular conduction velocity would be necessary.

Arrhythmogenicity
It is well known that regional unidirectional conduction blocks and conduction delays facilitate the initiation and perpetuation of reentrant arrhythmias. In this context, conduction disturbances caused by alterations of gap junctional cell-to-cell communication seem to have an important impact on myocardial arrhythmogenicity. In the canine model, it was demonstrated that the origin of ventricular tachycardias caused by reentrant circuits correlated with the localization of disturbed Cx43 gap junctional distribution in the border zone of induced myocardial infarction.19,27 Under these conditions, the electrophysiological characteristics of individual myocytes in the peri-infarct tissue are found to be normal.28–31 Therefore, in that system, the key factor of arrhythmogenesis appeared to be a disturbance of cell-to-cell communication.

There is evidence that not only the type of gap junctional protein but also the pattern of heterotypic and heteromeric channel formation influences the flow of electrical current.25,26,31–33 An alteration in number and spatial distribution of myocyte gap junctions causes heterogeneous pulse propagation, which can induce conduction delay or block and tachyarrhythmias.15,18,19,27 A decrease in the number of gap junctions might alter end-to-end connections of the myocytes differently than site-to-site connections. Thus the conduction time may increase as a result of 2 different factors. First, the diminished number of gap junction channels could decrease the conduction velocity per se. Second, the vector of the electrical wave front is forced to change because of the lowered number of gap junctions resulting in prolonged activation ways.19,20,34,35 This results in a longer conduction time, a heterogenous pulse propagation, and an increased possibility to initiate and perpetuate tachyarrhythmias.

In wild-type mice, atrial or ventricular tachyarrhythmias were not inducible by atrial or ventricular stimulation.36 This finding is supported by the results of the present study. In none of the Cx40+/− or Cx40+/− mice were atrial arrhythmias inducible by atrial burst stimulation. In contrast, atrial tachyarrhythmias were frequently detected after atrial burst stimulation in Cx40+/− mice. This underlines the function of connexins in arrhythmogenesis. The documented arrhythmias can be divided into 2 different subgroups. One type was characterized by regular atrial activation and a fast, regular ventricular activation. In this tachycardia, termination by overdrive pacing gave strong evidence for an excitable reentrant circuit as underlying mechanism. The second type was characterized by a slow and irregular ventricular activation and an absence of distinct P waves. This arrhythmia terminated spontaneously. The irregularity of R-R intervals and the absence of P waves suggest atrial fibrillation as underlying arrhythmia. To date, atrial fibrillation is interpreted as the result of multiple coexisting intra-atrial reentrant wavelets. As yet, atrial fibrillation has not been observed in mice. It was assumed to be impossible in these species because the atrial myocardial mass was thought to be too small to maintain multiple coexisting reentrant wavelets under normal circumstances. However, the reentrant circuit is determined by the length of the activation way and the conduction velocity. A marked conduction delay caused by Cx40 deficiency may facilitate coexisting wavelets even in small atria.

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References


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