Electrophysiologic Effects of Lidocaine on Sinus Node and Atrium in Patients with and without Sinoatrial Dysfunction

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SUMMARY Electrophysiological studies were conducted in 13 patients with normal sinus node function and 14 with sinus node dysfunction before and after intravenous lidocaine. Mean ± SEM sinus cycle length significantly shortened from 810 ± 34.3 to 774 ± 34.3 msec in patients with normal sinus node (P < 0.001) and from 1061 ± 67.6 to 1016 ± 64.5 msec in patients with sinus node dysfunction (P < 0.025) after lidocaine. Mean sinus recovery time was 1027 ± 49.4 before and 1026 ± 52.5 msec after lidocaine in patients with normal sinus node (NS) and 1269 ± 97.7 before and 1170 ± 73.8 msec after lidocaine in patients with sinus node dysfunction (P < 0.05). Mean calculated sinoatrial conduction time was 87 ± 9.5 before and 90 ± 9.2 msec after lidocaine in patients with normal sinus node (NS) and 80 ± 10.3 before and 96 ± 10.2 msec after lidocaine in patients with sinus node dysfunction (P < 0.001). Mean atrial effective and functional refractory periods were not significantly changed with lidocaine.

Thus lidocaine shortened sinus cycle length in both groups, without affecting atrial refractoriness. Lidocaine appeared to depress perinodal tissue only in patients with sinus node dysfunction. The abbreviation of sinus recovery time in patients with sinus node dysfunction could reflect increased sinus automaticity and/or increased perinodal refractoriness, allowing entrance block to occur. This mechanism may explain why sinus arrest has been noted in some patients during lidocaine administration.

LIDOCAINE has been associated with the development of sinus arrest in some patients during or following intravenous administration.†‡ Despite this, only one systematic evaluation of lidocaine effects on human sinus node and atrium has been done.§

In the present study, we have used atrial stimulation techniques to evaluate the electrophysiological effects of lidocaine on sinus node and atrium in patients with and without sinus node dysfunction.

Methods

Patient Selection

The study group was composed of 27 patients undergoing electrophysiological studies because of suspected tachyarrhythmias (6), conduction defects (11), and sinoatrial dysfunction (10). Thirteen patients (1–13) were classified as having normal sinoatrial function. Criteria for inclusion in this group were as follows: 1) no history of documented atrial flutter or fibrillation; 2) absence of persistent sinus bradyarrhythmia, sinus nodal block, or sinus arrest; 3) normal sinus recovery times (less than 1680 msec) and calculated sinoatrial conduction times (less than 152 msec);10, 11 4) normal atrial effective and functional refractory periods (less than 350 and 400 msec) during sinus rhythm.12

Fourteen of the patients had sinoatrial dysfunction as defined by the presence of one or more of the following abnormalities: 1) persistent resting sinus bradycardia (sinus rates less than 60/min) (14 to 23); 2) documented recurrent episodes of sinoatrial block (24); 3) abnormal sinus nodal response to atrial extrastimulus testing, e.g., presence of only Zone I (nonreset due to interference) response with absence of sinus reset (25);13 4) prolonged atrial effective and functional refractory periods (26 and 27).

Electrophysiological Studies

All patients were in sinus rhythm and none had had cardiac medications for at least 72 hours before electrophysiological study. Five of the patients (6, 7, 9, 17 and 27) were on a maintenance dose (0.25 mg) of digoxin, which was withheld three days before the study. Informed written consent was obtained from all patients. His bundle electrograms were recorded using a tripolar catheter passed through a femoral vein.14 A quadripolar catheter was positioned at the high right atrium near the vicinity of sinus node for atrial pacing (distal 2 poles) and for recording high right atrial electrograms (proximal 2 poles). Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-20 Electronics for Medicine) at paper speeds of 100 and 200 mm/sec. Simultaneous electrocardiographic leads I, II, III, and V1 were also recorded.

Atrial pacing was performed at increasing rates in 10 beats/min increments. Sinus node recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at rates ranging from 60 to 150 beats/min. For purposes of comparison before and after lidocaine, three sinus recovery times were measured and averaged at a paced rate of 130/min.15 Maximum sinus node recovery time was defined as the longest atrial asystolic period after sudden cessation of pacing at any of the tested heart rates.

Atrial effective and functional refractory periods were measured with atrial extrastimulus technique at an equivalent driven atrial cycle length before and after lidocaine in 24 patients, 11 with normal, and 13 with abnormal sinoatrial function. In the remaining three patients, these were measured during sinus rhythm (not at equivalent sinus length) and thus were not utilized for comparison purposes. Sinus node responses to atrial extrastimuli (A1) were
LIDOCAINE EFFECTS ON SINUS NODE/Dhingra et al.

Table 1. Effects of Lidocaine in Patients with Normal Sinoatrial Function

<table>
<thead>
<tr>
<th>Pt/Age (yr)/Sex</th>
<th>Sinus cycle length (msec)</th>
<th>SRT (msec)</th>
<th>Max. SRT (msec)</th>
<th>Calculated SACT (msec)</th>
<th>Refractory periods at equivalent CL (msec)</th>
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</table>

Abbreviations: C = control; L = Lidocaine; SRT = sinoatrial node recovery time; Max = maximum; SACT = sinoatrial conduction time; AERP = atrial effective refractory period; AFPR = atrial functional refractory period; CL = cycle length.

categorized as previously described, by noting the time of occurrence of the first spontaneous sinus beat (A2) following A1.11 Sinoatrial conduction time was calculated by delivering A3 during spontaneous sinus rhythm as described by Strauss et al.12 For each patient, this was obtained by measuring the difference between return cycle (A2-A3 interval) during the zone of reset and spontaneous sinus cycle (A2-A1 interval) and dividing by two. Unlike Engel and co-workers,13 we did not utilize estimated sinoatrial conduction time (the sum of retrograde and antegrade sinoatrial conduction time, e.g., the difference between A3-A2 and A1-A2) for analysis purposes. Our method assumes that antegrade and retrograde conduction times are the same. A mean sinoatrial conduction time was calculated for each patient using all reset responses (normal mean ± SD, 92 ± 30 msec).11 Sinus node responses were graphed as previously described by our laboratory.11

Lidocaine was administered intravenously after control recordings in a dose of 1 mg/kg as initial bolus injection followed by a continuous drip of 2–4 mg per minute.12 Blood levels of lidocaine were not analyzed; this dose should produce a serum level of 2–5 μg/ml.13–15 Measurements were initiated 10 min after the bolus injection. Student’s paired t-test was used to analyze the statistical significance of data.

Results

Patients with Normal Sinoatrial Function (tables 1 and 3)

All the 13 patients were males with ages ranging from 37 to 82 years (mean ± SEM, 59 ± 3.7 years). Control sinus cycle lengths ranged from 550 to 990 msec with a mean of 810 ± 34.3 msec. During lidocaine administration, sinus cycle lengths ranged from 540 to 950 msec with a mean of 774 ± 34.4 msec (P < 0.001). Control sinus node recovery times ranged from 650 to 1350 msec with a mean of 1027 ± 49.4 msec. During lidocaine infusion, sinus node recovery times ranged from 670 to 1360 msec with a mean of 1026 ± 52.5 msec (NS) (fig. 1A and B). Control maximum

Figure 1. Recordings demonstrating sinus nodal recovery times (SRT) before and during lidocaine administration in a patient (case 3) with normal sinus node function (A and B) and a patient (case 19) with sinus node dysfunction (C and D). Shown are electrocardiographic leads I, II, III, and V1, and a bipolar intracardiac high right atrial electrogram (HRA). Paper speed is 100 mm/sec and timelines are at one second intervals. Atrial pacing spikes are labeled with arrows; the pacing rate is 130/min. Panels A and C are before and B and D are during lidocaine administration. The SRT are A) 950 msec, B) 945, C) 2220, D) 1625 at a heart rate of 130 beats/min.
### Table 2. Electrophysiological Data Before and After Lidocaine in Patients with Sinoatrial Dysfunction

<table>
<thead>
<tr>
<th>Pt/Age (yr)/Sex</th>
<th>Sinus cycle length (msec)</th>
<th>SRT (msec)</th>
<th>Max. SRT (msec)</th>
<th>Calculated SACT (msec)</th>
<th>Refractory periods at equivalent CL (msec)</th>
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* = Patient had intermittent S-A block.
** = Zone of Interference (or Zone 1) accounted for 100% of scanned cycle.
For abbreviations see table 1.

Sinus node recovery times ranged from 650 to 1460 msec (mean 1116 ± 55.4 msec) before and from 670 to 1570 msec (mean 1087 ± 64.7 msec) during lidocaine administration (NS).

During atrial extrastimulus testing, a zone of sinus non-reset due to interference was defined in all patients both before and during lidocaine administration. This zone (mean ± SEM) accounted for the last 25 ± 1.9% of the sinus cycle length before and 24 ± 1.8% during lidocaine infusion (NS). Similarly, the zone of sinus reset was unchanged with lidocaine, accounting for 27 ± 2.9% of sinus cycle prior to and 29 ± 2.9% following lidocaine (NS). Zones of sinus interpolation were defined in two patients before lidocaine administration. In one of these, interpolated responses were abolished by lidocaine. In the remaining patient, there was no change in the zone of interpolation with lidocaine. One patient had a sinus echo zone prior to lidocaine. This zone was unaffected by lidocaine administration. No patient developed a new zone of interpolation or echo zone during lidocaine administration.

Calculated sinoatrial conduction times ranged from 35 to 150 msec with a mean of 87 ± 9.5 msec during control. During lidocaine administration, sinoatrial conduction times ranged from 48 to 147 msec with a mean of 90 ± 9.2 msec (NS) (fig. 2A and B).

At an identical driven cycle length (mean cycle length of 535 ± 11.2 msec), measured in 11 patients, atrial effective refractory periods ranged from 180 to 300 msec, with a mean of 241 ± 11.6 msec during control. During lidocaine administration, atrial effective refractory periods ranged from 190 to 260 msec, with a mean of 228 ± 7.9 msec (NS). Atrial functional refractory periods, measured in 11 patients, ranged from 220 to 430 msec (mean 286 ± 17.9 msec) before and from 240 to 350 msec (mean 270 ± 10.7 msec) during lidocaine (NS).

### Table 3. Summary of Electrophysiological Findings (mean ± SEM) After Lidocaine in Both Groups

<table>
<thead>
<tr>
<th>Sinus cycle length</th>
<th>SRT</th>
<th>Max. SRT</th>
<th>Calculated SACT</th>
<th>Refractory periods driving at identical CL</th>
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<td>AERP</td>
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</table>

**Patients with Sinoatrial Dysfunction (tables 2 and 3)**

There were 12 males and two females in this group, with ages ranging from 50 to 81 years (mean 61 ± 2.3 years). Control sinus cycle lengths ranged from 620 to 1400 msec with a mean of 1061 ± 67.6 msec. During lidocaine infusion, sinus cycle lengths ranged from 610 to 1360 msec with a mean of 1016 ± 64.5 msec ($P < 0.025$). Sinus node recovery times, during control, ranged from 860 to 2210 msec, with a mean of 1269 ± 97.7 msec. During lidocaine administration, recovery times ranged from 830 to 1620 msec with a mean of 1170 ± 73.8 msec ($P < 0.05$) (fig. 1C and D). Maximum sinus node recovery times ranged from 860 to 2520 msec (mean 1376 ± 116 msec) prior to and from 830 to 1920 msec (mean 1292 ± 90.6 msec) following lidocaine (NS).
The mean (± SEM) zone of nonreset due to interference accounted for the last 19 ± 2.8% of the sinus cycle length before and 24 ± 2.4% during lidocaine administration (P < 0.05). A zone of sinus reset was present in all except one patient in whom Zone I accounted for 100% of scanned sinus cycle length both before and during lidocaine. The zone of reset accounted for 42 ± 4.5% of sinus cycle length prior to and 35 ± 4.8% following lidocaine (P < 0.05). Interpolated responses and sinus echoes were present in two and three patients respectively during control state. Lidocaine effected no change in the presence and duration of these zones. Two additional patients developed a new echo zone during lidocaine administration.

Sinoatrial conduction time, calculated in 13 patients during control state, ranged from 34 to 145 msec with a mean of 80 ± 10.3 msec. Following lidocaine, calculated sinoatrial conduction times ranged from 53 to 160 msec, with a mean of 96 ± 10.2 msec (P < 0.001) (fig. 3A and B).

At an identical driven cycle length (mean cycle length of 583 ± 9.2 msec), atrial effective refractory periods, measured in 13 patients, ranged from 210 to 380 msec with a mean of 282 ± 15.0 msec during control. During lidocaine infusion, atrial effective refractory periods ranged from 210 to 380 msec with a mean of 270 ± 13.2 msec (NS). Atrial functional refractory periods, measured in 13 patients, ranged from 260 to 420 msec (mean 328 ± 13.5 msec) during control and from 270 to 420 msec (mean 321 ± 13.0 msec) during lidocaine administration (NS).
Discussion

A number of cases of sinoatrial dysfunction (severe sinus bradycardia and/or sinus arrest) during or immediately following lidocaine administration have been reported recently.1-8 These cases, reported separately, included six males and three females with ages ranging from 57 to 90 years. Lidocaine was administered in these patients for suppression of premature ventricular contractions in eight and for ectopic atrial rhythm in one. Ventricular dysrhythmia after acute myocardial infarction was present in five patients.5, 4, 6, 9 The sinoatrial dysfunction occurred with lidocaine doses (bolus injection) ranging from 50 mg to 200 mg with and without continuous intravenous drip of 1-4 mg/kg. In three cases, pre-existing sinus node dysfunction, as manifested by sinus bradycardia, was present prior to lidocaine administration.1, 3, 7 Pre-existing undetected sinus node abnormality suggested by the advanced age of many of these patients may have existed.19, 10 The presence of inferior myocardial infarction reported in four of the cases, also could have produced sinus node abnormalities.20 Ryden and co-workers92 reported the effects of intravenous lidocaine bolus (1 mg/kg) on heart rate in 21 patients with sinus bradycardia and acute myocardial infarction. They demonstrated a significant increase in sinus rate ranging from 3.7 to 6.7 beats/min in 19 of 21 patients between 2 to 4 min after lidocaine administration. However, in two patients, transient junctional and idioventricular rhythm developed with disappearance of sinus rhythm following lidocaine.

The electrophysiological basis for the above cases is unknown.1-8, 31 Depressed sinus automaticity and/or depressed sinoatrial conduction through perinodal tissue (S-A block) are possible explanations for the sinus bradycardia or arrest in these patients receiving lidocaine. Recent intracardiac catheter techniques allow more direct evaluation of sinoatrial function90-12 but have not been used extensively to evaluate the effects of lidocaine. Roos and Dunning8 demonstrated unchanged sinus node recovery times in 12 patients with normal sinus node function and seven with sinus node dysfunction after lidocaine (100 mg bolus).

The present study suggests that lidocaine in therapeutic doses (1 mg/kg bolus followed by 2-4 mg/minute drip) enhances sinus nodal automaticity in patients both with and without sinus node dysfunction, as manifested by small but significant decreases in sinus cycle length. This finding is in agreement with Ryden’s studies in patients,21 but is in contrast with animal experimental studies. Lieberman et al.25 and Mandel et al.22 reported negative chronotropic effects with large doses (5 to 10 mg/kg) of lidocaine in canines and rabbits. The effect of lidocaine may be vagally-mediated. Lieberman and co-workers22 demonstrated that under conditions of increased vagal activity (vagal stimulation) lidocaine maintained its effect of increasing the rate of sinus node, suggesting that lidocaine could be vagolytic.

Thus augmentation of heart rate produced by lidocaine observed in our study may reflect vagolysis and/or beta-sympathetic stimulation (central). Experimental studies by Kao and Jalar24 demonstrated that increases in cardiac output and arterial blood pressure resulting from lidocaine were abolished in decerebrate and vagotomized dogs. In the same experiments, through cross-circulation techniques, they showed that the cardiovascular effects of lidocaine were central (on autonomic nerve centers) rather than peripheral. Lidocaine has also been shown to cause an increase in systolic blood pressure, in venous capacitance in the calf and in blood flow in man.26 Whether or not these actions of lidocaine on peripheral vessels play a part in affecting reflex sinus nodal automaticity is not known.

In the present study, the effects of lidocaine on sinus node recovery time varied. In patients with normal sinoatrial function, recovery times did not change with lidocaine. This is in agreement with the observations of Roos et al.9 In contrast, lidocaine caused slight but significant shortening of sinus node recovery times in our patients with sinus node dysfunction. This could reflect increased sinus automaticity (see above) and/or increased perinodal refractoriness caused by lidocaine (see below).28 Increased perinodal refractoriness might prevent some driven atrial impulses from penetrating the sinus node, mimicking shortening of recovery time.27

There are no previously reported data concerning the effects of lidocaine on sinoatrial conduction in man. Experimental studies in rabbit hearts by Yamaguchi et al.28 demonstrated lack of significant effects of lidocaine on conduction time from sinus node to crista terminalis. Parameswaran and co-workers,3 utilizing simultaneous recording of transmembrane potentials from sinus node and atrium in rabbits, demonstrated the development of sinoatrial exit block with lidocaine. Sinus rhythm during exposure to lidocaine was unchanged, suggesting a direct inhibition of perinodal tissue. Lieberman and co-workers22 demonstrated an increase in conduction time between the sinus node and left atrial appendage following lidocaine infusion. Although they did not measure the direct sinoatrial conduction time before and after lidocaine, it is conceivable that part of the conduction delay observed occurred through perinodal fibers.

In the present study, calculated sinoatrial conduction time was unchanged during lidocaine administration in patients without sinoatrial disease. In contrast, lidocaine slightly but significantly increased sinoatrial conduction time in patients with sinoatrial dysfunction. Calculated sinoatrial conduction time was normal in all patients with sinoatrial dysfunction (during control) except one in whom Zone I accounted for 100% of the scanned sinus cycle length. The incidence of prolonged calculated sinoatrial conduction time in patients with sinus node dysfunction is low, ranging from 20 to 30%.29, 30 The presence of normal sinoatrial conduction time in most of our patients with sinoatrial dysfunction reflected our criteria for patient selection (one or more abnormalities of sinus or atrial function) and our relatively higher value for normal sinoatrial conduction time (< 152 msec) compared to other studies.14, 29, 31, 32

Sinus echo responses to atrial extrastimuli appear to reflect slow conduction in perinodal fibers.29- 34 In patients without sinoatrial disease, these responses were unaffected by lidocaine. In contrast, lidocaine potentiated demonstration of echo responses in two patients with sinoatrial dysfunction, possibly reflecting development of slowing of perinodal conduction.

The effects of lidocaine on human atrial effective refractory periods have been reported previously by Josephson et al.25 and Roos et al.9 The lack of significant effects of lidocaine on atrial refractoriness in our patients both with
and without sinoatrial dysfunction is in agreement with these previously reported studies.

In the present study, the dosage and mode of lidocaine administration were in accordance with the widely recommended regimen of an initial bolus injection of about 1 mg/kg of body weight, followed by a continuous infusion of 1–4 mg/min.16,17 Therapeutic plasma concentrations of lidocaine are considered to be between 1.2 and 5.0 µg/mL.16,18 Although blood levels of lidocaine were not measured in our patients, the dosage schedule used in this study is expected to produce a plasma level well within this therapeutic range. Previous studies in man have shown that after a single intravenous injection of 1 mg/kg, plasma lidocaine levels are 8 µg/mL at 2 min, 3.5 µg/mL at 5 min, 2.5 µg/mL at 10 min, 1.5 µg/mL at 20 min, and 1.2 µg/mL at 30 min.16,21 The additive effects of the bolus and continuous infusion provide a lidocaine blood level greater than 1.5 µg/mL in approximately 20 min, rising gradually to a final level ranging from 2 to 5 µg/mL after several hours.28 Our studies were initiated 10 min after the bolus injection and were completed within one hour, suggesting that although steady state lidocaine levels were not obtained, they were within the therapeutic range.

The present study demonstrates the following effects of lidocaine on the sinus node: 1) Lidocaine shortened sinus cycle length in patients both with and without sinus node dysfunction and did not significantly affect atrial refractoriness. 2) Lidocaine depressed perinodal tissue refractoriness only in patients with sinoatrial dysfunction. The differential actions of lidocaine in the two groups of patients may reflect increased sensitivity to lidocaine in patients with pre-existent sinoatrial disease. The previously reported occurrences of sinus arrest with lidocaine in patients with prior sinus node dysfunction add support to this hypothesis.1,14 Furthermore, lidocaine in therapeutic doses has been reported to depress intraventricular conduction only in patients with pre-existent intraventricular conduction disease.43 The associated perinodal tissue disease that may also be present may contribute to the alteration of electrophysiological and pharmacological properties. Atropine has been shown to produce different electrophysiological effects depending on whether or not a patient has sinus node dysfunction.39,40

Clinical Implications

The present study implies that lidocaine has limited risk of serious sinus bradyarrhythmia in patients without sinus node disease. In contrast, lidocaine produced short but significant lengthening of sinoatrial conduction time in patients with sinoatrial dysfunction, a finding that may account for the instances of severe sinus bradycardia and sinus arrest noted with lidocaine administration.1,14 Thus caution should be used if lidocaine is considered for patients with known or suspected sinus node disease. Similarly since elderly patients may have subclinical sinus node disease, administration of lidocaine should be undertaken only after careful consideration.18 The present study did not assess the effects of large doses of lidocaine.

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References

Characteristics of Atioventricular Conduction and the Spectrum of Arrhythmias in Lown-Ganong-Levine Syndrome

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SUMMARY Electrophysiological characteristics of atrioventricular (A-V) conduction and refractoriness were examined in 12 patients with Lown-Ganong-Levine (LGL) syndrome referred for assessment of the following arrhythmias: (group I) regular narrow QRS tachycardia 6/12 (50%), (group II) atrial fibrillation (AF) 2/12 (17%), (group III) ventricular tachycardia (VT) 4/12 (33%). A-V node refractory periods were shorter, and enhanced A-V conduction more frequent (7/12, 58% vs 7/28, 25%) in LGL patients compared to similar studies in 28 normal controls. During laboratory study reciprocating tachycardia (RT) due to re-entry within the A-V node occurred in 4/12 (33%) LGL patients, and exhibited a shorter cycle length (294 ± 60.4 msec) than did the same arrhythmia in 11/28 (39%) controls (372 ± 51.8 msec, P < 0.05). Similarly, RT utilizing a concealed accessory pathway had a shorter cycle length (228 ± 3.5 msec) in 2/12 (17%) LGL patients than in 11/28 (39%) controls (314 ± 24.3 msec, P < 0.001). In AF, the shortest R-R intervals in 4/12 (33%) LGL patients (2 group I, 2 group II) were shorter than in 15/28 (54%) control patients (254 ± 42.2 msec vs 325 ± 64.2 msec, P < 0.05). The mean R-R intervals did not differ significantly (LGL 372 ± 89 msec vs control 428 ± 82.6 msec).

This study suggests that the characteristics of A-V conduction and refractoriness may permit development of more rapid heart rates during certain arrhythmias in LGL patients compared to normal controls. Furthermore, the occurrence of VT in patients with LGL syndrome indicates that symptomatic arrhythmias require specific diagnosis.

THE FREQUENT OCCURRENCE of “rapid heart action” in patients exhibiting a short P-R interval and a normal QRS complex on surface ECG has been reported, and is commonly referred to as the Lown-Ganong-Levine (LGL) syndrome. Although several reports have presented results of electrophysiological studies in patients with this syndrome, in few cases has there been any literature that the electrophysiological observations and the arrhythmias encountered by the patient have been explored. Consequently, the basis for an association between a short P-R interval and paroxysmal cardiac arrhythmias remains unclear. The purpose of this investigation was to study atrioventricular (A-V) conduction and refractoriness in patients with LGL syndrome, and to evaluate the role played by these electrophysiologic characteristics in the occurrence of symptomatic arrhythmias in this syndrome.

Methods

LGL Patients

Between January 1974 and April 1977, 12 patients (mean age 30 ± 17.0 years) with the LGL syndrome (defined below) were studied in the Clinical Electrophysiology Laboratory at Duke University Medical Center. All patients were referred for evaluation of intermittent cardiac arrhythmias. In order to be included in this analysis each of the following criteria had to be met: (1) a positive history of paroxysmal rapid heart action; (2) electrocardiographically documented tachyarrhythmias (atrial fibrillation or flutter, narrow QRS complex tachycardia, ventricular tachycardia, or ventricular fibrillation); (3) at least two electrocardiograms obtained during sinus rhythm at a time when the patient was taking no medications, demonstrating a normal P wave axis, P-R interval of 120 msec or less, and normal QRS duration (100 msec or less in patients 15 years of age or older, 90 msec or less in patients aged 5–14 years); and (4) no electrocardiogram demonstrating a P-R interval greater than 120 msec, at a time when the patient was taking no medication.

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