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

DAVID G. BENDITT, M.D., EDWARD L. C. PRITCHETT, M.D.,
WILLIAM M. SMITH, PH.D., ANDREW G. WALLACE, M.D.,
AND JOHN J. GALLAGHER, M.D.

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,1,2 and is commonly referred to as the Lown-Ganong-Levine (LGL) syndrome.2 Although several reports have presented results of electrophysiologic studies in patients with this syndrome,3-16 in few cases has the relation between the electrophysiologic observations and the arrhythmia(s) experienced by the patient been explored.14-16 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);17 (4) no electrocardiogram demonstrating a P-R interval greater than 120 msec, at a time when the patient was taking no medication.
The electrophysiologic and electrocardiographic findings in these 12 patients form the basis of this report. All patients (or where necessary both the patient and the patient's parents) gave informed consent for these studies. Prior to electrophysiologic study a complete physical examination, chest X-ray, and ECG were obtained on each patient; at time of study all cardioactive medications had been discontinued for an interval exceeding 48 hours.

Under local anesthesia using sterile technique, two 6F quadrupolar electrode catheters for recording and stimulating were percutaneously introduced via the right femoral vein and advanced under fluoroscopic control to the apex of the right ventricle (RV), and to the high lateral border of the right atrium (RA). A third 6F quadrupolar catheter was introduced via an antecubital vein, usually the left, and advanced to the coronary sinus (CS) in 10/12 patients. In two patients, the CS could not be catheterized. A 6F tripolar electrode catheter was also introduced percutaneously via the right femoral vein and positioned across the tricuspid valve to record a His bundle electrogram (HBE). Following introduction of all catheters, 100 units/kg of heparin sodium was given intravenously.

Standard ECG lead V1, and/or lead II, and electrograms from the RV, the lateral RA, the His bundle, and where available the proximal and distal CS were recorded simultaneously and stored on magnetic tape at 3/4 inches/second. Intracardiac electrograms were recorded at filter frequencies of 50–1000 Hz. Graphic records were obtained either simultaneously at the time of study or at a later time by playback from tape onto a Mingograf 800-8 channel ink-jet recorder at paper speeds of 100–200 mm/second. A simultaneous 10 msec time code was recorded with the data. Stimulation studies were performed using a specially designed stimulator* which delivered impulses of 2 msec duration, employing the minimum impulse intensity permitting consistent capture. All electrical equipment was carefully grounded.

The technique of electrophysiologic study was similar to that described previously for investigation of tachyarrhythmias in this laboratory.18–22 Following catheter placement conduction intervals (PA, AH, HV intervals) were obtained during sinus rhythm. Using the extrastimulus technique23 refractory periods were determined from the RV and the RA in all patients, and from the CS in 10/12 patients. Depending upon the patient's sinus cycle length in the laboratory, an average of two (range 1–4) refractory period measurements were obtained at each pacing site, employing basic pacing cycle lengths (A1–A1) 700, 600, 500, 400, 350 and 300 msec. Atrial pacing with progressively decreasing cycle lengths was then performed in order to determine the shortest cycle length sustaining 1:1 A-V conduction and the change in conduction intervals with decreasing pacing cycle length.

In seven patients (six with regular narrow QRS tachycardia and one patient with ventricular tachycardia as well as a regular narrow QRS tachycardia) the study protocol included the following additional studies in order to confirm or exclude the presence of an accessory A-V pathway.18–22, 24–27

1) Retrograde atrial activation sequence during tachycardia and during induced atrial echo beats was determined from the local atrial electrograms on the RA, CS and His bundle electrode catheters. In addition, detailed septal and RA activation sequences during tachycardia were mapped in 4/7 patients employing a special 7F bipolar mapping electrode catheter developed in this laboratory.20, 21

2) Premature ventricular depolarizations at progressively shorter coupling intervals were induced from the RV apex during tachycardia in 6/7 patients. In one patient tachycardia did not occur during the study.

In patients in whom an accessory atrioventricular conduction pathway was diagnosed by (1) and (2), atrial pacing near the presumed site of the accessory pathway and induction of atrial fibrillation (AF) by rapid atrial pacing was carried out. Failure to elicit ventricular pre-excitation by these techniques established that the accessory pathway manifested antegrade block.20, 24–26

In all patients in whom AF was recorded the shortest R-R interval as well as the average R-R interval (determined over several minutes) were measured.

Control Patients

In order to assess the relation between characteristics of A-V conduction and arrhythmias in patients with LGL syndrome, this relation was also examined in a control group consisting of patients having a normal P-R interval (greater than 120 msec and less than 210 msec) and arrhythmias comparable to those of LGL patients.

Since January 1974, 32 patients with a normal P-R interval and either regular narrow QRS tachycardia* or atrial fibrillation/flutter* have undergone electrophysiological study at Duke University Medical Center. Prior to that time criteria for diagnosis of RT with re-entry within the A-V node did not require exclusion of an accessory A-V pathway with antegrade conduction block (see Definitions). As a result, studies performed prior to January 1974 have been excluded. In addition, the number of patients studied with ventricular tachycardia and no known heart disease was small, and these patients were not included in the control group.

Of the 32 patients with a normal P-R interval, four patients (two with regular narrow QRS tachycardia, two with AF) were excluded from the control group since they had been studied either incompletely or in the presence of cardioactive drugs. Each of the remaining 28 control patients (19 women, nine men; mean age 45 ± 14.2 years) had been referred for evaluation of recurrent symptomatic tachyarrhythmias. Informed consent was obtained from each patient, and each underwent electrophysiological study employing a protocol similar to that described for LGL patients.

In the 22 control patients with regular narrow QRS tachycardia, reciprocating tachycardia (RT) with re-entry within the A-V node was diagnosed in 11/22 (50%) (see Definitions), while RT utilizing a concealed accessory pathway occurred in 11/22 (50%). In addition, the ventricular response during atrial fibrillation was recorded during electrophysiologic study in 15/28 (54%) control subjects (4/6 presenting with atrial flutter/fibrillation, 11/22 presenting with regular narrow QRS tachycardias).

Antegrade A-V nodal refractory period measurements

*Designed by Michael Feazor, Ph.D. and built by Philip Talbert, Duke University Department of Medicine.
were obtained in 17/28 (61%) control patients. Table 3 (Control A) summarizes the values of atrial effective refractory period (atrial ERP), A-V nodal effective refractory period (AVN ERP) and A-V nodal functional refractory period (AVN FRP) obtained in this group of patients. These data are compared to A-V nodal refractory period measurements in the complete LGL group at comparable basic pacing cycle lengths.

Enhanced A-V nodal conduction (see Definitions) was present in 7/28 (25%) control patients.

Definitions

**Ventriculo-atrial (V-A) conduction time.** The interval from the earliest recording of ventricular activation to the earliest rapid component of the bipolar atrial electrograms obtained by an electrode catheter positioned at one of several atrial sites.

**Maximum A-H interval prolongation.** The maximum prolongation of the A-H interval (over that in sinus rhythm) associated with 1:1 A-V conduction during progressively rapid atrial pacing from sinus cycle length to a minimum cycle length of 300 msec (200/min).

**Enhanced A-V conduction.**20 An abnormality of A-V conduction was considered to be present if the following criteria were met: (1) A-H interval in sinus rhythm was less than or equal to 60 msec; (2) 1:1 A-V conduction was maintained during atrial pacing at cycle lengths less than 300 msec (200/min); (3) maximum A-H interval prolongation (defined above) was equal to or less than 100 msec.

**Reciprocating tachycardia (RT) due to re-entry utilizing an accessory A-V pathway** was diagnosed by the following criteria:

1. Induction of premature ventricular depolarizations at progressively shorter coupling intervals during tachycardia resulted in pre-excitation of the atria with an activation sequence identical to that of the tachycardia at a time when the His bundle was refractory.27

2. V-A time increased following onset of functional bundle branch block in the course of reciprocating tachycardia.29 This finding implicated the participation in the tachycardia of an accessory A-V pathway on the same side as the bundle branch block, but the absence of this finding did not exclude a septal pathway.29

3. Eccentric retrograde atrial activation sequence during tachycardia (may not occur with septal pathways).18, 19, 21

**RT due to re-entry within the A-V node** was diagnosed if the V-A times ≤ 0 msec and/or the following criteria were satisfied: (1) exclusion of the participation of an accessory A-V pathway in the tachycardia by criteria noted above; (2) retrograde atrial activation sequence initiated earliest in the low medial RA, and indistinguishable from the normal retrograde conduction sequence (excludes sinus node re-entry).21

These criteria do not distinguish arrhythmias caused by re-entry within the A-V node from those re-entering solely within the base of the atrium.

**Classification of A-V node refractory period curves:** Atrial and A-V node refractory periods were measured using the extrastimulus technique.23 Each A-V node refractory period measurement was plotted in graphical form23 and A-V refractoriness was characterized using a modification of the classification proposed by Wit et al.23 When this graph was a smooth continuous relationship, the curve was classified either Type I or Type II. In instances where an abrupt break in the plot of H1-H2 versus A1-A2 was detected, the graph was termed discontinuous.29

Results

Clinical Features

Table 1 details the clinical and electrocardiographic findings in 12 patients (6 women, 6 men: mean age 30 ± 17.0 years) with LGL syndrome. The arrhythmia resulting in referral was a regular narrow QRS complex tachycardia (range of ventricular responses 120–280/min) in six (group I), and paroxysmal atrial fibrillation in two (group II). Of the remaining four patients (group III), two had ventricular tachycardia (VT) alone, and two had both VT and ventricular fibrillation (VF). In addition to VT and VF, one patient in group III also had a history of episodic atrial flutter/fibrillation, as well as documented paroxysmal regular narrow QRS complex tachycardia.

Only one patient (WP) had a history of heart disease, having had an anterior myocardial infarction six years prior to onset of palpitations. Despite his history, this patient was included in the LGL group since he had been asymptomatic for several years prior to development of paroxysmal atrial fibrillation.

Electrophysiological Laboratory Findings

Tables 2 and 3 summarize the laboratory findings in 12 patients with LGL syndrome.

**A-V Conduction**

Figure 1 depicts the pattern of A-H interval change during atrial pacing studies in LGL patients compared to results obtained during similar studies in patients with a normal P-R interval.3 In sinus rhythm (mean cycle length 669 ± 152.4 msec) the mean A-H interval was 46 ± 11.7 msec, while during progressively rapid atrial pacing the maximum A-H interval prolongation was 54 ± 59.3 msec. In 7/12 (58%) patients (5/6 group I, 1/2 group II, 1/4 group III) enhanced A-V conduction was present.

**A-V Node Refractory Periods**

Table 3 lists the mean values and standard deviation for refractory periods obtained in LGL patients at three RA pacing cycle lengths (600, 500, 400). These data are compared to refractory period values at corresponding pacing cycle lengths in our normal P-R control subjects with comparable arrhythmias (table 3, Control A). The equality of mean values of refractory periods measured in LGL and Control A groups was tested using Student's t-test. The statistic and associated degrees of freedom were calculated using a method for comparing groups of unequal variances and sample sizes.22

Except for the shortest pacing cycle length (400 msec), A-V node ERP and FRP were significantly shorter in LGL patients than in Control A patients. Atrial ERP did not differ between the two groups.

In order to substantiate this observation, refractory period data in LGL patients were also compared to previously published refractory period values in patients...
TABLE 1. Clinical Features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of Symptoms</th>
<th>Symptoms</th>
<th>Documented arrhythmias</th>
<th>Associated cardiac disease</th>
<th>12 lead ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>12</td>
<td>M</td>
<td>1 year</td>
<td>palP</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.11 .08 N N</td>
</tr>
<tr>
<td>PJ</td>
<td>31</td>
<td>F</td>
<td>4 years</td>
<td>palpitations</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.10 .08 N N</td>
</tr>
<tr>
<td>HO</td>
<td>54</td>
<td>M</td>
<td>30 years</td>
<td>palpitations, dizziness, syncope, seizures</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.10 .08 N N</td>
</tr>
<tr>
<td>MP</td>
<td>40</td>
<td>F</td>
<td>10 years</td>
<td>palpitations, dizziness, syncope, seizures, nausea, vomiting, chest pain</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.11 .08 N N</td>
</tr>
<tr>
<td>LQ</td>
<td>14</td>
<td>M</td>
<td>2 years</td>
<td>palpitations, dizziness, chest pain</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.12 .08 N N</td>
</tr>
<tr>
<td>ES</td>
<td>16</td>
<td>M</td>
<td>2-3 years</td>
<td>palpitations, chest pain</td>
<td>regular narrow QRS tachycardia</td>
<td>none</td>
<td>.10 .10 N N</td>
</tr>
<tr>
<td>MC</td>
<td>29</td>
<td>F</td>
<td>7 years</td>
<td>palpitations, chest pain</td>
<td>paroxysmal AF</td>
<td>none</td>
<td>.09 .08 N N</td>
</tr>
<tr>
<td>WP</td>
<td>59</td>
<td>M</td>
<td>1 month</td>
<td>palpitations, dizziness, chest pain</td>
<td>paroxysmal AF</td>
<td>CAD</td>
<td>.12 .10 N N</td>
</tr>
<tr>
<td>RO</td>
<td>48</td>
<td>M</td>
<td>2 years</td>
<td>palpitations, syncope (X4), seizures, CPR</td>
<td>VT</td>
<td>none</td>
<td>.12 .08 N N</td>
</tr>
<tr>
<td>PS</td>
<td>31</td>
<td>F</td>
<td>2 years</td>
<td>palpitations, syncope (X5), CPR</td>
<td>VT, VF</td>
<td>none</td>
<td>.12 .08 N N</td>
</tr>
<tr>
<td>JT</td>
<td>14</td>
<td>M</td>
<td>1 month</td>
<td>palpitations, syncope, CPR</td>
<td>VT</td>
<td>none</td>
<td>.12 .06 N N</td>
</tr>
<tr>
<td>JSS</td>
<td>13</td>
<td>M</td>
<td>1 month</td>
<td>palpitations, syncope, CPR</td>
<td>VT, VF</td>
<td>none</td>
<td>.12 .08 N N</td>
</tr>
</tbody>
</table>

Abbreviations: CPR = cardiopulmonary resuscitation required; VT = ventricular tachycardia; VF = ventricular fibrillation; AF = atrial fibrillation; HR = heart rate/minute; CAD = coronary artery disease; N = normal.

with a normal P-R interval (table 3, Control B). Postoperative patients, or patients with abnormal electrocardiograms were excluded from the Control B group. In addition, since A-V node refractory period values are age dependent, statistical comparisons were made following subdivision of both LGL patients and Control B patients into two age subgroups (less than 16 years, greater than or equal to 16 years).

A-V node ERP and FRP were significantly shorter in the LGL group compared to the total Control B group at almost every pacing cycle length tested, while atrial ERP did not differ (table 3). For the most part this relation was unchanged when the age subgroups were compared; however, it was less striking in the subgroup less than 16 years of age.

In 10/12 (83%) LGL patients A-V node refractory period curves were categorized (table 2). In one patient (HO) frequent initiation of tachycardia resulted in abbreviation of refractory period measurements and a complete refractory period curve was not obtained, while in a second patient (MC) the plot of H1-H2 versus A1-A2 did not deviate from the line of identity (fig. 4) and was not classified. In 3/12 (25%) patients (2 group I, 1 group III) the A-V refractory period curves were discontinuous (fig. 2).

Arrhythmias

During study, arrhythmias similar to those which had been previously documented, occurred or were precipitated by pacing techniques in 10/12 (83%) patients (table 2).

Group I. In group I, a regular narrow QRS complex tachycardia occurred during study in 5/6 (83%) patients, and in the remaining patient frequent atrial echo beats were observed.

Reciprocating tachycardia (RT) due to re-entry within the A-V node was diagnosed in 3/6 (50%) group I patients and was suggested by the retrograde activation sequence of induced atrial echo beats in the one patient in whom tachycardia did not occur. However, in the latter patient a concealed accessory conduction pathway was not unequivocally excluded.

RT due to re-entry utilizing a concealed accessory pathway was proven in 2/6 (33%) group I patients. In each patient the accessory pathway was localized in the A-V groove on the posterior aspect of the left ventricular free wall (fig. 3).

In addition to a regular narrow QRS tachycardia, atrial fibrillation (AF) was induced during laboratory study in 2/6 (33%) group I patients. In these two patients (SB, LQ) enhanced A-V conduction was present, and the ventricular response to AF was similar in both patients: average R-R interval 323 msec (186/min) and 300 msec (200/min), and shortest R-R intervals 250 msec and 230 msec, respectively.

Group II. Atrial fibrillation occurred during electrophysiological study in both group II patients.

In one group II patient (MC) atrial pacing and refractory period studies indicated complete functional bypass of
Table 2. Electrophysiological Laboratory Findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sinus rhythm</th>
<th>CL min with 1:1 AV conduction* (msec)</th>
<th>ΔAH† (msec)</th>
<th>Enhanced AV conduction</th>
<th>Pattern of AV node refractory periods</th>
<th>Arrhythmia during study</th>
<th>Method initiating arrhythmia during study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>425 15 55 35</td>
<td>260 (231)</td>
<td>11</td>
<td>+</td>
<td>Type I</td>
<td>APRT 261 230</td>
<td>Premature depolarizations in RA and CS</td>
</tr>
<tr>
<td>PJ</td>
<td>700 30 45 35</td>
<td>220 (174)</td>
<td>20</td>
<td>+</td>
<td>Type I</td>
<td>Re-entry in A-V node 132 330</td>
<td>Premature depolarizations in RA and CS</td>
</tr>
<tr>
<td>HO</td>
<td>725 25 45 50</td>
<td>320 (188)</td>
<td>75</td>
<td>-</td>
<td>not obtained</td>
<td>Re-entry in A-V node 245 245</td>
<td>Premature atrial depolarizations and spontaneous PVC</td>
</tr>
<tr>
<td>MP</td>
<td>690 25 60 35</td>
<td>225 (267)</td>
<td>30</td>
<td>+</td>
<td>discontinuous</td>
<td>Re-entry in A-V node 267 225</td>
<td>Premature depolarizations in RA, CS or RV</td>
</tr>
<tr>
<td>LQ</td>
<td>890 30 45 40</td>
<td>250 (240)</td>
<td>55</td>
<td>+</td>
<td>Type II</td>
<td>Re-entry in A-V node 250 240</td>
<td>Premature atrial depolarizations and rapid RA pacing</td>
</tr>
<tr>
<td>ES</td>
<td>470 35 35 35</td>
<td>240 (250)</td>
<td>5</td>
<td>+</td>
<td>discontinuous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td>515 30 20 20</td>
<td>240 (250)</td>
<td>0</td>
<td>+</td>
<td>Type I</td>
<td>AF 162 370</td>
<td>RA pacing</td>
</tr>
<tr>
<td>WP</td>
<td>540 35 45 40</td>
<td>350 (171)</td>
<td>85</td>
<td>-</td>
<td>not classified</td>
<td>AF 120 500</td>
<td>RA pacing</td>
</tr>
<tr>
<td>RO</td>
<td>880 25 50 40</td>
<td>350 (171)</td>
<td>70</td>
<td>-</td>
<td>Type II</td>
<td>multiple ventricular responses 220-300 200-270</td>
<td>No sustained tachycardia</td>
</tr>
<tr>
<td>PS</td>
<td>623 30 65 30</td>
<td>330 (182)</td>
<td>215</td>
<td>-</td>
<td>discontinuous</td>
<td>Re-entry in A-V node VT/VF 300-330 180-200</td>
<td>Premature ventricular depolarizations, RT followed spontaneous termination of VT</td>
</tr>
<tr>
<td>JSS</td>
<td>655 35 50 35</td>
<td>240 (250)</td>
<td>10</td>
<td>+</td>
<td>Type II</td>
<td>VT 130-136 441-462</td>
<td>Rapid RA pacing with 1:1 AV conduction</td>
</tr>
<tr>
<td>JT</td>
<td>610 35 40 50</td>
<td>360 (167)</td>
<td>70</td>
<td>-</td>
<td>Type II</td>
<td></td>
<td>Premature depolarization at RV apex, RV outflow or RA</td>
</tr>
<tr>
<td>Mean</td>
<td>669 29 46 37</td>
<td>282 (212)</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CL min = minimum cycle length during atrial pacing permitting sustained 1:1 AV conduction.
†ΔAH = maximum A-H interval prolongation between sinus rhythm and either a paced cycle length of 300 msec (300/min) or to the shortest cycle length With 1:1 AV conduction whichever was greater (see Definitions).

Abbreviations: CL = cycle length; RA = right atrium, CS = coronary sinus; RT = reciprocating tachycardias; APRT = RT utilizing an accessory pathway; re-entry in the A-V node = RT due to re-entry within the A-V node.
TABLE 3. A-V Nodal Refractory Periods—RA Pacing

<table>
<thead>
<tr>
<th>Pacing cycle length or range (msec)</th>
<th>Atrial ERP (msec)</th>
<th>AVN ERP (msec)</th>
<th>AVN PRP (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGL Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 6</td>
<td>255 ± 40.3</td>
<td>276 ± 39.1</td>
<td>332 ± 39.1</td>
</tr>
<tr>
<td>N = 7</td>
<td>250 ± 40.2</td>
<td>276 ± 38.9</td>
<td>332 ± 38.9</td>
</tr>
<tr>
<td>N = 10</td>
<td>240 ± 38.5</td>
<td>273 ± 38.5</td>
<td>321 ± 37.3</td>
</tr>
<tr>
<td>LGL &lt;16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 3</td>
<td>250 ± 38.5</td>
<td>273 ± 38.5</td>
<td>321 ± 37.3</td>
</tr>
<tr>
<td>N = 3</td>
<td>240 ± 38.5</td>
<td>273 ± 38.5</td>
<td>321 ± 37.3</td>
</tr>
<tr>
<td>N = 4</td>
<td>230 ± 37.9</td>
<td>259 ± 39.2</td>
<td>305 ± 39.9</td>
</tr>
<tr>
<td>N = 6</td>
<td>220 ± 37.3</td>
<td>257 ± 37.4</td>
<td>343 ± 54.0</td>
</tr>
<tr>
<td>Control A*</td>
<td>235 ± 39.2</td>
<td>307 ± 44.0</td>
<td>411 ± 65.9</td>
</tr>
<tr>
<td>N = 14</td>
<td>P = 0.02</td>
<td>P = 0.01</td>
<td></td>
</tr>
<tr>
<td>N = 9</td>
<td>P = 0.02</td>
<td>P = 0.02</td>
<td></td>
</tr>
<tr>
<td>N = 6</td>
<td>225 ± 37.3</td>
<td>257 ± 37.4</td>
<td>343 ± 54.0</td>
</tr>
<tr>
<td>Control B†</td>
<td>215 ± 48.7</td>
<td>282 ± 37.8</td>
<td>408 ± 53.5</td>
</tr>
<tr>
<td>N = 10</td>
<td>N = 18</td>
<td>N = 23</td>
<td></td>
</tr>
<tr>
<td>450-549</td>
<td>P = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>P = 0.04</td>
<td>P = 0.05</td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>189 ± 27.1</td>
<td>291 ± 49.2</td>
<td>348 ± 59.8</td>
</tr>
<tr>
<td>N = 20</td>
<td>N = 10</td>
<td>N = 16</td>
<td></td>
</tr>
<tr>
<td>Control B†</td>
<td>191 ± 47.2</td>
<td>279 ± 43.6</td>
<td>400 ± 58.5</td>
</tr>
<tr>
<td>&lt;16 years</td>
<td>N = 10</td>
<td>N = 7</td>
<td>N = 10</td>
</tr>
<tr>
<td>450-549</td>
<td>P = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>P = 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>176 ± 15.4</td>
<td>274 ± 45.8</td>
<td>435 ± 43.2</td>
</tr>
<tr>
<td>N = 10</td>
<td>N = 7</td>
<td>N = 11</td>
<td></td>
</tr>
<tr>
<td>Control B†</td>
<td>232 ± 43.8</td>
<td>301 ± 33.1</td>
<td>414 ± 59.9</td>
</tr>
<tr>
<td>≥16 years</td>
<td>N = 15</td>
<td>N = 11</td>
<td>N = 13</td>
</tr>
<tr>
<td>450-549</td>
<td>P = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>P = 0.001</td>
<td>P = 0.04</td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>202 ± 30.4</td>
<td>333 ± 30.3</td>
<td>354 ± 35.0</td>
</tr>
<tr>
<td>N = 10</td>
<td>N = 3</td>
<td>N = 5</td>
<td></td>
</tr>
</tbody>
</table>

*Statistical comparison made between LGL patients (Total) and control group A at comparable pacing cycle length and age.
†Statistical comparison made between LGL patients and control group B at comparable pacing cycle length and age.

Physiologic atrioventricular (A-V) conduction delay (fig. 4). In this patient the average and shortest R-R intervals during AF were 370 msec (162/min) and 220 msec, respectively. Furthermore, the administration of separate occasions of digoxin 1.0 mg i.v., propranolol 0.1 mg/kg i.v. (total dose 6 mg) or quinidine 300 mg orally every 6 hours for three days, did not affect significant change of ventricular response.

The second group II patient (WP), although manifesting subnormal A-H interval (ordinate) in 12 patients with LGL syndrome, compared to control data in patients with a normal P-R interval.*

FIGURE 1. Effect of atrial pacing cycle length (abscissa) on A-H interval (ordinate) in 12 patients with LGL syndrome, compared to control data in patients with a normal P-R interval.*

FIGURE 2. Graph of \( H_1-H_2 \) (ordinate) versus \( A_1-A_2 \) (abscissa) illustrating an abrupt discontinuity during an antegrade AV refractory period determination. Repetition of \( A_1-A_2 \) coupling intervals, between 210 and 240 msec, demonstrates discrete separation and overlap of refractory period curves.
tachyarrhythmia (130–136/min, 441–462 msec) exhibiting right bundle branch block configuration were documented (fig. 5 left). Prior to referral for electrophysiological study, treatment in hospital with intravenous lidocaine, and oral combinations of propranolol and quinidine or procainamide failed to prevent recurrent episodes of tachycardia. At the time of study the patient was in sinus rhythm and on no medications. Figure 5 right illustrates that the tachycardia initiated in the laboratory was similar in both morphology and rate to the arrhythmia exhibited spontaneously by this patient.

In patient PS, several episodes of relatively regular wide QRS tachycardias with heart rates up to 280/min (214 msec) were recorded on monitor strips in the emergency room. Although complete ECG recordings of this arrhythmia were not obtained, a left bundle branch block morphology was present. During electrophysiological study ventricular tachycardia with a similar morphology was initiated (fig. 6). In this case the rhythm was noted to be more irregular (cycle length varied between 220 and 300 msec) suggesting the possibility of a more rapid underlying tachycardia (approximate cycle length 110–115 msec) with variable 2:1 and 3:1 exit block. Interestingly, spontaneous termination of this VT in the laboratory was frequently associated with onset of RT due to re-entry within the A-V node resulting in a regular narrow QRS complex tachycardia (fig. 6).

In one other group III patient (JSS), sudden collapse with documented VT/VF in the emergency room was the first documented tachyarrhythmia. During electrophysiological study enhanced A-V conduction with persistence of 1:1 A-V conduction at atrial pacing cycle lengths as short as 240 msec (heart rate 250/min) was associated with gradual widening of the QRS complex indicative of progressive intraventricular conduction delay (fig. 7) and was followed by onset of VT. In this patient VT was hemodynamically un-
stable and tended to degenerate rapidly into VF. It is not possible in this case to compare morphologically the spontaneously occurring arrhythmia to that recorded during electrophysiological study.

The fourth group III patient (RO) had had several syncopeal episodes associated with palpitations, and required DC cardioversion on one occasion when both VT and VF occurred. In this patient sustained tachycardia did not occur in the laboratory.

Relation of A-V Node Conduction Characteristics to Arrhythmias

Reciprocating tachycardia with re-entry within the A-V node occurred during study in 4/12 (33%) LGL patients, and had a shorter mean cycle length (294 ± 60.4 msec) than in 11/28 (39%) control subjects (372 ± 51.8 msec, P < 0.05). Similarly in 2/12 (17%) LGL patients with RT utilizing a concealed accessory pathway, the mean cycle length during tachycardia (228 ± 3.5 msec) was shorter than in 11/28 (39%) Control A subjects with the same arrhythmia (314 ± 24.3 msec, P < 0.001).

During AF the shortest R-R intervals in 4/12 (33%) LGL patients were less (254 ± 42.2 msec) than in 15/28 (54%) Control A subjects (325 ± 64.2 msec, P < 0.05). The mean R-R interval during AF was also shorter in LGL patients (372 ± 39 msec vs 428 ± 82.6 msec), although the difference was not statistically significant.

The development of faster heart rates (shorter mean cycle length) in RT and shorter R-R intervals in AF was associated with more frequent occurrence of enhanced A-V conduction in the LGL group as a whole (7/12, 58%) and particularly in groups I and II (6/8, 75%) compared to Control A subjects (7/28, 25%).

There was no apparent relationship between cycle length of VT in group III patients (table 2) and the characteristics of A-V nodal conduction. Although enhanced A-V conduction was present in one group III patient (JSS) in whom VT was initiated by rapid atrial pacing, this rhythm was un-

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Panel A) Refractory period curve (pacing cycle length 500 msec) from a patient (MC) with paroxysmal atrial fibrillation. The plot of $H_1-H_2$ (ordinate) versus $A_1-A_2$ (abscissa) fails to deviate from the line of identity. Measurement of A-V node ERP and FRP is limited by the occurrence of atrial refractoriness in this case. Panel B) Plot of A-H interval (solid circles) and H-V interval (empty circles) versus atrial pacing cycle length. Neither the A-H interval nor the H-V interval prolong during progressively rapid atrial pacing.
stable (fig. 6) and its rate could not be compared to VT in other group III patients.

Although there was only a small number of LGL patients in each arrhythmia subgroup, there did not seem to be any difference in the characteristics of A-V conduction or refractoriness between these subgroups.

Discussion

Although characteristics of A-V conduction and refractoriness in patients with LGL syndrome have been reported,\textsuperscript{3-15} the relationship between electrophysiologic observations and occurrence of symptomatic tachyarrhythmias in patients with this syndrome has been largely unexplored. The present study provides a basis for understanding the role played by abnormal A-V conduction characteristics in certain arrhythmias exhibited by these patients.

Characteristics of A-V Node Conduction and Refractoriness

Electrophysiologic features of A-V conduction and refractoriness in the present study were similar to findings previously reported in patients with LGL syndrome.\textsuperscript{3-15} Compared to values obtained during conduction system studies in subjects with a normal P-R interval, the short P-R interval in patients with LGL syndrome resulted primarily from an abbreviated A-H interval. In addition, characterization of A-V node conduction by atrial pacing in these patients demonstrated markedly subnormal A-H interval prolongation (fig. 1). Although two patients did exhibit abrupt prolongation of the A-H interval at critical pacing cycle lengths, both had discontinuous refractory period curves presenting the possibility that a "slow" A-V conduction pathway had been engaged.\textsuperscript{28, 33-35}

Previous studies in patients with LGL syndrome as well as in patients with short P-R intervals, normal QRS complexes and no arrhythmia have reported both normal and short A-V node refractory period values.\textsuperscript{8, 16} Our findings indicate that A-V node refractory periods in LGL patients are shorter than refractory periods measured in patients with a normal P-R but are not different from those recorded in patients with a short P-R interval without a history of tachyarrhythmias.\textsuperscript{8, 10} Furthermore, refractory period values did not differ among the three LGL patient subgroups. Thus atrial and A-V node refractory periods neither distinguish LGL patients from other patients with short P-R intervals nor do they appear to be related to the type of symptomatic arrhythmias presented.

Arrhythmias Observed

In common with previous reports\textsuperscript{2, 8, 9, 12} the most frequent rhythm disturbance in this study was a regular narrow QRS complex tachycardia (6/12, 58% patients). Electrophysiologic study during this arrhythmia resulted in the diagnosis of RT utilizing a concealed A-V conduction pathway in two patients, and RT due to re-entry within the A-V node in four patients (three group I, one group III).

In three patients with RT due to re-entry in the A-V node discontinuous refractory period curves were observed. This finding has been suggested to indicate the presence of "dual" A-V nodal pathways\textsuperscript{28, 33-35} and has been used to implicate re-entry within the A-V node as a mechanism for recurrent regular narrow QRS tachycardias in certain patients.\textsuperscript{28, 34-35} including a few patients with LGL syndrome.\textsuperscript{11, 14} However, since a discontinuous refractory period curve does not exclude participation of a latent accessory A-V pathway, the presence of such a curve is inadequate in itself to identify RT due to re-entry within the A-V node.

A distinctive feature of this study was the frequent occurrence of severe ventricular arrhythmias (group III 4/12, 33%). In part, this may be related to the selected nature of the patient population referred for study. However, while life-threatening ventricular arrhythmias have been noted only sporadically in patients with LGL syndrome,\textsuperscript{13, 14} the observation that ventricular as well as supraventricular arrhythmias occur in this syndrome is important and merits further study.
Relation between Electrophysiologic Findings and Symptomatic Arrhythmias

Electrocardiographic and electrophysiologic observations in patients with LGL syndrome have suggested the presence of functional bypass of physiologic conduction delay in the region of the A-V node. In a few cases these findings have been ascribed to anatomic tracts bypassing part or all of the area of conduction slowing, or to the presence of a small or incompletely matured A-V node. On the other hand, laboratory studies in patients with short P-R intervals but without symptomatic cardiac arrhythmias have demonstrated electrophysiologic features indistinguishable from those recorded in patients with LGL syndrome. Although anatomic studies are not available in the former group of patients, it is apparent that unique characteristics of A-V node conduction and refractoriness associated with a short P-R interval on ECG are not in themselves adequate explanation for the occurrence of symptomatic cardiac arrhythmias.

Complete functional antegrade bypass of physiologic A-V conduction delay was uncommon in the LGL patients studied. The single patient with this finding presented with a rapid ventricular response during paroxysmal AF, and was
never observed to have RT. Furthermore, of the patients with RT, none exhibited electrophysiologic findings suggestive of functional antegrade A-V node bypass.

Recently in patients with accessory A-V conduction pathways, it has been shown that the additional presence of enhanced A-V conduction was associated with more rapid heart rates during RT and AF than was seen in patients without this finding.29 The difference in heart rates during tachycardia was entirely due to shorter A-H intervals in patients with enhanced A-V conduction.29 In the present study enhanced A-V conduction was a frequent finding particularly in group I and group II patients (6/8, 75%), and was associated with faster heart rates during RT and shorter R-R intervals in AF than occurred during similar arrhythmias in patients with a normal P-R interval.

Although enhanced A-V conduction does not account for the occurrence of RT in LGL patients, the frequent association of this finding with a short P-R interval on surface ECG may permit development of more rapid heart rates during these arrhythmias. Furthermore the combination of enhanced AV conduction and abbreviated A-V node refractory periods may similarly result in more rapid heart rates and thereby more marked symptoms during AF, in a manner analogous to that observed in patients with Wolff-Parkinson-White syndrome.41 42 In fact, the two sudden deaths in the series reported by Lown, Ganong and Levine occurred in patients subject to “paroxysmal auricular fibrillation.”

A relation between the characteristics of A-V conduction in patients with a short P-R interval and the occurrence of ventricular arrhythmias was suggested by the report of R-on-T phenomenon during AF in a patient with LGL syndrome.43 In our patients VT was initiated in the laboratory by an appropriately timed atrial premature depolarization in one case, and during rapid RA pacing in association with enhanced A-V conduction in a second patient. However, the exact relation between the spontaneous occurrence of ventricular arrhythmias in these patients and the characteristics of A-V conduction which have been documented remains to be clarified.

Our findings indicate that patients with LGL syndrome manifest a variety of rhythm disorders, some of a life-threatening nature. Both the type of the arrhythmia(s) and the electrophysiologic mechanisms sustaining the arrhythmia(s) require individual evaluation in each patient, and neither can be assumed to be related to the presence of a short P-R interval. On the other hand, the characteristics of A-V conduction and refractoriness in patients with a short P-R interval susceptible to RT and/or AF permit development of rapid heart rates, and may explain why these patients are frequently symptomatic. In patients susceptible to ventricular arrhythmias, short A-V node refractory periods and enhanced A-V conduction may be associated with the initiation of these arrhythmias by a premature atrial depolarization or by a spontaneous atrial tachyarrhythmia.

Acknowledgment

The authors wish to express their gratitude to the many cardiology fellows who participated in these studies; to Laura Cook, R.N. and to Donald Kopp, L.P.N., the staff of The Electrophysiology Laboratory; to Jackie Kasell, electronics consultant; to Don Powell and David Hugetti who prepared the illustrations; and to Bonnie Farmer and Ann R. Clayton who prepared the manuscript.

References

27. Sellers TD, Gallagher J, Cope GD, Tonkin AM, Wallace AG:
Re-entrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

5. Mechanism of Action of Diphenylhydantoin

NABIL EL-SHERIF, M.D., AND RALPH LAZZARA, M.D.

SUMMARY The mechanism of action of diphenylhydantoin (DPH) on re-entrant ventricular arrhythmias (RVA) was studied in dogs 3-7 days following ligation of the anterior descending coronary artery utilizing direct recordings of the re-entrant pathway (RP) from the epicardial surface of the infarction zone (IZ). DPH in a therapeutic dose consistently prolonged refractoriness of potentially RP in the IZ. This resulted in further impairment and/or block of conduction in the RP and was directly responsible for DPH ability to abolish RVA. On the other hand, DPH had no significant effect on conduction in the adjacent normal zone. Prior to abolition of RVA initiated by premature beats (PBs), DPH resulted in: 1) narrowing of the critical range of coupling intervals of PBs that resulted in re-entry (i.e., the re-entry zone), 2) shift of the narrowed re-entry zone to longer cardiac cycle lengths, and 3) lengthening of the coupling interval of the first re-entrant beat, as well as slowing the rate of re-entrant tachycardia. Thus DPH, similar to lidocaine, owes its antiarrhythmic action in RVA to its selective depressant effect on ischemic cells forming part of the RP.

Since initial experimental reports by Harris and Kokernot1 and Mosey and Tyler2 diphenylhydantoin (DPH) has been shown to be an effective agent in abolishing various experimental and clinical cardiac arrhythmias in a variety of situations including digitalis toxicity and acute myocardial infarction.3-14 However, the mechanism of the antiarrhythmic action of DPH has given rise to considerable controversy. Most investigators agree that the drug depresses spontaneous diastolic depolarization and is effective in arrhythmias due to enhanced automaticity.12, 14, 18 The controversy centers on the effects of DPH on electrophysiologic parameters such as membrane responsiveness and conduction velocity in cardiac cells, which can be major determinants in the establishment or abolition of re-entrant arrhythmias. Bigger et al.12 and Strauss et al.18 found that DPH in therapeutic concentrations did not decrease membrane responsiveness or conduction velocity. On the contrary, it actually increased these two parameters in addition to abbreviation of both the action potential duration and effective refractory period especially in depressed cardiac cells. The efficacy of DPH in abolishing re-entrant rhythms was thus attributed to improvement of conduction in the re-entrant pathway.12, 13, 17-18 On the other hand, other investigators have found that DPH effects on cardiac cells are not dissimilar to those of quinidine,20 producing marked retardation of conduction velocity and depression of membrane responsiveness particularly in the presence of higher extracellular levels of potassium.16, 21-28 These findings would suggest that DPH, similar to quinidine, may interrupt re-entrant cycles by conversion of a one-way block into a two-way block.16

We have recently analyzed the mechanism of action of lidocaine in re-entrant ventricular arrhythmias in dogs 3-7 days post myocardial infarction24 utilizing a remarkably stable canine model in which direct recordings of the elec-
Characteristics of atrioventricular conduction and the spectrum of arrhythmias in lown-ganong-levine syndrome.
D G Benditt, L C Pritchett, W M Smith, A G Wallace and J J Gallagher

Circulation. 1978;57:454-465
doi: 10.1161/01.CIR.57.3.454

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/57/3/454

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/