The Effect of Lidocaine on Reentry Within the His-Purkinje System in Man

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SUMMARY The effects of intravenous lidocaine were assessed in 11 patients with normal intraventricular conduction in whom reentry within the His-Purkinje system (RE-HPS) occurred consistently over a narrow range of ventricular (S,S) coupling intervals. RE-HPS was characterized by a spontaneous beat (V) inducible by critically timed premature stimuli (S) during constant ventricular drive (S,S), and was dependent upon critical retrograde conduction delay within the HPS (S,H interval). Lidocaine abolished RE-HPS in six of 11 patients (group 1) and shortened the zone of RE-HPS in five of 11 patients (group 2). In group 1 after lidocaine, critical S,H intervals for RE-HPS were not attained at any S,S in four patients and critical S,H intervals were equaled but not exceeded in two patients without resulting in RE-HPS. In group 2 after lidocaine, RE-HPS was present in all patients at S,H intervals comparable to control values; however, significantly closer S,S intervals were necessary to achieve these requisite S,H delays (p < 0.005). The longest S,H intervals at comparable S,S intervals were significantly shortened by lidocaine in 11 of 11 patients (p < 0.001). Thus, lidocaine causes a significant decrease in retrograde refractoriness within the HPS in patients with normal intraventricular conduction.

A FORM OF REENTRY involving both bundle branches and the bundle of His has recently been shown in man.1 During retrograde refractory period studies, Akhtar and associates observed that, in more than 50% of patients, a closely coupled premature ventricular beat (V) resulted in a subsequent spontaneous beat (V), the morphology of which was similar to V. It was postulated that, at close ventricular coupling intervals, the premature impulse (V) encountered retrograde block within the right bundle branch (RBB) and was conducted with delay retrogradely via the left bundle branch (LBB) to the bundle of His. The V impulse was then antegrade conducted via the RBB (providing sufficient time had elapsed for its recovery), whereupon the ventricles were reactivated, resulting in a spontaneous beat (V). The reentrant beat (V) was always preceded by a His bundle deflection and associated with a longer HV interval than that of sinus beats. The major determinants of this form of reentry within the His-Purkinje system (RE-HPS) are compatible with the requisites for reentry in any cardiac tissue: unidirectional block, delayed conduction and recovery of excitability.2, 3 This form of reentry provides a clinical experimental model in which the electrophysiologic effects of commonly used cardiovascular drugs can be evaluated. The present study was undertaken to assess the effects of lidocaine on RE-HPS in patients with normal intraventricular conduction.

Methods

Right-heart catheterization was performed in the postabsorptive, nonsedated state in 11 patients. The experimental procedure was explained and signed consents were obtained. No patient was taking cardioactive medication at the time of the study, and no patient had clinical or electrocardiographic evidence of acute myocardial ischemia, prior myocardial infarction or spontaneous ventricular arrhythmias. All patients had normal intraventricular conduction as defined by a QRS duration of less than 100 msec on the surface ECG and an HV interval of 55 msec or less during spontaneous sinus rhythm. In addition, all patients had normal serum electrolytes, liver function tests, blood urea nitrogen and serum creatinine concentrations.

Under local anesthesia a quadripolar electrode catheter was percutaneously introduced into a right antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium near its junction with the superior vena cava. The proximal pair of electrodes was used to record a high atrial electrogram and the distal pair to stimulate the atrium. A tripolar catheter was percutaneously introduced into the right femoral vein and positioned in the region of the tricuspid valve to record electrical activity from the bundle of His, as previously described.4 A bipolar electrode catheter was introduced into a right antecubital vein and fluoroscopically positioned at the right ventricular apex for ventricular stimulation.

Intracardiac electrograms (recorded at 40–500 Hz), standard ECG leads I, II, III and V, (recorded at 0.1–200 Hz), and time lines generated at 10, 100 and 1000 msec were simultaneously displayed on a multichannel oscilloscope and recorded on magnetic tape. Recordings were subsequently reproduced on photographic paper at a speed of 150 mm/sec. Using a programmable digital stimulator and the extrastimulus method, both antegrade and retrograde...
refractory period measurements were made at one or more basic cycle lengths \( (A_1A_1 \text{ or } V_1V_1) \). After every eighth beat of the basic drive, a premature beat \( (A_2 \text{ or } V_2) \) was introduced at progressively shorter coupling intervals \( (A_1A_3 \text{ or } V_1V_3) \) up to the point of atrial or ventricular refractoriness. Electrical stimulation was performed using 1.5-msec impulses delivered through an isolation unit at the least milliamperage that permitted consistent atrial or ventricular capture. All equipment was carefully grounded. A slow, i.v. infusion of 5% dextrose in water was started in each patient before initiation of electrophysiologic studies. Blood pressure was monitored with a sphygmomanometer at 15-minute intervals throughout the study.

RE-HPS was observed in all 11 patients who were entered in this protocol. Upon completion of control studies, each patient received i.v. lidocaine as a \( 1 \) mg/kg bolus, followed immediately by a constant infusion at a rate of \( 4 \) mg/min. After a 10-minute equilibration period, electrophysiologic studies were repeated. Venous blood samples for plasma lidocaine levels were drawn from the arm not used for the infusion immediately before dosing and after repeat ventricular refractory period studies (during continuous drug infusion). Plasma lidocaine assays were carried out by Astra Pharmaceuticals, Inc., using a standard chromatographic technique. Statistical data were analyzed using the \( t \) test for paired data.

**Definition of Terms**

\( S_1, A_1, H_1 \), and \( V_1 \) represent the stimulus artifact, the atrial electrogram, the His bundle electrogram and the ventricular electrogram of the basic drive beat, respectively.

\( S_2, A_2, H_2 \), and \( V_2 \) represent the stimulus artifact, the atrial electrogram, the His bundle electrogram and the ventricular electrogram of the premature beat, respectively.

**Atrioventricular (AV) nodal conduction time** is approximated by the AH interval, which is measured from the onset of the low right atrial electrogram to the onset of the His bundle deflection (normal values for this laboratory 60-140 msec).

**His-Purkinje conduction time** is approximated by the HV interval, which is measured from the onset of the His bundle deflection to the onset of ventricular activation (normal values for this laboratory 30-55 msec).

**Effective refractory period (ERP) of the atrium** is defined as the longest \( S_1S_2 \) interval at which \( S_2 \) fails to depolarize the atrium.

**ERP of the AV node** is defined as the longest \( A_1A_2 \) interval at which \( A_2 \) fails to depolarize the His bundle.

**Functional refractory period (FRP) of the AV node** is defined as the shortest \( H_1H_2 \) interval that results from any \( A_1A_2 \), provided that AV conduction is not limited by atrial refractoriness.

**ERP of the HPS** is defined as the longest \( H_1H_2 \) interval at which \( H_2 \) fails to conduct to the ventricles.

**Relative refractory period (RRP) of the HPS** is the longest \( H_1H_2 \) at which \( H_2 \) conducts to the ventricles with a longer HV interval than that of the basic drive beat or with a QRS of aberrant configuration. The limitations of this definition have been discussed previously.6,7

**ERP of the ventricle** is defined as the longest \( S_1S_2 \) interval at which \( S_2 \) fails to depolarize the ventricle during ventricular stimulation.

**Retrograde conduction intervals.** During ventricular pacing, the onset of ventricular depolarization was taken from the stimulus artifact (S). The SH and SA intervals were measured from the stimulus artifact to the onset of the retrograde His bundle electrogram and low atrial electrogram, respectively. When \( S_2 \) resulted in more than one ventricular beat (i.e., \( V_3 \)), the HV interval of subsequent beats (\( H_2V_3 \)) was measured from the onset of the His bundle electrogram to the earliest detectable ventricular activity on the standard ECG or His bundle electrogram recording.

The foregoing definitions apply to conduction along normal pathways at any given basic atrial or ventricular cycle length in the absence of antegrade or retrograde functional bypass tracts.

**Results**

The essential clinical data for the 11 patients are summarized in table 1. Patients were divided into two groups based upon their response to lidocaine. In patients 1-6 (group 1), lidocaine abolished the reentry phenomenon. In patients 7-11 (group 2), lidocaine modified, but did not abolish, reentry.

**Table 1. Clinical Data**

| Patient | Age (years) | Sex | Diagnosis     | Resting ECG |
|---------|-------------|-----|---------------|-------------|
| 1       | 77          | M   | ASHD          | STT Ab      |
| 2       | 61          | M   | NHD           | Normal      |
| 3       | 58          | F   | NHD           | Normal      |
| 4       | 46          | M   | PMD           | STT Ab + APB|
| 5       | 25          | F   | NHD           | Normal      |
| 6       | 55          | M   | ASHD          | STT Ab + AF |
| 7       | 37          | M   | NHD           | Normal      |
| 8       | 57          | M   | HHD           | Normal      |
| 9       | 67          | M   | PMD           | STT Ab + APB|
| 10      | 33          | M   | MVP           | Normal      |
| 11      | 19          | M   | RHD           | LVH         |

Abbreviations: NHD = no heart disease; ASHD = arteriosclerotic heart disease; HHD = hypertensive heart disease; PMD = primary myocardial disease; MVP = mitral valve prolapse; RHD = rheumatic heart disease; STT Ab = ST-segment and T-wave abnormalities; APB = atrial premature beats; AF = atrial fibrillation; LVH = left ventricular hypertrophy.
### Table 2. Antegrade Electrophysiologic Data Before and After Lidocaine

| Pt | Sinus CL | AH interval (NSR) | HV interval (NSR) | PCL-AVNWB |
|----|----------|-------------------|------------------|-----------|
|    | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Group 1 |     |      |     |      |     |      |     |      |
| 1 | 900 | 840 | 140 | 135 | 50 | 50 | 460 | * |
| 2 | 870 | 800 | 120 | 100 | 50 | 50 | 330 | * |
| 3 | 700 | 650 | 90 | 90 | 40 | 40 | 330 | 330 |
| 4 | 800 | 830 | 110 | 110 | 40 | 40 | 370 | 330 |
| 5 | 890 | 1000 | 85 | 90 | 50 | 50 | 310 | 310 |
| 6 | AF | AF | AF | AF | 50 | 50 | AF | AF |

Mean ± SD 832 ± 83 824 ± 124

### Table 3. Retrograde Electrophysiologic Data Before and After Lidocaine

| Pt | HV interval (NSR) | Basic VCL (S1, S2 intervals) | Critical S2 H2 for RE-HPS |
|----|-------------------|-----------------------------|--------------------------|
|    |                   | RE-HPS                      |                          |
|    |                   | Pre | Post | Pre | Post | Pre | Post |
| Group 1 |     |      |     |      |     |      |     |      |
| 1 | 50 | 700 | 310-280 | * | 240 | * |
| 2 | 50 | 700 | 320-270 | * | 235 | * |
| 3 | 40 | 700 | 320-230 | * | 210 | * |
| 4 | 40 | 800 | 320-270 | * | 230 | * |
| 5 | 50 | 800 | 330-260 | * | 260 | * |
| 6 | 50 | 500 | 260-190 | * | 170 | * |

Mean ± SD 46 ± 5 700 ± 109

| Group 2 |     |      |     |      |     |      |     |      |
| 7 | 40 | 700 | 310-240 | 240-230 | 290 | 290 |
| 8 | 40 | 800 | 350-300 | 300-280 | 230 | 220 |
| 9 | 40 | 700 | 330-250 | 280-250 | 200 | 200 |
| 10 | 50 | 800 | 320-250 | 260-240 | 280 | 280 |
| 11 | 40 | 600 | 340-230 | 260-230 | 200 | 205 |

Mean ± SD 42 ± 4 720 ± 114

All values are expressed in milliseconds.

*Not observed at atrial paced rates up to 200 beats/min.

†Refractory period studies limited by atrial refractoriness.

Abbreviations: NSR = normal sinus rhythm; CL = cycle length; PCL-AVNWB = paced atrial cycle length at onset of atrioventricular nodal Wenckebach block; ERP = effective refractory period; AVN = atrioventricular node; FRP = functional refractory period; RRP = relative refractory period; HPS = His-Purkinje system; AF = atrial fibrillation. Pre = control values; Post = post-lidocaine values.
**Table 2. (Continued)**

| Paced CL | Atrial ERP | ERP AVN | FRP AVN | RRP HPS |
|----------|------------|---------|----------|----------|
|          | Pre        | Post    | Pre      | Post     | Pre     | Post    |
| 700      | 280        | 310     | 400      | 340      | 525     | 490     |
| 600      | 220        | 210     | 260      | 270      | 360     | 360     | 400     | <360    |
| 800      | 290        | 250     | 310      | ⊺         | 420     | 410     | 420     | <410    |
| 800      | 200        | 200     | ⊺         | ⊺         | 390     | 390     | 400     | <390    |
| AF       | AF         | AF      | AF       | AF       | AF      | AF      |
| 680 ± 83 | 256 ± 42   | 244 ± 43| 323 ± 70 | 305 ± 49 | 419 ± 63| 408 ± 49| 406 ± 11| 386 ± 25|

**Table 3. (Continued)**

| Range of H2V3 intervals | Longest S2H3 interval | Ventricular ERP | Plasma lidocaine concentration (μg/ml) |
|-------------------------|-----------------------|----------------|--------------------------------------|
|                         | Pre                   | Post           | Pre       | Post           | Pre       | Post     |
| 60-70                   | *                     | 290            | 200       | 270            | 250       | 1.4      |
| 70                      | *                     | 270            | 235       | 260            | 260       | 1.8      |
| 60-80                   | *                     | 290            | 180       | 220            | 230       | 2.0      |
| 50-70                   | *                     | 290            | 220       | 260            | 250       | 5.5      |
| 60-85                   | *                     | 305            | 260       | 250            | 240       | 3.8      |
| 60-70                   | *                     | 210            | 150       | 180            | 190       | 3.8      |
| 60 ± 6 to 75 ± 7        |                       | 275 ± 34       | 207 ± 39  | 240 ± 34       | 236 ± 25  | 3.05 ± 1.5|
| 60-70                   | 60-70                 | 340            | 290       | 230            | 220       | 2.5      |
| 65-75                   | 70-75                 | 280            | 240       | 290            | 270       | 2.6      |
| 55-80                   | 60-75                 | 280            | 250       | 240            | 240       | 1.8      |
| 55-70                   | 60-75                 | 360            | 320       | 240            | 230       | 1.9      |
| 60-80                   | 75-80                 | 280            | 225       | 220            | 220       | 5.0      |
| 59 ± 4 to 73 ± 5        | 65 ± 7                | 308 ± 37       | 265 ± 38  | 244 ± 31       | 236 ± 24  | 2.7 ± 1.3|

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FIGURE 1. The effect of lidocaine on antegrade refractoriness within the His-Purkinje system. Tracings from top to bottom represent standard ECG leads I, II and V1, high right atrial electrogram (HRA), His bundle electrogram (HBE) and time lines (T). The basic atrial cycle length (A1A1) is constant at 800 msec. (A) Control: an atrial premature depolarization (A2) coupled to a basic drive beat (A1) at an interval of 500 msec results in an H1H2 interval of 545 msec. This is the longest H1H2 interval at which aberrant ventricular conduction (right bundle branch block [RBBB]) occurred and, therefore, defines the antegrade refractory period of the RBB (relative or effective) during the control period. (B) After lidocaine, the same A1A2 coupling interval shown in panel A results in an identical H1H2 interval (545 msec); however, conduction of A2 occurs without RBBB aberration. (C) The shortest H1H2 interval (500 msec) observed after administration of lidocaine. A2 is conducted normally without evidence of RBBB aberration or prolongation of the H2V2 interval. Although the absolute magnitude of the antegrade refractory period of the RBB could not be determined after drug administration (i.e., RBBB was never observed), it is apparent that lidocaine shortened this measurement by at least 45 msec in this patient.
Antegrade Conduction and Refractory Period Studies (table 2)

In both groups of patients, lidocaine caused small but statistically insignificant decreases in the mean sinus cycle length, mean AV nodal conduction time, and atrial paced cycle length at which Mobitz type I second-degree AV nodal block occurred, mean ERP of the atrium, and the mean ERP and mean FRP of the AV node. The His-Purkinje conduction time (HV interval) remained unchanged during both sinus rhythm and atrial pacing at increment rates.

During control antegrade refractory period studies, the RRP of the HPS was encountered in patients 2, 4 and 5 in group 1 and in patients 7, 8 and 11 in group 2. In all six patients, refactoriness was manifested as RBB block aberration. Lidocaine significantly shortened the RRP in all six patients (i.e., RBB aberration occurred at shorter H2H2 intervals after drug administration). The mean decrease for all six patients was greater than 25 msec (p < 0.01). Determination of the absolute magnitude of this decrease was precluded by the FRP of the AV node in five of six patients. An example of the effect of lidocaine on the relative refractory period of the HPS is given in figure 1.

Retrograde Electrophysiologic Studies

Retrograde electrophysiologic data before and after lidocaine are presented in table 3. Patients 9 and 11 consistently had AV dissociation at all ventricular drive rates, and patient 6 had atrial fibrillation. All other patients had 1:1 retrograde atrial capture during the basic ventricular drive.

ERP of Ventricular Muscle

The ERP of ventricular muscle was not significantly different for group 1 and group 2 patients during the control period. In both groups, lidocaine caused a small but statistically insignificant decrease in the mean ERP of the ventricle.

Refractoriness of the HPS

In all patients, the S2H2 interval was inversely related to the ventricular (S1S2) coupling interval (i.e., the S2H2 interval lengthened progressively as the S1S2 interval decreased). The longest S2H2 interval observed over a full range of ventricular coupling intervals was used as an index of retrograde refactoriness within the HPS. No significant difference in this measurement existed between groups 1 and 2 in the control period, although the average value in group 2 was greater by 12% (275 vs 310 msec). In both groups, lidocaine caused a statistically significant decrease in the longest obtainable S2H2 interval (p < 0.001) at comparable ventricular coupling intervals. In group 1, the average decrease was 68 msec, a 24% change from control, while in group 2 the average decrease was 43 msec, a 14% change from control. In both groups, the range of H2V4 intervals after administration of lidocaine did not differ significantly from control values.

Reentry Within the HPS: Control Studies

The range of ventricular (S1S2) coupling intervals over which reentry occurred is referred to as the zone of reentry (table 3). For the control period, there were no significant differences in the maximum or the minimum S1S2 intervals at which reentry occurred in group 1 and group 2 patients. Once a given S1S2 interval resulted in reentry, RE-HPS persisted at shorter S1S2 intervals up to the point of ventricular muscle refactoriness. Four patients demonstrated a gap phenomenon within the zone of reentry. In both groups, the morphology and axis orientation of the reentrant beat (V4) closely resembled that of the basic drive (V3) and premature (V4) beats. However, the QRS duration of V4 uniformly exceeded that of V3 and V2. The reentrant beat (V4) was always preceded by a His bundle deflection (H2), and the H2V4 interval always exceeded the HV interval observed during sinus rhythm (table 3). During the control period there were no significant differences in the ranges of H2V4 intervals in group 1 and group 2 patients. In addition, there was no significant difference in the critical (minimum) S2H2 interval at which reentry occurred in the two groups of patients.

Effects of Lidocaine on RE-HPS

Lidocaine abolished reentry in group 1 (six patients) and significantly modified the zone of reentry in group 2 (five patients).

Group 1

In patients 1, 3, 4 and 6 in group 1, the longest obtainable S2H2 delay after lidocaine was less than the minimum S2H2 delay that resulted in reentry before drug administration (figs. 2 and 3). In patients 2 and 5, the longest S2H2 delay after lidocaine was identical to the minimum value at which reentry occurred before administration of the drug.

Group 2

Lidocaine did not abolish RE-HPS in group 2 patients, but significantly decreased the range of ventricular (S1S2) coupling intervals at which reentry occurred. After lidocaine, the critical (minimum) S2H2 delay at which reentry occurred did not differ significantly from control values. In all group 2 patients, however, significantly shorter S1S2 coupling intervals were required to achieve the critical S2H2 delay for reentry after lidocaine (p < 0.001). This resulted in a marked narrowing of the zone of reentry in all five patients in this group (table 3 and figs. 4 and 5). The mean values for the shortest S1S2 intervals at which reentry occurred were limited by the ERP of the ventricle and were not significantly different before and after lidocaine.

Gap Phenomenon Within the Zone of Reentry

During control studies, patients 1, 3, 8 and 10 had small retrograde gaps within the zone of reentry. An
example of this phenomenon is given in figure 2. Over a narrow range (10–20 msec) of S<sub>1</sub>S<sub>2</sub> intervals encompassed within the zone of reentry, the S<sub>2</sub> impulse encountered retrograde block within or proximal to both bundle branches and failed to depolarize the bundle of His. During these periods of retrograde block, REHPS system did not occur. However, at closer S<sub>1</sub>S<sub>2</sub> intervals, the S<sub>2</sub> impulse encountered conduction delay proximal to the site of previous retrograde block, allowing sufficient time for distal recovery and resumption of retrograde conduction to the bundle of His. With propagation to the bundle of His restored, reentry was again observed. This recurrence of reentry at closer S<sub>1</sub>S<sub>2</sub> intervals was always associated with longer S<sub>1</sub>H<sub>2</sub> intervals than those observed immediately before the onset of retrograde gap. In patients 1 and 3...
in group 1 and patient 8 in group 2, the zone of retrograde gap was abolished by lidocaine. In patient 10 in group 2, the zone of retrograde gap was unchanged after lidocaine.

**Plasma Lidocaine Concentrations**

The individual plasma lidocaine concentrations ranged from 1.4–5.5 μg/ml (table 3). The average plasma concentrations were not significantly different between groups.

**Blood Pressure**

A small and transient decrease in arterial blood pressure was observed in four of 11 patients immediately after administration of the lidocaine bolus. At the end of the 10-minute equilibration period, however, no patient had a significant decrease in arterial blood pressure compared with control values.

**Side Effects**

Mild subjective dizziness occurred in two patients immediately after administration of the initial lidocaine bolus. These symptoms were transient and did not necessitate a reduction in the rate of the lidocaine infusion. No other adverse side effects were observed.

**Discussion**

Although the precise anatomic pathway of the V₃ phenomenon cannot be stated with certainty, available evidence strongly suggests that the reentrant circuit involves both bundle branches and the bundle of His. This form of RE-HPS might be abolished if one or more of the following conditions were met: (1) failure to achieve the requisite retrograde (S₂H₂) conduction delay in the LBB, thereby allowing insufficient time for recovery of excitability in the RBB; (2) sufficient retrograde penetration of the premature (S₂) impulse into the RBB to result in delayed recovery and, therefore, unavailability of this structure for antegrade conduction of the reentrant impulse; (3) elimination of unidirectional retrograde block (i.e., complete retrograde penetration of the RBB by the premature impulse); (4) the development of bidirectional retrograde block (i.e., failure of the premature impulse to reach the bundle of His via either the RBB or the LBB); and (5) prolongation of the ERP of the ventricular muscle, rendering this tissue inexitable by the reentrant impulse. Under conditions 2 and 5, it is apparent that reentry might fail to occur even if the maximum retrograde (S₂H₂) conduction delay achieved by the premature impulse were equal to or greater than the minimum requisite S₂H₂ delay for reentry during the control period. Under these circumstances, sufficient delay of recovery of excitability in the RBB or ventricular muscle would prevent completion of the reentry circuit. Evidence for at least partial penetration of the RBB by closely coupled ventricular premature beats can be derived from the fact that RE-HPS did not occur at shorter S₂H₂ intervals after lidocaine. The antegrade RRP of the HPS (manifested as RBB block) was shortened by lidocaine in all six patients in whom it could be measured. Therefore, it is reasonable to expect that if retrograde penetration of the RBB by S₂ had not occurred after lidocaine, this pathway would have been available for antegrade conduction earlier than during the control period and, thus, that RE-HPS would have occurred at shorter S₂H₂ intervals after the drug. Evidence for bidirectional retrograde block described under condition 4 was observed during the retrograde gap phenomenon, wherein reentry occurred on either side of the gap zone but did not occur when retrograde conduction to the bundle of His failed (figs. 2 and 4). Condition 5 was not operative in this study because lidocaine did not significantly affect the ERP of the ventricle in either group of patients.

**Figure 2.** Reentry within the His-Purkinje system during control ventricular refractory period studies in patient 1. Format and abbreviations as in figure 1. The basic paced ventricular cycle length (S₁S₁) is constant at 700 msec. (A) A premature ventricular depolarization (S₁) is coupled to a basic drive beat (S₁) at an interval of 330 msec. This results in an S₂H₂ interval of 180 msec, which is insufficient for reentry to occur, as evidenced by the absence of a V₂ response. (B) A premature ventricular depolarization (S₂) coupled to a basic drive beat at an interval of 310 msec achieves an S₂H₂ delay of 240 msec, which is sufficient for reentry within the His-Purkinje system (RE-HPS) to occur, as evidenced by the presence of a third ventricular beat (V₃). This is the longest ventricular (S₂S₂) coupling interval and the shortest S₂H₂ interval at which RE-HPS was observed during control studies. The QRS morphology and axis orientation of the reentrant beat (V₃) closely resemble that of both the basic drive beat (V₁) and the paced premature beat (V₂). (C) At a ventricular (S₂S₂) coupling interval of 300 msec, the paced premature beat is blocked proximal to the bundle of His, as evidenced by the absence of a retrograde His bundle deflection. RE-HPS is absent when retrograde conduction to the bundle of His fails. (D) The ventricular coupling interval is reduced to 280 msec and conduction to the bundle of His resumes (retrograde gap phenomenon), as evidenced by the presence of a retrograde His bundle deflection (H₂). RE-HPS reappears when retrograde conduction to the bundle of His is resumed. The reentrant beat (V₃) now exhibits a right bundle branch block configuration, suggesting that retrograde activation of H₂ may have occurred via the right bundle branch. This variation in QRS morphology of V₃ was not observed in other patients either before or after lidocaine. The S₂H₂ interval of 290 msec (panel D) was the longest observed during control studies. At closer ventricular coupling intervals, the effective refractory period of the ventricle was encountered.
In patients 1, 3, 4 and 6 in group 1, RE-HPS failed to occur after lidocaine, because the minimum or requisite \( S_2H_2 \) delay was not achieved after administration of the drug. In these four patients, the longest \( S_2H_2 \) delays after lidocaine were 60–110 msec shorter than those during the control period (table 3). These relatively large differences in \( S_2H_2 \) intervals suggest the possibility that lidocaine abolished unidirectional (retrograde) block in the RBB in these patients (condition 3). This would permit even the most closely coupled premature (S2) impulses to activate the bundle of His retrogradely via the RBB. Whether this magnitude of difference in \( S_2H_2 \) intervals reflects abolition of unidirectional retrograde block in the RBB (condition 3) or a decrease in retrograde conduction time in the LBB, resulting in insufficient time for recovery in the RBB (condition 1), cannot be ascertained from these data. Another possibility is that the presence of decreased retrograde conduction time in the LBB, in addition to extensive but incomplete retrograde penetration of the premature impulse into the RBB, resulted in delayed recovery of excitability in this structure (condition 2). This latter mechanism is the most likely explanation for the behavior in patients 2 and 5 in group 1. In both patients, reentry failed to occur despite the fact that the longest obtainable \( S_2H_2 \) interval after lidocaine was exactly equal to the critical or requisite value for reentry during the control period. Decreased retrograde conduction time in the LBB could explain the shorter \( S_2H_2 \) intervals after lidocaine, and decreased retrograde refractoriness in the distal RBB resulting in more retrograde penetration of the RBB and unavailability for antegrade conduction could explain failure of reentry after lidocaine despite attainment of the critical \( S_2H_2 \) interval.

It is also possible, however, that in patients 2 and 5, retrograde conduction to the bundle of His via the RBB persisted at all coupling intervals after administration of lidocaine. If sufficient retrograde conduction delay (without block) were achieved in the RBB after lidocaine, it is possible that \( S_2H_2 \) intervals equal to or greater than the critical \( S_2H_2 \) interval during control studies might be attained without resulting in reentry. This could occur only if lidocaine shortened the retrograde ERP of the RBB to a greater extent than it shortened the retrograde RRP of the RBB. This might result in delayed retrograde excitation of the bundle of His via the RBB by even the most closely coupled premature beats that, at comparable coupling intervals, encountered retrograde block within the RBB during the control period. For activation of the bundle of His to occur in this manner, retrograde conduction time from the stimulating electrode to the bundle of His would have to be shorter via the RBB than via the LBB at all coupling intervals. Attainment of extremely long \( S_2H_2 \) intervals as a result of retrograde conduction to the bundle of His via the RBB appears unlikely, however. While lidocaine significantly shortens both the action potential duration and the ERP of Purkinje fibers, the decrease in action potential duration is of greater magnitude than the decrease in ERP. Further, in this study, reentry uniformly occurred in every patient in whom the \( S_2H_2 \) intervals after lidocaine exceeded the critical \( S_2H_2 \) for reentry during the control period (table 3). This observation provides firm evidence that, after administration of lidocaine, when the \( S_2H_2 \) interval exceeded the minimum requisite value for reentry observed during control studies, retrograde conduction of S2 to the bundle of His via the RBB could not have occurred, because the RBB was uniformly available for antegrade conduction of the reentrant impulse (V3).

In group 2 patients, RE-HPS persisted after administration of lidocaine. In addition, the mean value for the critical \( S_2H_2 \) interval for reentry during the control period was nearly identical to the critical \( S_2H_2 \) interval for reentry after lidocaine (table 3). However, in each of the five patients in this group, significantly shorter ventricular (S2,S2) coupling intervals (average 62 msec) were required to achieve the critical \( S_2H_2 \) interval for reentry after lidocaine (table 3, figs. 4 and 5). It appears likely, therefore, that the same mechanisms involved in explaining elimination of reentry in group 1 patients were operative in modifying the zone of reentry in group 2 patients, and that all these mechanisms involved a decrease in retrograde refractoriness within the HPS induced by lidocaine.

Patients in groups 1 and 2 appear to differ primarily in the extent to which retrograde refractoriness within

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**Figure 3.** Absence of reentry within the His-Purkinje system (RE-HPS) after lidocaine in patient 1. Format and abbreviations as in figure 1. The basic ventricular cycle length is 700 msec. All tracings were taken after lidocaine. At S1,S2 coupling intervals of 330 msec (panel A) and 300 msec (panel B), retrograde conduction delay within the His-Purkinje system is minimal, and the retrograde His bundle deflection remains obscured within the local ventricular electrogram. The retrograde gap phenomenon is not present after administration of lidocaine (fig. 2C). (C) The S1,S2 interval is decreased to 290 msec and an S2H2 delay of 190 msec is achieved. This S2H2 interval is 100 msec shorter than the S2H2 delay of 190 msec is achieved. This S2H2 interval is 100 msec shorter than the S2H2 interval attained at the identical ventricular coupling interval before lidocaine (fig. 2D). (D) At the closest S1,S2 coupling interval attainable before ventricular muscle refractoriness, a maximum S2H2 interval of 200 msec is achieved. This S2H2 interval is 40 msec shorter than the requisite S2H2 interval for reentry in this patient (fig. 2B) and 90 msec shorter than the longest S2H2 interval observed during the control period (fig. 2D). RE-HPS (V3) is absent in all panels because the requisite or critical S2H2 interval (240 msec) was never attained after lidocaine. In comparing S2H2 intervals before (fig. 2) and after lidocaine (above), it is evident that the drug caused a significant decrease in retrograde refractoriness within the His-Purkinje system.
The basic ventricular cycle length is 800 msec. (A) At a ventricular coupling interval of 350 msec, a critical \( S_1H_2 \) delay of 230 msec is achieved and reentry occurs, as shown by the presence of a third beat \( (V_3) \). This was the longest ventricular coupling interval at which RE-HPS occurred during the control period. (B) At a ventricular coupling interval of 340 msec, the premature beat \( (V_2) \) is blocked proximal to the bundle of His, as evidenced by the absence of a retrograde His bundle deflection. RE-HPS is absent when retrograde conduction to the bundle of His fails. (C) At a ventricular coupling interval of 330 msec, retrograde conduction to the bundle of His resumes (retrograde gap phenomenon) and RE-HPS occurs. (D) At the closest \( S_1S_2 \) coupling interval attainable before ventricular muscle refractoriness, a maximum \( S_2H_2 \) interval of 280 msec is achieved and RE-HPS persists.
FIGURE 5. Modification of the zone of reentry within the His-Purkinje system (RE-HPS) after lidocaine in patient 8. Format and abbreviations as in figure 1. The basic ventricular cycle length is 800 msec. All tracings were taken after lidocaine. At ventricular coupling intervals of 340 msec (A) and 310 msec (B), insufficient retrograde HPS conduction delay is achieved for reentry to occur (note the absence of V4). Also note the absence of the retrograde gap phenomenon after lidocaine (fig. 4B). (C) At a coupling interval of 300 msec, the critical S2H2 interval of 220 msec is achieved and RE-HPS occurs, as evidenced by the presence of a spontaneous ventricular complex (V4) after H2. Because of decreased retrograde HPS refractoriness induced by lidocaine, significantly shorter ventricular coupling intervals (300 msec vs 350 msec) are required to achieve the critical S2H2 interval for reentry after administration of the drug (fig. 4A). The S2H2 interval of 220 msec is 60 msec shorter than that achieved at the identical ventricular coupling interval during the control period (fig. 4D). The fourth QRS complex represents reentry within the atrioventricular node induced by V2. (D) At the closest coupling interval attainable before ventricular muscle refractoriness, a maximum S2H3 interval of 240 msec is achieved and RE-HPS persists.
the HPS was decreased by lidocaine. During the control period, there were no statistically significant differences between groups in any of the following measurements: (1) the critical $S_2H_2$ interval for reentry, (2) the longest ventricular ($S_2S_4$) coupling interval at which reentry first occurred, and (3) the longest $S_2H_2$ interval at comparable ventricular coupling intervals. Therefore, an inherent difference in retrograde refractoriness within the HPS does not explain the different responses to lidocaine in the two groups. Further, plasma concentrations of lidocaine were comparable in both groups. In group 1 patients, administration of lidocaine resulted in a 68-msec decrease (24%) from control in the longest $S_2H_2$ interval at comparable ventricular coupling intervals; in group 2 patients, the average decrease in this measurement was 43 msec, a 14% decrease from control. The smaller decrease in retrograde HPS refractoriness in group 2 compared with group 1 patients explains the longer $S_2H_2$ intervals and, therefore, the occurrence of reentry at close ventricular coupling intervals after lidocaine in group 2 patients. These observations suggest that the difference between group 1 and group 2 patients is best explained by greater sensitivity of group 1 patients to the effects of lidocaine on retrograde HPS refractoriness. In both groups, however, lidocaine caused a significant decrease in all measurements of retrograde refractoriness within the His-Purkinje system. The fact that the plasma lidocaine concentration was $\leq 2 \mu g/ml$ in five of the 11 patients shows that the effect of lidocaine on retrograde HPS refractoriness appears at lower plasma concentrations than those generally required for the suppression of spontaneous ventricular arrhythmias.

The phenomenon of RE-HPS provides a useful clinical experimental model in which the effects of antiarrhythmic drugs on retrograde refractoriness within the HPS can be assessed. In experimental preparations, lidocaine significantly shortens the action potential duration and ERP of normal Purkinje fibers, an effect that is most marked at the gate region. Electrophysiologic studies in man have shown that lidocaine decreases the antegrade ERP and RRP of the HPS. This study extends these observations and establishes that lidocaine causes a significant decrease in retrograde refractoriness within the HPS in patients with normal intraventricular conduction.

The clinical significance of these findings with reference to the possible mechanism of action of lidocaine in suppressing ventricular arrhythmias is uncertain. In our experience (unpublished observations) and that of others, macroreentry within the HPS is not operative in most clinical cases of sustained ventricular tachycardia. However, reentry over smaller pathways within the ventricles may be responsible for some clinically observed ventricular arrhythmias. Because slow conduction and unidirectional block are required for reentry to occur in any cardiac tissue, regardless of the size of the pathway, it is reasonable to assume that lidocaine influences reentrant ventricular arrhythmias by altering conduction and refractoriness. Studies in experimental animals have shown that lidocaine causes further slowing of conduction and prolongs refractoriness in infarcted zones of ventricular myocardium, and that these effects are associated with the abolition of reentrant ventricular arrhythmias. Thus, it is unlikely that the electrophysiologic effects of lidocaine observed in this study are operative in the suppression of ischemia-related ventricular arrhythmias. However, it is possible that some ventricular arrhythmias associated with ischemia or infarction may be suppressed by lidocaine as a result of decreased refractoriness within the HPS.

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