Relationships Between Increased Automaticity and Depressed Conduction in the Main Intraventricular Conducting Fascicles of the Human and Canine Heart

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Escapes from the injured fascicle (EIF) were investigated in 281 cases of bundle branch block (BBB), and during 35 experiments in which rate-dependent BBB was provoked in the intact canine heart. During vagal stimulation, EIF occurred in 27 of the 35 canine experiments, in seven of 24 patients with phase 4 (bradycardia-dependent) BBB, and in nine of 31 patients with fixed BBB. Changes in the degree of fascicular injury and phase 4 BBB were accompanied by correlative changes in the frequency and coupling interval of the EIF, indicating the existence of a close relationship between degree of injury, phase 4 BBB and EIF or enhanced automaticity within the affected fascicle. Therapeutic doses of isoproterenol and lidocaine were tested and were shown to have a simultaneous and sometimes concordant effect on the BBB and the EIF. Occasionally in the acute experiments on dogs, commonly in chronic patients, or at times in patients under the effects of lidocaine, a dissociation or desynchronization between the phase 4 BBB and the EIF was documented. This dissociation implies the existence of other physiologic factors, which may eventually cause the occurrence of concealed or abortive escapes. The fact that phase 3 (tachycardia dependent) and phase 4 BBB can be identified in patients or provoked experimentally in the intact canine heart, with or without EIF, provides with a model of great potential value for studying effects of antiarrhythmic drugs.

Additional Indexing Words:
Rate-dependent bundle branch block
Lidocaine
Isoproterenol
Escapbeats Model for studying antiarrhythmic drugs Purkinje fibers
Membrane responsiveness Myocardial injury

In the past, automaticity and conduction were thought to be independent physiologic properties of the specific tissues of the heart. Recently, however, evidence has accumulated indicating that some conduction disturbances may be related with changes in automaticity, and vice versa. Singer et al. demonstrated that an increase in automaticity or more specifically the rate of spontaneous diastolic depolarization (SDD), may cause slow conduction or block in Purkinje fibers. Rosenbaum et al. showed that bradycardia-dependent or phase 4 bundle branch block (BBB) is related, among other factors, to enhanced SDD, and that this is a common physiologic response to some forms of fascicular injury.

When Purkinje fibers are studied in a bath preparation, the relationship between enhanced SDD and impaired conduction can be documented with microelectrode techniques. In the intact heart, this relationship can be established only indirectly, when BBB is associated with escape beats arising from the affected fascicle. In the present study, this association was demonstrated in a series of clinical cases, and reproduced experimentally in the canine heart. It could thus be shown that changes in the degree of fascicular injury and phase 4 BBB were accompanied by correlative changes in the frequency and coupling interval of the fascicular escapes. In addition, drugs known to influence automaticity were tested and were shown to have a simultaneous effect on both the BBB and the fascicular escapes.
Material and Methods

Experimental Observations

Forty mongrel dogs weighing 12 to 20 kg were anesthetized by i.v. injection of sodium pentobarbital (30 mg/kg) and placed under controlled respiration. The chest was opened through a midsternal thoracotomy and the pericardium was incised. Electrodes for conventional electrocardiographic recording were placed and a unipolar lead similar to V1 was connected onto the right ventricle. In 32 experiments, the electrical activity of the His bundle (H) and left bundle branch (LB) was recorded through fine teflon-coated wires inserted into the area of the H and LB. For recording the H, Scherlag's technique was used. For recording the LB, the technique consisted of hooking the LB just below the junction of the noncoronary and right coronary aortic cusps. To accomplish this, the needle transporting the wires was plunged through the middle of the right ventricular wall and the ventricular septum.

A pulse generator (Medtronic 5837) was used to stimulate prematurely or to overdrive the atria by a bipolar catheter placed against the lateral wall of the right atrium. The vagal nerves in the neck were exposed and left intact. The stimulation current was used for vagal stimulation. Bipolar leads from the H and LB were led into high-gain preamplifiers (Sanborn 350-2700 C) and filters between 15 and 5000 cps were used. The ECGs were recorded by means of standard electrocardiographic preamplifiers (Sanborn 350-3200 A). All the records were displayed on a 6-channel photographic recorder (Sanborn 4560 Series Recorder), and paper speeds between 50 and 200 mm/sec were used. Control recordings were obtained to determine the configuration of the atrial and ventricular deflections and normal conduction times, including A-H, H-V, A-LB and LB-V intervals. Controls included determination of the effects of premature atrial stimulation, rapid atrial pacing, and vagal stimulation.

The right bundle branch (RB), LB, and divisions of the LB were reached according to techniques previously reported. The chosen fascicle was slightly injured in order to affect conduction only partially or transiently. This was accomplished by gently scratching or pressing down the fascicle with a blunt needle introduced through the ventricular wall. After injury, total BBB occurred, but in approximately 3 to 10 min, conduction returned to normal at the spontaneous cardiac activity. At that moment, premature stimulation or rapid atrial pacing or vagal stimulation, reproduced the BBB. These maneuvers were repeated in rapid sequence during 10 to 20 min until a moment was reached when the BBB could no longer be provoked. All throughout each sequence, the occurrence of escapes from the injured fascicle (EIF) and their coupling intervals were registered and correlated with the changes in conduction. Similarly, in 1954, Drury and Mackenzie introduced an intraventricular conduction delay with vagal stimulation after damaging one bundle branch allowing conduction in the bundle to recover.

Clinical Studies

Carotid sinus massage was performed on 281 patients with BBB. The response was variable and ranged from cases in which slowing of the heart rate was minimal to cases in which pauses of up to 8.00 sec were provoked, although this latter response was uncommon. Pauses of between 1.00 and 2.00 sec were common, and pauses of 3.00 to 4.00 sec were not exceptional. In general, the critical R-R interval for phase 3 BBB was around 1.00 sec, and only exceptionally it extended beyond 1.50 sec. Accordingly, if pauses of 1.50 to 2.00 sec were provoked without normalization of conduction, the BBB was considered to be stable or fixed. The critical R-R interval for phase 4 BBB was more variable, ranging commonly between 1.20 and 1.60 sec, but extending in some cases up to 3.00 to 6.00 sec and even more. When these long pauses unveiled phase 4 BBB, it was because escape beats did not occur, or only intermittently. If escape beats or phase 4 BBB did not occur before 2.00 sec, a pause of at least this duration was set as the limit for inclusion in the present study. Thus, 24 cases in which phase 4 BBB was demonstrated and 31 cases of fixed BBB were selected for further analysis.

Drugs

In six patients and during two experiments, the effects of lidocaine and/or isoproterenol were tested. Lidocaine was given by a bolus i.v. injection, and isoproterenol by an i.v. infusion. The doses will be indicated when describing the results.

Results

Identification of escape beats

Two main varieties of escapes were recorded during the experimental studies. Junctional or His bundle escapes occurred commonly after vagal stimulation and were characterized by independent H and LB deflections followed, after a normal H-V interval, by a narrow QRS in the controls (fig. 1A and 2A), or by a BBB pattern after fascicular injury (fig. 2E). These escape beats were unaffected by the experimental procedure and were irrelevant to the present study except for two reasons: a) Occasionally, early junctional escapes precluded the possible occurrence of EIF. b) Commonly, the junctional escapes had a much longer coupling interval than the coupling of the EIF, indicating that the latter were related to a marked increase in automaticity (fig. 1 and 2).

The EIF occurred only after fascicular injury and were identified according to the following criteria: a) the QRS was wide, b) was not preceded by H or LB deflections, and c) showed a BBB pattern opposite to the provoked BBB (fig. 1 and 2). Classification of BBB patterns was based on accepted criteria.

The same two varieties of escapes occurred in the patients. However, since His bundle recordings were not available (except in two cases), EIF were identified only on the basis of a wide QRS not preceded by atrial activity and showing a BBB pattern opposite to the existent BBB. Further support for the hypothesis that these escapes truly arose from the injured fascicle will be presented later. Junctional escapes were less common in the patients and were characterized by a ventricular complex not preceded by a P wave and either a normal QRS when falling on the normal con-
Experiment 19 in dog. A (top) Control tracing. A His bundle escape occurs after a pause of 6800 msec induced by vagal stimulation. There are no ventricular escapes. B (lower, left) Immediately after injuring the right bundle, the sinoatrial beats show a right bundle branch block pattern, and a ventricular escape, arising from the injured fascicle (EIF) and showing a left bundle branch block pattern, occurs after a pause of only 590 msec. C (lower, right) One hour later, after complete normalization of conduction in the RB, the LB was injured. The sinoatrial beats now show a LBBB pattern, and an EIF with a RBBB pattern occurs after a pause of 620 msec. Abbreviations: V1 = ECG lead V1; II = lead 2; H = His bundle recording; L = left bundle branch recording. White arrows indicate beginning of vagal stimulation.

Effects of Experimental Fascicular Injury upon Conduction and the Occurrence of EIF

Phase 4 BBB was produced in 35 experiments and EIF occurred in 27 of them. Figure 2 shows the sequence of one of the experiments in which the RB was injured. Four stages were documented. During stage 1 (first 6 min), complete and totally rate-independent RBBB occurred, and EIF were frequent and had a short coupling interval that increased progressively in duration (panels B to D). Stage 2 was defined by the appearance of a normal conduction range, separating an early or phase 3 (tachycardia dependent) RBBB range from a late or phase 4 RBBB range. During this stage (around 8 min), the EIF were less frequent and their coupling became longer (strip E). Stage 3 (around 8 min) was characterized by the fact that phase 4 RBBB occurred at much longer intervals than during stage 2, and by the absence of phase 3 RBBB. During this stage, the EIF became even less frequent and their coupling even longer (strip F). Stage 4 was characterized by normalization of conduction for any diastolic interval, and by disappearance of the EIF. Figure 3 illustrates this sequence schematically. The normal conduction range was extremely narrow at the...
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beginning of stage 2 and widened progressively in a few minutes at the expense of both the phase 3 and phase 4 block ranges (mostly the latter) in such a way that the phase 4 BBB shifted progressively to the right. The EIF appeared together with the BBB, and when injury diminished and the phase 4 BBB moved to the right, it was accompanied by a shift of the EIF in the same direction. During this shift, the coupling of the EIF was commonly slightly longer than the critical diastolic interval for phase 4 block. In 23 of the 35 experiments in which phase 4 BBB was provoked, the sequence of events followed, with minor differences, was that described in figures 2 and 3.

Phase 4 Bundle Branch Block and EIF in the Human

Of the 24 cases in which phase 4 BBB was demonstrated, seven (29.1%) showed EIF, and from the 31 cases of fixed BBB, nine (29.0%) showed also EIF. Figures 4 and 5 illustrate the conduction changes and their relation to the occurrence of escapes, as recorded from one of the most typical clinical cases, a 70-year-old woman with subacute antero-septal ischemia and intermittent LBBB. The sequence was similar to the one observed in the canine experiments, except that it lasted several weeks. Figure 4 shows the main features of the first ECG when the ischemia was more extensive. There was phase 3 LBBB (beats number 4 and 5), phase 4 LBBB (beats 6, 7, and 8), and incomplete LBBB (as compared with normal conduction which occurred a few days later) during the intermediate range (beats 1, 2, 3, and 10). In addition, two types of escapes were present: (a) EIF (beats 13 to 15), and (b) junctional escapes showing an incomplete LBBB pattern when falling on the intermediate range (beat 11), or a complete LBBB pattern when falling on the phase 4 range (not shown).

The top diagram in figure 5 shows how these beats were distributed (201 beats from a long continuous tracing during which carotid sinus massage was performed several times). The phase 3 LBBB range was unusually long, indicating a great prolongation of refractoriness. The intermediate range was extremely narrow and showed a small degree of incomplete LBBB, indicating that this corresponded to the begin-

Figure 3
Schematic representation of the sequence of changes in conduction and in the occurrence and coupling interval of the EIF after injuring any of the ventricular conducting fascicles. Numbers 1 to 4 correspond to the four stages described in the text. E = escape from injured fascicle.

Circulation, Volume XLIX, May 1974

Figure 4
Case 1, table 1 and case 1, table 2. Selected strips from the first V1 tracing recorded from a patient with intermittent LBBB and anteroseptal ischemia. Beats number 1, 2, 3, and 10 show a small degree of incomplete LBBB; beats 4 and 5 show phase 3 LBBB; beats 6, 7, and 8 show phase 4 LBBB (beat 6 was also preceded by a long pause following a period of normal conduction with short R-R interval) and beat 11 is a junctional escape, showing incomplete LBBB because it falls within the intermediate conduction range. Beats number 13 to 15 are EIF. The intermediate conduction range is extremely narrow (see also top diagram in figure 5), and the EIF falls slightly beyond the beginning of the phase 4 block range.

Figure 5
Case 1, table 1 and case 1, table 2. Sequence of conduction changes from the patient whose recordings are shown in figure 4. Black bars to the left = phase 3 LBBB; black bars to the right = phase 4 LBBB; striped bars = incomplete LBBB; white bars = normal conduction; white arrows = range of junctional escapes which show either normal intraventricular conduction (when falling within the normal conduction range) or BBB pattern (when falling within the phase 4 block range); black arrows = range of EIF. R-R intervals, in hundredths of a second.
EFFECTS OF ISOPROTERENOL AND LIDOCAINE

Since phase 4 BBB and the EIF appear to be related to enhanced SDD,6-10 drugs known to affect this physiologic property may be expected to cause changes on both the conduction disturbance and the escape beats. With this idea in mind, several drugs were tested, but because of their special pertinence to the present study, only some preliminary effects of isoproterenol and lidocaine will be presented here (tables 1 and 2). Isoproterenol was difficult to test in the canine experiments due to the occurrence of multiple and repetitive ectopic beats, but in five clinical studies the following effects were observed (table 1): A) The phase 4 BBB range shifted significantly to the left (cases 1 and 2), or occurred during a range occupied by normal conduction in the control (cases 3 and 4). B) The phase 3 BBB range also shifted significantly to the left (case 1), or was totally replaced by normal conduction (cases 2, 3, and 4). C) As a consequence of effects A and B, the normal conduction range also shifted to the left, but its duration increased or decreased according to which of the two predominated. D) The coupling interval of the EIF became progressively shorter, and also progressively, returned to its control value when the drug was discontinued in one patient (case 5); EIF which were not present in the control occurred in another patient (case 3); in one other patient in which only junctional escapes were present in the control, the coupling of these escapes was greatly shortened, and EIF were not observed (case 1); finally, in two other patients in which no escapes were present in the control, only junctional escapes occurred during the infusion of the drug (cases 2 and 4).

Both in the clinical and experimental studies, lidocaine caused the following effects (table 2): A) The EIF showed a longer coupling or more commonly were totally suppressed, as were junctional escapes when also present. B) When the normal conduction range was narrow, conduction in the affected fascicle was blocked entirely (studies 1, 7, and 8). C) When the normal conduction range was wider, the effects were more variable: the phase 3 BBB range lengthened in one patient (case 2), and did not change in one other patient (case 5); the phase 4 BBB range shifted to the left in one patient (case 3), and did not change in another patient; and the normal conduction range varied accordingly. All the effects of lidocaine, as well as those of isoproterenol, were transient and disappeared in a few minutes.

The two upper strips in figure 6 illustrate the effects of isoproterenol (an i.v. infusion of 0.25 micrograms/min) on a patient with LBBB and EIF. The control study showed EIF with coupling intervals of 2.12, 1.82, and 1.76 sec (during carotid sinus massage). During the peak effect of the drug (middle strip), the coupling intervals dropped to 1.50, 1.38 and 1.32 sec, and became progressively longer when the drug was discontinued. In the same patient, a bolus i.v. injection of 40 mg of lidocaine suppressed totally the EIF (third strip). No simultaneous effects upon conduction occurred due to the fact that the day of the study the BBB had become fixed. However, phase 4 and phase 3 BBB had been present five days prior to the study. Figure 7 shows the effects of isoproterenol (an i.v. infusion of 0.35 to 2.40 µg/min) on the patient of figure 4 and 5, at a moment when the normal conduction range was narrow and junctional escapes predominated. Both the phase 4 and phase 3 BBB ranges shifted to the left, the latter more than the
Table 1

**Effects of Isoproterenol on Conduction and Escapes**

<table>
<thead>
<tr>
<th>Case</th>
<th>Conduction disturbance</th>
<th>Dose</th>
<th>Ph 3 BBB range</th>
<th>Normal IV conduction range</th>
<th>Ph 4 BBB range</th>
<th>EIF coupling</th>
<th>Junctional escapes coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermittent LBBB</td>
<td>Control</td>
<td>0.94 – 1.28 sec</td>
<td>1.04 – 1.32 sec</td>
<td>1.33 – 2.82 sec</td>
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<td>1.56 – 3.21 sec</td>
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<td></td>
<td></td>
<td>Isoproterenol</td>
<td>0.57 – 0.80 sec</td>
<td>0.68 – 1.26 sec</td>
<td>1.18 – 1.55 sec</td>
<td>—</td>
<td>1.33 – 1.76 sec</td>
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<td></td>
<td></td>
<td></td>
<td>2.8 µg/min</td>
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<tr>
<td>2</td>
<td>Intermittent LBBB</td>
<td>Control</td>
<td>0.90 – 0.98 sec</td>
<td>0.92 – 1.28 sec</td>
<td>1.26 – 3.70 sec</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Isoproterenol</td>
<td></td>
<td>0.78 – 1.24 sec</td>
<td>1.08 – 1.33 sec</td>
<td>—</td>
<td>1.14 – 1.40 sec</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1 µg/min</td>
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</tr>
<tr>
<td>3</td>
<td>Intermittent LBBB; LAH</td>
<td>Control</td>
<td>0.92 – 1.25 sec</td>
<td>1.28 – 5.04 sec</td>
<td>—</td>
<td>—</td>
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<td></td>
<td>Isoproterenol</td>
<td></td>
<td>0.86 – 1.83 sec</td>
<td>1.76 – 2.16 sec</td>
<td>RBBB + LAH</td>
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<td></td>
<td></td>
<td></td>
<td>1 µg/min</td>
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<td></td>
<td></td>
<td>2.48 – 2.88 sec</td>
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<tr>
<td>4</td>
<td>Intermittent LBBB; LAH</td>
<td>Control</td>
<td>0.84 – 0.88 sec</td>
<td>1.03 – 3.84 sec</td>
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<td></td>
<td>Isoproterenol</td>
<td>0.98 – 1.32 sec (ILBBB)</td>
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<td>0.60 – 1.86 sec</td>
<td>1.98 – 2.36 sec</td>
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<td>1.5 µg/min</td>
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<td>5</td>
<td>Fixed LBBB</td>
<td>Control</td>
<td>0.82 – 3.28 sec</td>
<td></td>
<td>RBBB</td>
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<tr>
<td></td>
<td></td>
<td>Isoproterenol</td>
<td>0.92 – 1.32 sec</td>
<td></td>
<td>RBBB</td>
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<td></td>
<td></td>
<td></td>
<td>1 µg/min</td>
<td></td>
<td>1.22 – 1.71 sec</td>
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</tbody>
</table>

Abbreviations: Ph 3 BBB: phase 3 bundle branch block; Ph 4 BBB: phase 4 bundle branch block; EIF: escapes of the injured fascicle; LBBB: left bundle branch block; ILBBB: incomplete left bundle branch block; RBBB: right bundle branch block; LAH: left anterior hemiblock; IV = intraventricular.
### Table 2

**Effects of Lidocaine on Conduction and Escapes**

<table>
<thead>
<tr>
<th>Case</th>
<th>Conduction disturbance</th>
<th>Dose</th>
<th>Ph 3 BBB range</th>
<th>Normal IV conduction range</th>
<th>Ph 4 BBB range</th>
<th>EIF coupling</th>
<th>Junctional escapes coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermittent LBBB</td>
<td>Control</td>
<td>0.84 – 1.22 sec</td>
<td>1.20 – 1.46 sec</td>
<td>—</td>
<td>—</td>
<td>1.38 – 1.56 sec</td>
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<tr>
<td></td>
<td></td>
<td>Lidocaine 1 mg/kg</td>
<td></td>
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<td>Intermittent LBBB</td>
<td>Control</td>
<td>0.75 – 1.04 sec</td>
<td>1.07 – 1.73 sec</td>
<td>1.80 – 3.20 sec</td>
<td>RBBB</td>
<td>1.52 – 1.72 sec 1.62 – 1.82 sec</td>
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<tr>
<td></td>
<td></td>
<td>Lidocaine 1.8 mg/kg</td>
<td>1.00 – 1.15 sec</td>
<td>1.08 – 1.92 sec</td>
<td>1.86 – 3.68 sec</td>
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<tr>
<td>3</td>
<td>Intermittent LBBB; LAH</td>
<td>Control</td>
<td>0.55 – 0.94 sec</td>
<td>0.78 – 4.44 sec</td>
<td>5.06 – 5.16 sec</td>
<td>RBBB + LAH</td>
<td>2.28 – 4.55 sec</td>
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<td></td>
<td>Lidocaine 1 mg/kg</td>
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<td>0.59 – 3.88 sec</td>
<td>3.12 – 5.14 sec</td>
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<td>4</td>
<td>Intermittent LBBB; LAH</td>
<td>Control</td>
<td>0.58 – 0.77 sec</td>
<td>0.72 – 4.30 sec</td>
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<td>RBBB + LAH</td>
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<td>0.90 – 4.14 sec</td>
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<td>0.70 – 1.30 sec</td>
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<td>RBBB</td>
<td>1.28 – 1.35 sec 1.50 – 1.69 sec</td>
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<td>Lidocaine 1 mg/kg</td>
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<td>0.64 – 0.72 sec</td>
<td>0.69 – 1.14 sec</td>
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<td>6</td>
<td>Fixed LBBB</td>
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<td>0.82 – 3.28 sec</td>
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<td></td>
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<td>1.16 – 3.40 sec</td>
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<td>7</td>
<td>Intermittent RBBB</td>
<td>Control</td>
<td>0.28 – 0.39 sec</td>
<td>0.46 – 0.94 sec</td>
<td>0.80 – 1.94 sec</td>
<td>LBBB</td>
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<td>Lidocaine 2 mg/kg</td>
<td>Total RBBB</td>
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<td>Intermittent RBBB</td>
<td>Control</td>
<td>0.40 – 0.44 sec</td>
<td>0.42 – 0.94 sec</td>
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<td>LBBB</td>
<td>0.92 – 1.56 sec</td>
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<td></td>
<td></td>
<td>Lidocaine 2 mg/kg</td>
<td>Total RBBB</td>
<td></td>
<td></td>
<td>LBBB</td>
<td>1.21 – 1.88 sec</td>
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</tbody>
</table>

Abbreviations: Ph 3 BBB: phase 3 bundle branch block; Ph 4 BBB: phase 4 bundle branch block; EIF: escapes of the injured fascicle; LBBB: left bundle branch block; RBBB: right bundle branch block; LAH: left anterior hemiblock.
RELATION OF AUTOMATICITY & CONDUCTION

Case 1, table 1 and case 1, table 2. Effects of isoproterenol (an i.v. infusion of 0.35 to 2.40 micrograms/min), on the same patient illustrated in fig. 4 and 5. Symbols as in figure 5.

former; accordingly, the normal conduction range shifted also to the left and increased in duration. At the same time, junctional escapes with a short coupling became extremely frequent, and showed a LBBB pattern because of falling on the phase 4 BBB range. EIF did not occur. Panel A in figure 8 shows the effects of 50 mg of lidocaine on the same patient on a different day. The junctional escapes were suppressed, the normal conduction was abolished, and the BBB became totally rate-independent. Panel B shows the effects of 60 mg of lidocaine on another patient, at a moment when the normal conduction range was extremely wide and EIF were present. The EIF were suppressed, and both the phase 3 and phase 4 BBB ranges shifted to the left. Panel C shows the effects of 20 mg of lidocaine (2 mg/kg) during an experiment on the canine heart at a moment when phase 3 and phase 4 BBB were present, with a narrow intermediate range, and with frequent EIF. The EIF were suppressed and the normal conduction range was abolished.

Discussion

Relationship Between Phase 4 BBB and Escapes from the Injured Fascicle

Singer et al., in their study on isolated strands of Purkinje fibers, were able to document that an enhancement of SDD caused both slow conduction (or block) and automatic beats. In the present study, a similar correlation between increased automaticity and depressed conduction was determined indirectly on the basis of electrocardiographic observations from the intact canine and human hearts. Thus, the following findings support the view that escape beats actually arose from the affected fascicle: 1) The EIF were never present in the controls during the experimental studies, and occurred only and consistently after fascicular injury. 2) The EIF showed a pattern of complete BBB, opposite to the provoked BBB. Escapes with a homolateral BBB pattern occurred only twice in 35 experiments. 3) With a lower incidence (29.0%), EIF also occurred in patients with BBB, showing again the opposite BBB pattern. Escapes with a homolateral BBB pattern occurred only once in 24 patients with phase 4 BBB. 4) The coupling of the EIF maintained a close relationship with the phase 4 BBB range under different and changing conditions. 5) Drugs known to increase or decrease the slope of SDD had a concomitant effect on both the phase 4 BBB range and the EIF.

In these observations, the EIF behaved as if they were arising from the distal region of fascicular injury, or were being conducted distally but not proximally. Theoretically, EIF arising from the proximal region of injury, or being conducted proximally and not distally, should be expected to cause a homolateral BBB pattern, and be difficult to distinguish from junctional escapes falling within the phase 4 BBB range. However, escape beats with such characteristics occurred only exceptionally (in two experiments and in one patient). Our present view of EIF is probably an oversimplification, and variations in the precise location of the escape focus within the injured region, in the conduction range upon which the EIF fall, and in the orthograde and retrograde conduction times, may eventually cause a wider spectrum of EIF. However, the fact remains that the greatest number of EIF behaved as described above, although the reasons for such behavior are still unclear.

Phase 4 Bundle Branch Block Without Escapes

Rarely in the acute experiments, commonly in the chronic clinical cases, and sometimes under the in-
fluence of lidocaine, phase 4 BBB occurred in the absence of EIF, indicating that the effects of injury upon automaticity and conduction can be dissociated or desynchronized. This dissociation suggests the participation of other physiologic factors, and at least two main explanations can be considered.

1. **SDD does not reach threshold**

   A shift of the threshold potential toward zero is a *sine qua non* condition for phase 4 BBB to occur. Accordingly, in an uniformly injured fascicle, the coupling of the EIF tends to be longer than the critical interval for phase 4 BBB because the climbing slope of SDD takes a shorter time to reach the level for abnormal conduction than the level for firing. However, it is unlikely that this factor may by itself prevent firing in the presence of a significantly enhanced SDD. Therefore, in the chronic clinical cases, it has been postulated that hypopolarization may be more important than SDD in the production of phase 4 BBB, and under such conditions, phase 4 BBB might occur without EIF, or with extremely late EIF which is difficult to demonstrate in patients. Another possibility is that SDD is actually enhanced, but after reaching a level sufficient to cause phase 4 BBB, it remains stable without climbing further.

2. **SDD reaches threshold. Concealed or abortive escapes**

   Although injury may cause an enhancement of SDD, it is reasonable to assume that extensive injury may cause so much damage that SDD may not occur. In addition, it should be considered that an area of injury is probably inhomogeneous, and greatly damaged fibers may be close to others with less injury and more SDD. If in the latter cells the firing threshold is reached, the impulses may be precluded from being conducted to the rest of the heart due to the blocking effect of the injury in neighboring areas, particularly in narrow tracts such as the conducting fascicles. Under such conditions, the escapes may be concealed or restricted to small groups of cells. An abortive escape, which does not invade a large amount of tissue, may have no effect on subsequent events.

**Concomitant Effects of Isoproterenol and Lidocaine Upon Automaticity and Conduction**

Since catecholamines cause an enhancement of SDD in normal Purkinje fibers, the fact that isoproterenol shortened the coupling of EIF was not unexpected. In addition, it was thought that, at the same time, the phase 4 BBB range would move to the left, shortening or abolishing the normal conduction range. However, although the phase 4 BBB range shifted to the left as expected, the normal range did not shorten significantly because the phase 3 BBB also moved to the left. Thus, in patients with intermittent BBB, isoproterenol shortens refractoriness in the injured fascicle and at the same time enhances automaticity, thereby moving the phase 4 BBB and the EIF to the left. Since reports regarding dromotropic effects of catecholamines are conflicting, it is interesting that in the present study on injured Purkinje fibers of the human heart, isoproterenol improved conduction at rapid rates and suppressed conduction further at slow rates. The shortening of refractoriness may be indirectly related to the restoration of membrane potential toward normal values caused by catecholamines in injured Purkinje fibers. In two of the studies, the occurrence of very early atrial extrasystoles with normal intraventricular conduction suggested that the shortening of refractoriness was intrinsic to the drug effect and not related, at least entirely, to the concomitant increase in heart rate. Lidocaine, which depresses SDD in normal Purkinje fibers and in fibers in which SDD has been enhanced by catecholamines, caused a suppression or delay of the EIF. It was also thought that such a marked effect on the EIF would be accompanied by a shift of the phase 4 BBB range to the right with widening of the normal conduction range, particularly because lidocaine may also shorten action potential duration and refractoriness. However, in several studies the contrary occurred, the normal conduction range was abolished and the BBB became rate-independent. A possible way of accounting for this result in which automaticity and conduction were simultaneously depressed is by postulating that lidocaine caused a significant depression of membrane responsiveness. Since it has been shown that at therapeutic doses lidocaine has little effect on membrane responsiveness or that it may even improve it in normal Purkinje fibers, our results suggest that the opposite effect may occur in abnormal or critically injured fibers. This suggestion is supported by the fact that it was particularly when the normal conduction range was narrow (indicating a greater degree of injury) that lidocaine had the effect of depressing conduction further; whereas when the normal conduction range was wider (indicating less injury), the depressing effect upon conduction was less significant or absent. Since previous reports on the effects of lidocaine upon intraventricular conduction are also conflicting, the present results indicating that lidocaine may depress conduction in injured fascicles of the intact human and canine heart are of great clinical significance, and furnish an explanation for.
the reported development of severe intraventricular or atrioventricular block during the administration of therapeutic doses of lidocaine. 13, 34, 37, 38

In spite of limitations, the results of the present study may be of great relevance. Recently, Rosen and Hoffman stated that "it clearly is essential to know the relative sensitivity of the normal and the abnormal Purkinje fibers to the antiarrhythmic drug," and gave examples of drugs which have different effects on certain physiologic properties of normal as compared with abnormal Purkinje fibers. Another pertinent statement was that "information about drugs effects should be obtained whenever possible from studies on the human heart, and if the results are to be related to the clinical efficacy of a drug, such studies should not be restricted to normal tissues." Indeed, the fact that phase 3 and phase 4 BBB can be identified in patients or provoked in the intact canine heart, and that under such conditions conduction and automaticity can be simultaneously changed with certain drugs, indicates that this model has great potential value for studying the effects of antiarrhythmic drugs.

References

34. Rosen KM, Lau SH, Weiss MV, Damato AN: The effect of

Circulation, Volume XLIX, May 1974
lidocaine on atrioventricular and intraventricular conduction in man. Am J Cardiol 25: 1, 1970
36. JOSEPHSON ME, CARACTA AR, LAU SH, GALLAGHER JJ, DAMATO
Relationships Between Increased Automaticity and Depressed Conduction in the Main Intraventricular Conducting Fascicles of the Human and Canine Heart
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Circulation, 1974;49:818-828
doi: 10.1161/01.CIR.49.5.818

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/49/5/818

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