Effects of Isoproterenol on Abnormal Intraventricular Conduction

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SUMMARY An isoproterenol infusion (1.0–4.0 µg/min) was administered to 15 patients with intermittent bundle branch block (BBB) and two patients with apparently fixed BBB. Three main effects were documented: (1) In all patients with phase 3, or tachycardia-dependent, BBB, isoproterenol caused a pronounced shortening of refractoriness in the affected fascicle. (2) In patients showing phase 4, or bradycardia-dependent, BBB, isoproterenol prolonged the phase 4 block range, probably because of enhanced diastolic depolarization. In one patient (four studies) in whom phase 4 block was not present, isoproterenol caused the appearance of a phase 4 block range. (3) In the two patients with fixed BBB, isoproterenol restored conduction, probably as a result of a hyperpolarizing effect. This study shows that isoproterenol tends to restore or improve conduction related to tachycardia-dependent block, but may impair conduction related to bradycardia-dependent block.

THE ELECTROPHYSIOLOGIC EFFECTS of isoproterenol on normal Purkinje fibers have been extensively investigated\(^4\) and consist, essentially, of a moderate shortening of the action potential duration and a considerable enhancement or induction of diastolic depolarization. Membrane responsiveness and conduction velocity are not affected,\(^2\),\(^4\) but in partially depolarized fibers, catecholamines may improve conduction by restoring a more normal membrane potential.\(^5\)\(^-\)\(^7\) Clinically, the HV interval remains unchanged in normal subjects,\(^8\),\(^9\) and one study\(^10\) suggests that isoproterenol may shorten the HV interval and the duration of refractoriness in patients with intraventricular or atrioventricular block. Except for that report, the effects of \(\beta\)-stimulating agents on abnormal intraventricular conduction in the human are not well known.

Bundle branch block (BBB) is probably the best example of abnormal intraventricular conduction in the human. However, variations are less likely to occur in cases of permanent BBB, so we decided to study the effects of isoproterenol on a series of patients with intermittent BBB. Such patients may be used as a model for studying indirectly the electrophysiologic actions of different drugs on diseased or abnormally functioning Purkinje fibers in the human.\(^11\)-\(^13\) The present study confirmed the usefulness of this model and showed that under the effect of isoproterenol, tachycardia-dependent BBB is diminished or eliminated through a considerable shortening of refractoriness, while simultaneously, bradycardia-dependent BBB is favored or provoked, probably through an enhancement of diastolic depolarization.

Materials and Methods

Fifteen patients with intermittent BBB were studied. Carotid sinus massage was performed in every case during a continuous ECG recording to document the existence and measure the extension of a phase 3 and phase 4 block range. The 15 cases were selected from a much larger series of patients with intermittent BBB and entered the study only when the maneuvers were effective in uncovering these conduction ranges, or in separating a phase 3 block range from a normal conduction range. Two patients who apparently had permanent or rate-independent BBB, but who were known to have intermittent BBB a few weeks before, were also included. During the vagal stimulation, junctional and ventricular escapes were sometimes documented. After this control study, carotid sinus massage was repeated during and after the administration of an i.v. drip of isoproterenol, for which 1 mg of the drug was dissolved in 500 ml of isotonic glucose solution. The infusion was started at a rate of 1 µg/min of isoproterenol during 5–10 minutes; if no significant changes in conduction were observed, the rate of infusion was raised in successive steps of 1 µg/min during 5–10 minutes; the infusion was interrupted either when clear changes in conduction were seen or when changes did not occur after the infusion of 4 µg/min, or when ventricular arrhythmias developed at any time (the latter occurred only in one patient, who was then excluded from the study). When conduction changes were observed, the vagal stimulation was repeated after the infusion, until the recorded changes returned to the control condition. All the tracings were recorded on a Sanborn direct-writing two-channel machine and conventional measurements were made to determine the variations in cardiac rate and extension of the conduction ranges, as well as in the coupling interval of the escape beats. The statistical significance of the results was assessed using the paired \(t\) test. Thirteen patients were studied only

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once, and 13 studies were performed in the other four (total of 26 studies). Three of the 17 patients showed right BBB, 13 showed left BBB, and one showed left anterior hemiblock. In the 15 cases with intermittent BBB, the intermittency had been shown to be invariably present in several tracings for periods of 1-24 months, and none was under acute or stressing conditions or the effect of any other drug at the time of the study. The diagnosis of BBB, complete and incomplete, intermittent (rate-dependent) or rate-independent, was based on criteria developed by the Task Force and the New York Heart Association.

The basis of our study can be summarized as follows. If BBB is intermittent, the longest cycle length at which BBB occurs measures the duration of refractoriness in the most affected fibers of the involved fascicle. This has been termed the phase 3 block range, and is equivalent to the "bundle branch or fascicular refractory period" determined in normals and is defined as "the longest H1H2 at which H2 is conducted to the ventricles with appropriate electrocardiographic pattern of complete BBB," with one important difference. While the study of refractoriness in normal subjects requires the use of the extrastimulus method and His bundle recordings, to study the phase 3 block range in our material, programmed electrical stimulation was unnecessary (or useless), because the prolongation of refractoriness was usually around 1.00 second or more. Therefore, to uncover and measure a phase 3 block range, the heart rate had to be slowed. At cycle lengths longer than the duration of refractoriness, the phase 3 block range is necessarily followed by a normal conduction range, which in turn may or may not be followed by a second, late or diastolic period of refractoriness, which has been termed the phase 4 block range.

The beginning of the phase 4 block range (which theoretically has no end) is determined by the shortest cycle length at which BBB occurs again or late in diastole, and this measurement has no equivalent in classic studies on refractoriness. The extension of the phase 3 and phase 4 block ranges is conventionally depicted in figures 1 and 2. In such diagrams, a shortening of the phase 3 or phase 4 block range is commonly referred to as a shift to the left or right of the two block ranges, and coincides with a widening of the intermediate normal conduction range. Opposite shifts indicate prolongation of the two block ranges with narrowing of the normal conduction range. A narrow normal conduction range suggests a greater degree of fascicular injury, as indicated by previous experimental and clinical observations, or may be caused by the effect of conduction-depressing drugs. It is on the above-described variables that the effects of isoproterenol were tested.

**Results**

The control study showed phase 3 and phase 4 BBB in nine studies, phase 3 BBB alone in 15, and rate-independent BBB in two. Junctional escapes occurred in six studies, ventricular escapes in three, and the two together in three. Isoproterenol provoked changes in

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**Figure 1.** Effects of isoproterenol in two patients with intermittent bundle branch block (BBB) (A and B) and in one patient with apparently fixed BBB (C). Black bars to the left show phase 3 block range and black bars to the right show phase 4 block range; white bars show normal conduction range; striped bars show incomplete BBB (spacing of the vertical lines indicates lesser degrees of BBB); arrows of continuous lines indicate range occurrence of junctional escapes; and arrows of interrupted lines show ventricular escapes. RR intervals are in msec. LBBB = left bundle branch block.
automaticity and conduction that occurred within the first 2 minutes and were related to the dose and duration of the infusion. There was an increase of the sinoatrial rate of 5–30 beats/min (average 13 beats/min). Although this sympathetic effect partially offset the action of the carotid sinus massage, pauses longer than 1500 msec could still be provoked in 14 studies.

Figure 1 shows three examples of the main changes caused by isoproterenol. The control study in figure 1A showed phase 3 and phase 4 BBB separated by an extremely narrow normal conduction range, and ventricular escapes with a highly variable coupling interval. Under such conditions, isoproterenol shifted both the phase 3 and phase 4 block ranges to the left, as well as the ventricular escapes. The normal conduction range was actually widened, because the shift of the phase 3 block range was greater than that of the phase 4 block range. In the study shown in figure 1B, isoproterenol caused a shortening of the phase 3 block range from 1100 to 930 msec, and also shortened the coupling of the junctional escapes. In the study of figure 1C, the control showed rate-independent BBB, and under the effect of isoproterenol normal conduction was restored (with a prolonged phase 3 block range), and junctional escapes were observed. Figure 2 illustrates four studies performed on different days within a 2-week period in one patient, and shows the acceptable reproducibility of the results and the relatively stable character of the conduction disturbance.

**Effects on Refractoriness and Conduction**

In 24 studies in which phase 3 BBB was documented, isoproterenol caused a shortening of the phase 3 block range (fig. 3) to 20–520 msec (mean 217.5 ± 22.6 msec) (p < 0.001). The duration of the phase 3 block range was 680–1300 msec (average 1013 msec) in the control study, and 520–1240 msec (average 793 msec) during the isoproterenol infusion. In 18 studies, the shortening was clearly dose-dependent; in six, the shortening was longer than 300 msec. Thus, isoproterenol caused a significant shortening of refractoriness in the affected fascicle, with improvement of conduction at relatively short cycle lengths (fig. 4).

In eight of the nine studies in which a phase 4 BBB was documented, before as well as during the administration of isoproterenol, the drug caused a
FIGURE 3. Duration of the phase 3 block range in 24 studies, before (black columns) and during (white columns) the administration of isoproterenol. In studies 2A, 2B and 2C the phase 3 block could not be documented during the isoproterenol infusion, and the interrupted columns indicate the shortest RR interval in each study.

prolongation of the phase 4 block range (fig. 5) that ranged between 30–410 msec (mean 297 ± 69.33 msec) (0.05 < p < 0.001). In addition, in four studies from the same patient (fig. 2) in whom phase 4 block did not occur in the control despite the presence of prolonged pauses provoked by vagal stimulation, isoproterenol caused phase 4 block after much shorter intervals. In one case (study 8), the phase 4 block range was not modified.

In summary, isoproterenol caused a shift to the left

FIGURE 4. Selected ECG strips from study 2A (see figs. 2 and 3) showing normalization of conduction (disappearance of phase 3 bundle branch block [BBB]) caused by isoproterenol. The two strips were recorded during carotid sinus massage. RR intervals are in msec. In the control, all beats closing RR intervals of 1170 msec or shorter show left BBB and only the fourth beat closing a RR interval of 1230 msec shows normal conduction. In the bottom strip all beats show normal conduction, and this is most remarkable in the two atrial extrasystoles (fourth and fifth beats), closing RR intervals of 610 and 660 msec, respectively, and particularly in the first atrial premature complex, which follows a preceding long diastolic interval of 1310 msec.
of the phase 4 block range or the new appearance of a phase 4 block range, with impairment of conduction at relatively long cycle lengths (fig. 6). In seven cases in which a certain degree of incomplete BBB persisted during the intermediate range in the control study, isoproterenol caused either a total normalization of conduction during this range or a significant reduction in the degree of BBB. Conduction was improved at intermediate cycle lengths. In the two patients with rate-independent BBB, isoproterenol caused a partial restoration of conduction (figs. 1C and 7).

Effects on Automaticity

The escape interval of both the junctional and ventricular escapes was variable and covered a wide range, during the control study as well as during the administration of isoproterenol. This was probably due to variability of the vagal stimulations and to variations in the sinus rate preceding each escape beat. However, when the shortest escape interval before and during the isoproterenol infusion were compared in 12 cases (19 studies) (fig. 8), the drug uniformly caused an acceleration of both the junctional and ventricular escapes (mean 1620 ± 443 msec) (0.01 < p < 0.001). In addition, in eight studies, isoproterenol caused early escapes that had not been present in the control (fig. 8). The ventricular escapes showed always a BBB pattern opposite to that of the dominant rhythm (fig. 6), so we assume that isoproterenol enhanced automaticity both in the affected fascicle as well as in the apparently normal junctional region.

Discussion

Isoproterenol caused a substantial shift of the tachycardia-dependent BBB range to the left in 15 cases of intermittent BBB, and a similar effect was noted in two previously reported cases.\(^\text{10}\) This may be explained by previous microelectrophysiologic studies that show shortening of the action potential duration and refractory period of normal Purkinje fibers by isoproterenol.\(^\text{1, 2}\) However, the smallness and inconstancy of the latter effect\(^4\) should be contrasted with the marked effect observed in our patients with intermittent BBB, in six of whom isoproterenol shortened the phase 3 block range more than 300 msec, and in one case, up to 520 msec. Therefore, conduction improved greatly at rapid rates. Although it is difficult to evaluate how much of the shortening was caused by the increase in rate provoked by the isoproterenol infusion, a marked shortening was also documented in several cases in which the increase in rate was only small or modest (fig. 4).

In contrast with the improved conduction at faster rates, isoproterenol provoked a deterioration of conduction at slower rates or after long pauses, by causing an earlier or new appearance of a bradycardia-dependent block range. It is reasonable to assume that this shift to the left of the phase 4 block range was caused by an increase in the slope of diastolic depolarization, and this interpretation is supported by the similar anticipation of escape beats occurring simultaneously in some of the patients (compare figures 5 and 8). This effect of isoproterenol is strong evidence for the hypothesis that phase 4 block is truly related to the presence of diastolic depolarization in the diseased fibers responsible for this particular type of conduction disturbance.\(^\text{7, 13, 16, 17, 21}\)

Catecholamines may improve conduction by restoring a membrane potential previously reduced by stretch, hypoxia or toxic concentrations of ouabain,\(^\text{6, 7}\) and reverse the depressed conduction caused by excessive doses of procainamide or quinidine.\(^\text{22}\) A possible equivalent to this effect occurred in several of our patients with intermittent BBB in which a pattern of incomplete BBB persisted during the intermediate conduction range, suggesting a slight or moderate degree of hypopolarization.\(^\text{13, 16, 17}\) In such cases, isoproterenol restored partially or totally the normal conduction range. The partial restoration of conduc-

![Figure 5](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.CIR.81.6.1361/-/DC1/fig5.png)
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during the RR interval of 20-30 msec. In addition, isoproterenol

inhibitory action of the vagus prevails over the stimulating effect of the sympathetic when both systems are simultaneously activ-
tated. The junctional automatic activity recorded

before as well as during the administration of isoproterenol probably arose from the His bundle and was clearly enhanced by the drug.

Our approach depends on the patient response to vagal stimulation in such a way that in many non-

responders, the study of intermittent BBB is prac-
tically impossible. In addition, carotid sinus massage does not allow stable slow rates, but rather, pro-

longed pauses of unpredictable length with no possible control of the preceding cycle length. Another problem is the possibility that the liberation of acetylcholine might eventually alter some of the variables under study.29-31 Nevertheless, vagal stimulation is the most accessible way of slowing instantaneously the heart rate in the human, and the proposed model, despite its limitations, is practically the only manner of studying the effects of drugs on abnormal Purkinje fibers in humans. Comparison of the

Figure 6. Selected ECG strips from study 2D showing deterioration of conduction caused by isoproterenol at long diastolic intervals. The four strips were recorded during carotid sinus massage. In the control, all beats closing RR intervals of 960-1290 msec show phase 3 left bundle branch block (BBB), and normal conduction is present when the RR interval is 1420-5110 msec. Phase 4 BBB was not documented. During the isoproterenol infusion, the fourth beat in the third strip shows phase 4 left BBB, closing a RR interval of 2030 msec. In addition, isoproterenol caused ventricular escapes with a right BBB pattern (second and third beat in bottom strip).
control studies and the drug effects under similar conditions minimizes some of the limitations.

In addition to its theoretical interest regarding the mechanisms of tachycardia- and bradycardia-dependent block, our study suggests that isoproterenol may be useful in some patients with left BBB in which there is a need to observe the normally conducted QRS pattern, in patients in whom a complete interruption of conduction in one of the bundle branches must be ascertained, and in patients in whom phase 4 block is suspected.

**Figure 7.** Restoration of conduction caused by isoproterenol in a patient with apparently fixed left bundle branch block (BBB). In the control all beats showed left BBB despite great variation in RR intervals, 880–5970 msec. Isoproterenol normalized conduction in all beats, closing RR intervals of 1050 msec or greater. Beats 3–5 in the sixth strip are junctional escapes.

**Figure 8.** Shortest escape interval before and during the administration of isoproterenol in 12 patients (19 studies). Stars indicate junctional escapes, control; rounded stars indicate junctional escapes, isoproterenol; open circles indicate ventricular escapes, control; black circles indicate ventricular escapes, isoproterenol; black rectangles indicate maximal diastolic intervals without escapes. Scale is in milliseconds.
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