Effects of Isoproterenol on Bradycardia-dependent Intra-His and Left Bundle Branch Blocks

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SUMMARY The electrophysiologic study of a patient with a history of fainting showed first- and second-degree Mobitz type 1 intraatrial and intra-His (IH) bundle blocks. Tachycardia and bradycardia-dependent IH block and bradycardia-dependent left bundle branch block were also present. Bradycardia-dependent block was probably caused by slight hypopolarization plus a slow rising slope of phase 4 depolarization and a shift of the threshold potential toward zero. Two months later a second electrophysiologic study was performed before, during and after administration of i.v. isoproterenol (IP). Shortening of atrium-His (AH) and IH (H2H3) conduction time during faster heart rates caused by IP infusion may be related to its hyperpolarizing effect. Simultaneously, a shifting to the left of both bradycardia-dependent IH and left bundle branch block ranges was recorded during vagally induced cardiac slowing. These findings suggest that IP produces an increase in the slope of phase 4 depolarization of the His bundle and left bundle branch fibers and a simultaneous and concordant effect at both levels of the intraventricular conduction system.

DIFFERENT DEGREES of atrioventricular (AV) conduction disturbances in the His bundle have been reported.1-12 In most cases of first- and second-degree intra-His (IH) block, as well as in other conduction abnormalities, the degree of block increases during the shorter cycle of a faster cardiac rate.13 However, Schuilenburg and Durrer described a higher degree of IH block due to longer cycles of a slower cardiac rate in man.14

The effects of isoproterenol (IP) on the automaticity and conduction properties of the His bundle are well known,15-18 and Rosenbaum et al.19 reported the effects of IP on rate-dependent intraventricular conduction abnormalities.16 However, a higher degree of bradycardia-dependent IH block due to IP has not been reported.

We describe the case of a patient with several types of conduction disturbances at different levels in whom IP caused a higher degree of bradycardia-dependent IH and left bundle branch block (LBBB).

Case Report

A 59-year-old man was admitted to the hospital because of syncopal episodes. He had no history of heart disease and physical examination revealed a heart rate of 45 beats/min and no other remarkable abnormality. Chest x-ray films and laboratory tests were normal. The ECG reflected sinus rhythm with a PR interval of 0.28 second and narrow QRS complexes (fig. 1A). Another ECG tracing showed a Mobitz type I AV block without changes in the QRS morphology. No drugs were administered.

After the patient gave informal consent, a His bundle electrogram (HBE) was recorded with the patient in a postabsorptive state according to standard technique,17 using a bipolar catheter with electrodes 1 cm apart. When splitting of the His potential was registered, a second bipolar electrode catheter was positioned at the lower portion of the His bundle. An additional bipolar electrode catheter was introduced through an antecubital vein for pacing or recording electromograms from the high right atrium near its junction with the superior vena cava. Filtered electromograms (40-500 Hz) were recorded simultaneously with surface leads on a Electronics for Medicine DR-8 photographic recorder at paper speeds of 50 and 100 mm/sec. Electrical stimuli were introduced by a Hewlett-Packard Model 7804A pacemaker. The heart rate was slowed by carotid sinus massage.

The patient was discharged and 2 months later was readmitted after frequent, short, fainting episodes. A transvenous bipolar endocardial electrode was placed in the right ventricle, and a second electrophysiologic study with the same technique was performed. Intravenous IP infusions in doses of 1-4 µg/min were tested to evaluate their effects on the AV conduction. Two days later the patient gave consent and a permanent-demand pacemaker with epicardial electrodes was implanted.

Results

The HBE recorded during sinus rhythm at a rate of 49 beats/min revealed that every A wave was followed at 100 msec by a biphasic proximal His bundle potential (H1), and that every V wave was preceded at 50 msec by a second smaller deflection (H2) (fig. 1B). The H1H2 interval was 80 msec and the H1V interval in the conducted beats was 130 msec.

The H1 potentials were validated by an increasing pacing rate that caused prolongation of the AH1 interval with occurrence of an AH1 Wenckebach phenomenon at a critical pacing rate (fig. 2A) and by shortening of the AH1 interval to 85 msec despite the increased atrial rate during i.v. IP infusion (fig. 3C). The H2 deflections were validated by an H2V interval of 50 msec in absence of signs indicating conduction delay in the right bundle branch and by simultaneous
FIGURE 1. (A) A 12-lead standard ECG. (B) Two His bundle electrograms (His 1 and His 2) simultaneously recorded with standard leads I, II and III during sinus rhythm showing two His potentials (H₁ and H₂). Although both deflections are registered by the bipolar catheter electrode positioned according standard technique (His 1), H₂ potentials are more remarkable in the His bundle electrogram recorded by a second catheter electrode located at the distal portion of the His bundle (His 2). Cycle lengths (RR) and conduction times are expressed in milliseconds.

FIGURE 2. (A) Simultaneous recording of standard ECG leads I, II and III and His 1, His 2 during atrial pacing performed near the sinus node to validate H₁ deflections. The second pacing stimulus (s) is blocked within the His bundle. There is a progressive prolongation of the sinoatrial (SA) conduction time from the second to the fourth paced beat (intraatrial Wenckebach sequence). Concomitantly, the AH₁ interval of the second and third paced beats increases until the fourth A wave is not followed by an H₁ potential, indicating second-degree Wenckebach type intranodal atrioventricular block. (B) Validation of the H₂ potential. Simultaneous recordings of distal (His 2) His bundle electrogram (HBE) and right bundle electrogram (RBE) during sinus rhythm show that the H₂ deflection is indeed a His bundle potential. The H₂V interval is normal and is 10 msec longer than the right bundle (RB)-V conduction time.
recording of H₂ and right bundle (RB) electrograms with a normal RB-V conduction time (fig. 2B). Thus, the main conduction delay could be located within the His bundle. In addition, conduction in the distal His bundle appeared to be normal, in view of the normal H₂V intervals.

Several unsuccessful attempts were made to obtain His bundle pacing. As a consequence of these maneuvers, right ventricular paced beats were recorded, and a lesser degree of ventriculoatrial (VA) conduction impairment in the presence of an AV block could be documented (fig. 4A). In addition, concealed retrograde conduction within the His bundle was deduced from the same tracing on the basis of unexpected prolongation of the AH₁ interval of some atrial beats (fig. 4B).

During atrial pacing performed for validation of the His deflections (fig. 2A), Mobitz type II AV block was registered in the surface ECG. However, the bipolar H₁ and H₂ electrograms revealed several types and levels of conduction disturbances. Although the second stimulus artifact was blocked within the His bundle (H₁ was not followed by H₂), the conduction through the atrium appeared slightly prolonged (55 msec) and was followed by progressive lengthening of the sinoatrial (SA) conduction time (from 55 to 75 msec) in a Wenckebach sequence. In addition, the AH₁ interval of the second and third stimuli showed progressive prolongation (from 100 to 145 msec) until the fourth A wave was not followed by an H₁ deflection, which indicated a second-degree Mobitz type I intranodal AV block.

The control tracing registered during the second electrophysiologic study showed an AH₄ interval of 110 msec, an H₁H₂ interval of 70 msec, and an H₂V interval of 50 msec. During cardiac slowing induced by carotid sinus massage, no changes were seen in the duration and configuration of either the His potentials or the QRS complexes up to a cycle length of 4940 msec. However, the first conducted beat after such pause reflected a longer H₁H₂ interval (80 msec) than the H₁H₂ interval of the control tracing, suggesting a bradycardia-dependent conduction disorder within the His bundle. Additional prolongation of the cycle length from 5550 to 8180 msec revealed different degrees of bradycardia-dependent LBBB, as can be deduced from the QRS changes without modification of the RB-V intervals. During atrial pacing, a tachycardia-dependent Mobitz type I IH block with a prolongation of the H₁H₂ interval from 75 to 220 msec was registered (fig. 5A). With a further increase in the pacing rate (fig. 5B), transition to a tachycardia-dependent Mobitz 2:1 IH block occurred. In addition, alternation of the SA intervals was registered. At this time IP infusion was started. Two minutes later the cycle length was shortened as a consequence of the sinus node response to the drug and the 2:1 AV block recurred (fig. 3A). The conducted beats showed bradycardia-dependent incomplete LBBB after diastolic pauses of 1840 msec. This type of block did not occur after longer diastolic pauses during control tracings. A few seconds after discontinuation of the IP infusion, a new record (fig. 3B) showed an improvement in AV conduction. A 1:1 AV response was
registered with a cycle length of 1080 msec, whereas a Mobitz type I AV block occurred during a slower atrial pacing rate in the control tracing. This improvement in AV conduction was also revealed by the HBE on the basis of a shortening in the AH, and H1H2 intervals of 25 and 10 msec, respectively (fig. 3C). Three minutes after discontinuation of the IP infusion (fig. 6), a higher degree of bradycardia-dependent IH block was recorded. This finding occurred with shorter diastolic pauses than those recorded in the tracings before medication. Concomitant with the change of H1H2 interval, a normal QRS complex was registered after a diastolic pause of 3080 msec, denoting that the bradycardia-dependent LBBB had returned to the control state. Finally, another tracing obtained 1 hour later revealed that the critical cycle length for bradycardia-dependent IH and LBBBs were 5020 and 5500 msec, respectively.

**Discussion**

The main conduction disturbance in our patient was located within the His bundle. Although recording of split His deflections might be technically difficult,14 in our patient they could be registered by only one bipolar electrode catheter during both electrophysiologic studies. However, a higher potential of each His deflection was obtained with selective location of two catheters in the upper and lower portions of the His bundle.

During sinus rhythm, first- and second-degree Mobitz type I IH block was shown. In addition, first-degree intraatrial block was detected. During faster pacing rates performed to validate the H deflections, a Wenckebach sequence was registered in the atria. However, failure of AV conduction first occurred at His bundle or AV nodal levels. The existence of Wenckebach periods and AV blocks within the atria demonstrated only by electrophysiologic studies in patients without other evidence of atrial disease have been recently emphasized.18-20 These findings support the importance of dividing PH conduction time into intraatrial (PA or SA) and AV nodal intervals in order not to overlook the role of conduction delays within the atria.19 Nevertheless, without a high right atrial potential recorded near the pacing catheter, one cannot be certain that the Wenckebach sequence occurs within the atria or represents a conduction delay between the electrode catheter and the atrial wall.21

Bradycardia-dependent intraventricular conduction disorders have received increased interest during recent years.22-24 Bradycardia-dependent IH block seems to be less common and has only been recently confirmed in the human14 and canine2 heart by His bundle electrocardiography.

Clinical and experimental studies of transient intraventricular conduction disorders suggest that bradycardia-dependent block can be developed as a result of a combination of factors,16, 23-25 including a loss of maximal diastolic potential, an abnormal slope of phase 4 depolarization and a reduction of membrane responsiveness associated with a shift of the threshold potential toward zero. In the present case the assumption that hypopolarization is only slight or moderate is reasonable, because severe hypopolarization would cause complete block and even total unresponsiveness of the involved fibers of the His bundle. In addition, slight hypopolarization is compatible with normal conduction.23 This finding is essential to explain the occurrence of the "normal" conduction range that separates bradycardia-dependent from
tachycardia-dependent IH conduction disorders. The beats described as showing "normal" IH conduction actually represent first-degree IH block, which suggests the presence of a population of cells within the His bundle with partially diastolic depolarization. In our patient the long intervals required for bradycardia-dependent IH block to occur favor a normal or slightly rising slope of phase 4 depolarization. On the other hand, the observation of long bradycardic interval (up to 8 seconds) without pacemaker escape may be attributed to a shift of threshold potential toward zero. However, membrane responsiveness, which is also directly reduced by injury, could operate as an additional factor favoring or increasing the degree of bradycardia-dependent block.

Figures 5A and B suggest that tachycardia-dependent first- and second-degree IH block were also present, because block was seen whenever the H1H2 intervals were reduced below a critical value by atrial pacing. The tachycardia-dependent IH block could be related to either prolonged duration of the transmembrane action potential (voltage-dependent factor) or to a time-dependent response in the affected cells.

In our patient, the concomitant occurrence of only incomplete LBBB of slight degree after very long diastolic intervals manifested the same physiologic behavior as in the His bundle. These findings, coupled with clinical and experimental observations that long bradycardic intervals are sometimes necessary to illustrate bradycardia-dependent conduction disorders, strongly imply that a normal or slightly rising rather than enhanced slope of phase 4 depolarization was probably operative in the His-LBB system. Our case supports observations that chronic IH
block is frequently accompanied by disease of the bundle branches.\(^1\, 6\, 11\)

Because the bradycardia-dependent IH block was registered in our patient during slower cardiac rates achieved by carotid sinus stimulation, a vagally induced conduction impairment was considered. We excluded this possibility because the AH, conduction time was not modified, it is generally accepted that the His bundle is not innervated by the vagus,\(^27\) lower AV nodal and His bundle fibers are not affected by acetylcholine,\(^27\) and lower His bundle escapes or rhythms are insensitive to atropine.\(^3\, 27\) However, several reports show acetylcholine effects in both the proximal portion of the His-Purkinje system of the canine heart in situ\(^28\) and in Purkinje fibers studied by the voltage clamping technique.\(^29\) These experiments showed a decrease in the slope of phase 4 depolarization by the action of the drug. This effect really tends to improve rather than to impair the conduction through both His bundle and bundle branch fibers because transmembrane potential is increased at the moment of excitation. Therefore, a vagal effect of carotid sinus stimulation mediated by acetylcholine cannot be considered as the cause of the bradycardia-dependent type of block in our patient.

Several studies have provided a wealth of information on the mechanisms of the effects of catecholamines and IP in normal and partially depolarized cardiac tissue.\(^30\-32\) The increase of conduction velocity in pathway fibers, and the restoration of AV conduction in patients with several types of AV blocks have been attributed to a hyperpolarizing effect on resting membrane potentials provoked by IP. Improvement in conduction has been described in AV blocks occurring either at AV nodal or His bundle levels.\(^5\, 15\) In addition, IP shortened the HV conduction time in patients with normal or prolonged HV intervals, and increased the cardiac rate necessary for provoking tachycardia-dependent bundle branch blocks.\(^16\, 18\)

The second most important effect of IP is to increase the slope of phase 4 depolarization in automatic cardiac fibers.\(^14\, 16\, 30\) This effect increases the intrinsic rate of active and latent pacemaker fibers, but allows propagated impulses to reach the transmembrane potential of conducting fibers at levels closer to zero, with a decrease in phase O depolarization.\(^16\, 33\) As Dhingra et al.\(^16\) emphasized, paradox worsening of conduction in the His-Purkinje system could occur by these two mechanisms of the same IP effect (fig. 3A). IP increases the sinus rate and 2:1 AV block occurred. The conducted beats showed an incomplete LBBB at a RR interval of 1840 msec. The fact that phase 4 LBBB range shifted significantly to the left and occurred during a range occupied by normal conduction in the control tracing, could be attributed to an increase in the slope of phase 4 depolarization in the injured cells of the LBB caused by IP. In a subsequent recording (fig. 3B), the critical range for 1:1 AV conduction shifted to the left and both AH and H-H\(_2\) conduction times decreased despite variations in the cycle lengths (fig. 3C). It is reasonable to assume that improvement in AV conduction resulted from a hyperpolarizing effect caused by IP in both the AV node and the His bundle fibers.

The most important finding in our patient was a higher degree of bradycardia-dependent IH block due to the IP effect. This conduction abnormality was recorded with a diastolic pause almost 40% shorter than those obtained before the infusion and was probably caused by an increase in the slope of phase 4 depolarization resulting from IP. To our knowledge, this finding has not been reported.

In addition, the occurrence of a higher degree of bradycardia-dependent IH and LBBB during or shortly after IP infusion shows that this drug may cause a simultaneous and concordant effect at both levels of the intraventricular conduction system.

Finally, it is necessary to comment on the different duration of the IP effect at the critical range for bradycardia-dependent IH and LBBBs. This effect is more prolonged in IH than in LBBB (fig. 6). Because the degree of block before the administration of the drug is higher at the His bundle level, one can assume that in our patient not only the intensity but also the duration of the IP effect is closely related to the severity of the conduction disturbance; that is, the higher the degree of conduction abnormality, the more persistent the IP effects. Certainly, this latter possibility requires further investigation.

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