Abolition and Modification of Reentry Within the His-Purkinje System by Procainamide in Man

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SUMMARY The effects of intravenous procainamide infusion of 10-14 mg/kg body weight (i.e., 750 mg) of procainamide (PA) on reentry within the His-Purkinje system (HPS) were studied in 13 patients using His bundle electrograms and ventricular extrastimulus method. PA abolished reentry in eight patients (group 1) and decreased the width of reentry zone in the remaining five (group 2). At comparable S1S2 intervals, the S1H2 intervals after PA were longer than control in all patients. In group 1 patients, after PA, reentry did not occur even at S1H2 intervals that were significantly longer than control critical S1H2 intervals. In two of eight patients in group 1, PA abolished reentry by converting unidirectional block into bidirectional block in the antegrade limb (right bundle) of the reentry circuit. In the remaining six patients reentry was abolished because of consistent retrograde block of S1 impulse at some point between the site of stimulation and the His bundle recording site. In group 2, reentry was initiated after PA at approximately the same S1S2 intervals as in control, but required significantly longer S1H2 intervals; in these patients the zone of reentry was shortened due to increase in effective refractory period of the ventricular muscle. PA significantly increased the functional refractory period of HPS and the effective refractory period of ventricular muscle. The results of this study differ from the previously reported effects of lower concentrations of PA which facilitated reentry within the same circuit. We conclude that the effects of PA on reentry are dose-related and can both facilitate and suppress reentry, depending on critical changes in conduction and refractoriness of the HPS.

REENTRY WITHIN the His-Purkinje system (HPS) where the path of reentry incorporates right and left bundle branches and the bundle of His has been demonstrated in man. In this form of reentry, a critically timed ventricular premature beat (V2) induced during a constant paced ventricular cycle is followed by a spontaneous ventricular beat (V4). Its occurrence depends on both critical coupling (S1S2) intervals and a critical degree of retrograde conduction delays within the HPS. Unlike the experimental models of reentry involving isolated isolated His bundle and Purkinje fibers, this clinical model is unique in that it permits the study of reentry within the HPS in intact heart. The ventricular extrastimulus method, using this reentry model, also facilitates the evaluation of drug effects simultaneously on conduction of HPS and refractoriness of both HPS and ventricular muscle, and thereby allows determination of the role of each of these parameters in the occurrence of reentry. Recently, we reported that the intravenous infusion of 500 mg of procainamide (PA) (5-8 mg/kg body weight) increased the width of zone of reentry, changed non-sustained into sustained reentry and permitted induction of reentry which could not be elicited before the administration of the drug. We attributed these arrhythmia-facilitating effects to a critical change in the relationship between conduction and refractoriness within the HPS induced by PA.

We postulated that higher doses of PA might prevent reentry within the same reentrant circuit by causing more pronounced changes in conduction and refractoriness of the HPS and by causing an increase in ventricular muscle refractoriness.

Methods

Right heart catheterization was performed in the postabsorptive, non-sedated state in 13 patients after obtaining an informed consent. The mean age of patients was 56.3 years (range 27-71 years). The electrophysiological studies were done for the following reasons: paroxysmal atrial tachycardia (three patients); sick sinus syndrome (five patients); mitral valve prolapse with atrial arrhythmias (three patients); exercise-induced ventricular tachycardia (one patient); and syncope of undetermined etiology (one patient). All but two (patients 2 and 5) had normal intraventricular conduction on ECG. None of the patients were on cardiac drugs for at least 48 hours before the study and all had normal serum electrolytes. His bundle electrograms were recorded as previously reported, using a tri- or quadripolar electrode catheter.Additional electrode catheters were placed in the high right atrium and right ventricle for local recordings and electrical stimulation. Atrial and ventricular stimulation was performed using a programmed digital stimulator that delivered rectangular impulses at 1.5 msec duration and twice diastolic threshold strength. Intracardiac electrograms along with the electrocardiographic leads, I, II, and V1 were recorded on paper moving at a speed of 100 mm/sec.

Antegrade and retrograde refractory periods were determined at one or more basic cycle lengths (A1, A2, or V1, V2, V3) using the extrastimulus method. The characteristics of the delivered stimuli or the site of stimulation were not changed in any patient during the course of the study.
All 13 patients consistently demonstrated reentry within the HPS during ventricular refractory period studies. In 11 patients the electrophysiological studies were performed before and 5 and 20 minutes after the intravenous administration of 10–14 mg/kg body weight (i.e., 750 mg) of PA infused at a rate of 50 mg/min. In the remaining two patients, similar studies were performed during control and immediately after the infusion of 500 mg of PA and again within 5 minutes after infusion of an additional 250 mg of PA. This additional dose of 250 mg of PA was given within 10 minutes after the infusion of 500 mg dose. The protocol for 500 mg study in these two patients is similar to our previous study. Blood samples for plasma PA levels were drawn before each repeat study. Plasma PA assays were carried out spectrophotometrically.

Statistical analyses were performed using the t test for paired data.

Definitions of Terms

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

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

Antegrade Conduction Intervals and Refractory Periods

These have been defined previously.

Retrograde Conduction Intervals

The stimulus artifact (S) marked the onset of induced ventricular depolarization and the S-H and S-A intervals were measured from S to the onset of the His bundle electrogram and low atrial electrogram, respectively. The H-A interval was measured from the onset of His bundle electrogram to the beginning of low atrial electrogram. When $S_2$ resulted in more than one ventricular beat the H-V interval of subsequent beats ($H_2$ $V_2$) was measured from the onset of the His bundle electrogram to the earliest point of ventricular activation as observed on the ECG or the ventricular electrogram.

Critical $S_2H_2$ interval is defined as the shortest $S_2H_2$ required for reentry.

Zone of reentry refers to the range of $S_2S_2$ coupling intervals during which reentry occurs consistently.

Zone of $S_2H_2$ block is defined as the range of $S_1S_2$ intervals during which retrograde block of the $S_2$ impulse occurs distal to the site of stimulation but proximal to the His bundle recording site. Such zones can only be identified if $H_2$ is clearly identified at longer $S_1S_2$ intervals prior to the blocked beat.

Retrograde Refractory Periods

Effective Refractory Period (ERP) of Ventricular Muscle

The longest $S_2S_2$ at which $S_2$ fails to evoke a ventricular response.

Functional Refractory Period (FRP) of the HPS

The shortest $V_1H_2$ in response to any $V_1V_2$ intervals.

Results

Although both antegrade and retrograde conduction and refractory period studies were performed in all patients except one (patient 9), this study presents only the results obtained during retrograde refractory period studies. The effects of PA on antegrade conduction and refractoriness were similar to the results previously reported. PA consistently prolonged H-V interval and increased refractoriness of the HPS.

The results obtained at both 5- and 20-minute studies after PA were similar. Although the data for both studies are presented in table 1, only the results obtained at 5 minutes will be discussed in the text. The patients were divided into two groups, depending on the effect of PA on reentry within the HPS. Group 1 consisted of eight patients (1–8) in whom reentry was abolished and group 2 consisted of five patients (9–13) in whom reentry was not abolished, but the width of reentry zone was decreased. Table 1 presents the electrophysiological data for retrograde studies on individual patients. Retrograde conduction during the basic ventricular drive was present in all patients except three (patients 3, 7 and 9). In patients 3 and 9 atrioventricular dissociation was present at all ventricular drive rates, and patient 9 had atrial fibrillation.

The His bundle electrogram was hidden within the ventricular electrograms of both the basic drive beats ($V_1$) and premature beats ($V_2$) with long $S_1S_2$ intervals. At shorter $S_1S_2$ intervals, retrograde conduction prolonged and the $H_2$ deflection emerged from the ventricular electrogram ($V_2$) (fig. 1A). After the $H_2$ electrogram became visible, decreasing $S_1S_2$ intervals resulted in increasing $S_1H_2$ intervals.

In all patients, within a certain range of $S_1S_2$ intervals (zone of reentry), a single reentrant beat ($V_3$) occurred when the $S_3H_2$ interval reached a critical value (fig. 1A). Once such critical degree of $S_3H_2$ delay was achieved, $V_3$ consistently occurred at progressively shorter $S_1S_2$ intervals until the $S_2$ impulse either encountered the ventricular muscle refractoriness or retrograde block within the Purkinje bundle branch system (see below). The QRS configuration of $V_3$ was similar to those of the basic drive ($V_1$) and premature beats ($V_2$).

Zone of Reentry

Table 1 shows the reentry zones in each of the patients during control studies. After PA, reentry was abolished in group 1 patients (figs. 1A, 1B, and 2 and table 1). In group 2 patients (figs. 3A and 3B) the reentry zone was decreased from an average of 68 msec before to an average of 33 msec 5 minutes after PA administration ($P < 0.005$). In the group 2 patients the average $S_1S_2$ interval at which reentry first occurred after PA was approximately the same as in control ($299 \pm 24$ vs $301 \pm 15$ msec).
Critical S2H2 Delays

During the control studies, critical S2H2 intervals ranged from 170-240 msec (mean 203 ± 25 msec). PA had the following effects on retrograde His-Purkinje conduction: 1) the coupling interval (S1S2) at which the H2 deflection emerged from the ventricular electrogram (V3) was longer than control in all patients; 2) at comparable S1S2 intervals the S2H2 intervals were longer than control values; 3) S2H2 intervals comparable to control critical S2H2 were attained in both group 1 and 2 patients; 4) in group 1 patients reentry did not become manifest even at S2H2 delays that were significantly longer than control critical S2H2 intervals; 5) in group 2, significantly longer S2H2 delays than in control were needed to initiate reentry (214 ± 27 vs. 286 ± 13.7 msec; P < 0.005) (figs. 3A and B) and 6) the critical S2H2 intervals in group 2 were longer than the longest S2H2 intervals in group 1 at all but three cycle lengths (in patients 10, 11 and 13) (table 1).

Longest S2H2 Intervals

In group 1 the longest S2H2 intervals after PA were equal to or longer than the longest control values in patients 1, 2, 6 and 8. In the remaining, longest S2H2 intervals exceeded the control critical S2H2 delays but were shorter than the control longest S2H2 intervals. In group 1 the average durations of the longest S2H2 intervals for control (257 ± 18.6 msec) and PA (243 ± 34 msec) were not significantly different. However, after PA reentry did not occur. In group 2, the longest S2H2 intervals after PA were longer than control values in all patients. In these patients, the average durations of the longest S2H2 intervals for control and PA were 253.7 ± 26 msec (range 210-300) and 299.3 ± 38 (range 220-340) (P < 0.005), respectively.

H-V Interval and H2V3 Interval

The average H-V interval during sinus rhythm was significantly longer after PA (58 ± 9 msec) than before (47 ± 8 msec) (P < 0.001). The H2V3 interval of reentrant beats was longer than the H-V interval of sinus beats both before and after PA. An inverse relationship existed between the S2H2 interval and the H2V3 intervals, i.e., the longer the S2H2 interval, the shorter the H2V3 interval. In group 2 the average shortest H2V3 interval after PA was significantly longer than control.

Zone of S2H2 Block

S2H2 block is a form of retrograde gap within the HPS where the S2 impulse blocks between the site of stimulation and the His bundle and is not followed by a His bundle deflection. Reentry did not occur when S2H2 block was present within the reentry zone, but was reestablished at shorter S1S2 intervals when S2 impulse resumed conduction to the bundle of His (fig 4).
Zones of $S_2H_2$ block ranging from 10–30 msec in duration were observed within the zone of reentry during control studies in five patients (1, 4, 6, 8 and 9) (fig. 4). After PA, the zones of $S_2H_2$ block became wider in all five patients and appeared in six other patients (3, 5, 7, 10, 12 and 13). In six patients in group 1 (3–8), PA abolished reentry by causing consistent block of $S_2$ impulse in both bundle branches up to the onset of ventricular muscle refractoriness (fig. 4).

FRP of the HPS

The FRP of the HPS could be determined in all patients both during control studies and after PA. This parameter increased after PA by an average of 54.7 msec (479 ± 36.6 vs 533.7 ± 33 msec; $P < 0.001$) in group 1, and by an average of 46.1 msec (485.6 ± 17.6 vs 530.5 ± 22.5 msec; $P < 0.001$) in group 2 patients.

ERP of Ventricular Muscle

The ERP of the ventricular muscle increased after PA in all patients at all cycle lengths tested. The increase averaged 27.4 msec (231.6 ± 23.7 vs 259 ± 28 msec; $P < 0.001$) and 40 msec (228.7 ± 19.6 vs 268.7 ± 14.6 msec; $P < 0.001$) in groups 1 and 2, respectively. In group 2 patients the increase in ERP of ventricle after PA caused a decrease in the width of reentry zone (figs. 3A and 3B).

Effects of 500 and 750 mg of PA on Reentry

PA in 500 mg doses increased the width of reentry zone by an average of 16 msec from control and caused repetitive reentry for more than one beat in both patients (7 and 8) receiving this dose (fig. 5, table 1). The $S_2S_2$ and $S_2H_2$ intervals at which reentry was initiated after 500 mg of PA were longer than control values (fig. 5, table 1). In these two patients, PA in 750 mg doses abolished reentry despite the attainment of conduction delays ($S_2H_2$ intervals) that were longer than the critical $S_2H_2$ intervals of control and 500 mg of PA studies (fig. 5, table 1).

Blood Pressure

In one patient PA caused significant hypotension (fall of > 25 mm Hg in systolic pressure). His blood pressure rapidly returned to normal after intravenous administration of fluids and leg raising. In the remaining patients systolic blood pressure decreased by 5–15 mm Hg.

Plasma PA Levels

Plasma concentrations at 5 and 20 minutes after the completion of infusion averaged 15.1 mg/l and 8.6 mg/l, respectively.

Discussion

In a previous study we reported that lower plasma PA concentrations increased the width of reentry zone and changed a non-sustained into a sustained reentry. This study shows that higher plasma concentrations of PA have an opposite effect on reentry within the HPS. These two studies explain the mechanism by which PA can both aggravate and suppress the same type of reentry dependent on critical changes in conduction and refractoriness of the HPS.
FIGURE 1A. Patient 6. Zone of reentry within the His-Purkinje system: control. The basic ventricular cycle length (S1S1) is 600 msec in all panels. In panel A, a premature ventricular beat, S2, introduced at an S1S2 interval of 270 msec, conducts retrogradely to the bundle of His with an S2H2 interval (retrograde His-Purkinje conduction time) of 140 msec and is blocked in the atrioventricular node. A sinus escape beat follows. As the S1S2 interval is decreased to 260 msec (panel B), the S2H2 increases to 200 msec and conducts retrogradely to the atria. Note low to high relationship of A2. V2 is followed by a reentrant beat (V3) which is preceded by an H2V3 of 70 msec which is longer than the H-V interval of sinus beat. Reentry (V3) continued to occur at closer S1S2 intervals and longer S2H2 delays (panel C) up to the onset of effective refractory period of the ventricular muscle, which was reached at an S1S2 interval of 200 msec (not shown in the figure). In this patient the zone of reentry (i.e., the range of S1S2 intervals, 270-210, over which reentry occurred) was 60 msec. The QRS axis of V3 is different from that of V2. This may be related to the asynchronous propagation of V3 impulse via the right bundle branch. HRA = high right atrial electrogram; HBE = His bundle electrogram. Time lines are 40 msec apart.
Figure 1B. Same patient as in figure 1A. Abolition of reentry within the HPS after procainamide. The basic ventricular cycle length is same as in figure 1A. At an $S_1S_2$ interval of 280 msec (panel A) $S_2H_2$ measures 255 msec. The $S_2$ impulse first encountered block in the infra His bundle region at an $S_1S_2$ interval of 270 msec (panel B) and was not followed by $H_2$ or $A_2$. The premature impulse ($S_2$) consistently blocked below the site of His bundle recording at shorter $S_1S_2$ intervals (panel C) up to the onset of effective refractory period of ventricular muscle which was reached at an $S_1S_2$ interval of 210 msec. In this patient reentry zone was abolished because of consistent retrograde block of $S_2$ distal to the site of stimulation but proximal to the site of His bundle recording. Had there been no such block, possibly reentry would have occurred in this patient because of greater $S_2H_2$ delays.
Figure 2. Patient 2. Reentry within the His-Purkinje system: control and after procainamide. The basic ventricular cycle length is 700 msec in all panels. During control period, V₃ first occurred at an S₁S₂ interval of 290 msec (panel A). The critical S₂H₂ interval is 210 msec. The H₂V₃ and H₂A₂ intervals measure 110 and 170 msec, respectively. A sinus beat follows. V₃ phenomenon occurred at shorter S₁S₂ intervals and longer S₂H₂ delays (panel B). The effective refractory period of the ventricle was reached at an S₁S₂ interval of 230 msec. Following procainamide (panels C and D) the S₂H₂ interval at identical S₁S₂ interval as in panel A measures 245 msec, but does not cause V₃. V₃ failed to occur at shorter S₁S₂ intervals and significantly greater S₂H₂ delays (panel D) than in control. After procainamide effective refractory period of ventricle was reached at an S₁S₂ interval of 270 msec. Junctional escape beats are seen in panels B, C and D. T = Time lines, 50 msec apart. Other abbreviations are the same as in figure 1.
Figure 3A. Patient 10. Zone of reentry within the HPS: control. The basic cycle length is 800 msec. The right ventricle is paced from the outflow tract. Reentry (V3 phenomenon) first occurred at an S1S2 interval of 300 msec (panel B). The critical S2H2 delay measures 200 msec. Reentry continued to occur at shorter S1S2 intervals and longer S2H2 delays (panel C) up to the onset of effective refractory period of the ventricle. The zone of reentry in this patient (300-230) is 80 msec. Time lines are 40 msec apart. Abbreviations are the same as in figure 1.
FIGURE 3B. Same patient as in figure 3A. Zone of reentry within the HPS: after procainamide. The basic cycle length \((S_1S_2)\) is the same as in figure 3A. \(V_3\) first occurs at an \(S_2S_3\) interval 300 msec (panel B) (same as in control study). The critical \(S_2H_2\) delay is significantly longer than in control. \(V_3\) phenomenon occurred at shorter \(S_1S_2\) intervals (panel C). The effective refractory period of the ventricle is reached at an \(S_1S_2\) interval of 260 msec (not shown in the figure), an increase of 40 msec from control. The zone of reentry (300-270) is shortened in this patient by 40 msec because of an increased effective refractory period of the ventricle.
An antiarrhythmic drug could abolish a reentrant arrhythmia by altering one or more of the following features of reentry: 1) restoring conduction in the region of the unidirectional block; 2) converting unidirectional block into bidirectional block; and/or 3) causing the time needed for recovery of excitability of the antegraded limb or ventricular muscle to exceed the conduction delay.

PA and Reentry

The most likely mechanisms by which PA abolished reentry in group 1 patients are illustrated in figure 6. As shown in panel B, increased refractoriness after PA may have created bidirectional block or prolonged the recovery of excitability without actual block in the right bundle branch, thus preventing antegraded conduction of V₂ through the right bundle branch with consequent absence of V₂. Possibly, partial retrograde penetration into the right bundle by V₂ impulse (due to PA-induced proximal delay within the ventricular muscle or at the muscle-Purkinje junction) without abolishing unidirectional block may have contributed to the delayed recovery of excitability and creation of bidirectional block in the right bundle branch. This mechanism seems applicable to patients 1 and 2, in whom S₂H₂ intervals significantly longer than control, critical S₂H₂ delays were attained but were not followed by V₂. Increased refractoriness after PA makes disappearance of unidirectional block in the right bundle branch an unlikely mechanism for abolition of reentry in these patients. The most likely mechanism responsible for abolition of reentry in patients 3–8 is illustrated in panel C. PA increased the ERP of the HPS and either widened or created the S₂H₂ block zones. In this instance, the V₂ impulse consistently encountered retrograde block in both bundle branches (panel C) or at the muscle Purkinje junction and was not followed by H₂ deflection or V₂ response.

Ventricular Muscle Refractoriness and Reentry

The results of our study suggest that refractoriness of ventricular muscle was not a primary determinant of reentry because the increased refractoriness of ventricular muscle after PA did not abolish reentry in any patient. Even though we did not determine the ERP of ventricular muscle following V₂, it is reasonable to assume that the ERP of ventricle after V₂ was shorter than that following V₁ because of shorter V₁V₂ cycle length. The absence of reentry after PA at S₂H₂ intervals that exceeded the ERP of ventricle made ventricular muscle a highly unlikely site of antegraded block and refractoriness of ventricle an unlikely determinant of reentry. After PA, reentry failed to occur because the refractoriness of antegraded limb (right
FIGURE 5. Patient 8. Dose-related effect of procainamide on His-Purkinje system reentry. The basic cycle length (CL) is 750 msec in all panels. Reference sinus beats are shown for control and procainamide studies. During control study (panels A and B) reentry occurred between S1S2 intervals of 300–240 msec. The critical S2H2 interval (panel A) and longest S2H2 interval (panel B) measure 220 and 270 msec, respectively. H-V interval measures 75 msec. After the infusion of 500 mg of procainamide (panels C and D), reentry is initiated at a longer S1S2 interval of 320 msec. The critical S2H2 delay of 240 msec is longer than the control value and V3 is followed by another reentrant beat, V4. Reentry for more than one beat occurred between S1S2 intervals of 320–300 msec. Reentry occurred at shorter S1S2 intervals and longer S2H2 delays (panel D). The longest S2H2 interval is 300 msec. Reentry is abolished (panels E and F) after an additional dose of 250 mg of procainamide (total 750 mg). Note the absence of reentry at an S1H2 interval of 290 msec (panel E) which is longer than the control longest S1H2 interval and the critical S2H2 interval of 500 mg of PA study (compare panels B and C with panel E). At a shorter S1S2 interval of 280 msec the S1 impulse retrogradely blocked proximal to the site of His bundle recording and is not followed by H2 deflection or V3 response. Such retrograde block of S1 impulse occurred at shorter S1S2 intervals to the onset of the effective refractory period of the ventricular muscle, which was reached at an S1S2 interval of 250 msec. Abbreviations are the same as in figure 1.

bundle branch) exceeded the conduction delay in the retrograde limb (left bundle branch) of the reentrant circuit.

His-Purkinje Conduction Delay, Block and Reentry

It is not surprising that in group 2 patients reentry could still be induced after PA, because conduction delays in these patients were longer than the longest S1H2 intervals of group 2 patients. Persistence of reentry is critically dependent on an appropriate balance between refractory periods (i.e., V1V2 and V2V3 intervals) and conduction times (i.e., S1H2 and H2H3 intervals) in antegrade and retrograde limbs of the reentrant circuit. Depending on the degree of conduction delay and the transition from a conduction delay into a block, PA may either facilitate, modify or terminate a reentrant ventricular arrhythmia. Similar observations have been reported with other drugs involving other types of reentry.20-22

Dose-Related Effect of PA on Reentry

The contrasting effects of lower concentrations of PA which facilitated reentry and the higher concentrations which abolished or favorably modified reentry raise the question: Which alterations in conduction and refractoriness are associated with abolition and which alterations are associated with facilitation of
However, at some intervals, the V₂ impulse is longer than the longest S₂H₂ intervals of control. Partial retrograde penetration into the RB by V₂ (due to PA-induced proximal delay within the ventricular muscle or at the muscle-Purkinje junction) without abolishing unidirectional block may have contributed to the longer recovery of excitability of RB and creation of bidirectional block. Panel C depicts the proposed mechanisms for abolition of reentry in patients 3–8. After PA, due to increased refractoriness of the His-Purkinje system, V₂ impulse encounters retrograde block in both bundle branches (panel C) or at the myocardial-Purkinje junction (not shown in the figure). In patients 3 and 8, in whom S₂H₂ intervals longer than the longest S₂H₂ intervals of control were attained before V₂ encountered retrograde block in both bundle branches, both mechanisms depicted in panels B and C may be operative in abolishing reentry. Shaded area represents slow conduction.

The occurrence of repetitive reentry in the previous study and the absence of such phenomenon in group 2 patients in the present study should be explained. The analysis of relationship between V₁V₂ and V₂V₃ intervals, an important determinant of repetitive reentry, revealed the following: During control studies, at the outer limits of reentry zone, the V₂V₃ intervals generally exceeded the V₂V₃ intervals (which approximately represent the arrival time of V₂ impulse at the left bundle), while at the inner limits, the V₂V₃ frequently exceeded the V₁V₂ intervals and the reentrant process was limited to a single beat (V₃) and always terminated in the retrograde limb of the reentrant circuit, i.e., V₃ was not followed by a His bundle deflection. At lower plasma PA concentrations, V₂V₃ were longer than V₁V₂ intervals (a result of greater V₂H₂ and H₂V₃ delays) both at the outer and inner limits of reentry zone, suggesting that the longer V₂V₃ intervals at the outer limits of reentry zone were critical for the occurrence of repetitive reentry. However, at comparable V₁V₂ intervals, the V₂V₃ intervals at higher plasma PA concentrations were longer than those attained at lower concentrations, but were not followed by V₄. Apparently, the V₁V₂, V₂V₃ relationship, though important, cannot adequately explain the presence or absence of repetitive reentry.

Another explanation for the dose-dependent effect of PA on reentry is that PA in lower doses causes slower conduction of V₂ impulse in the distal left bundle branch, allowing recovery of the more proximal left bundle branch, in turn permitting the propagation of V₃ to the bundle of His (H₃) and reexcitation of ventricles (V₄). PA in higher doses causes a greater degree of prolongation of refractoriness and depression of excitability of the left bundle branch, causing retrograde block of V₂ impulse in the left bundle branch, preventing repetitive reentry. Similarly, the absence of repetitive reentry during control studies may be explained as follows: The absence of depressed conduction in the distal left bundle branch might cause the V₂ impulse to arrive at the proximal left bundle branch before recovery of its excitability, preventing depolarization of the His bundle (H₃) and repetitive reentry. However, these are only possible explanations; more complex mechanisms may be involved in the occurrence or absence of repetitive reentry.

The results shown in the two patients in this study in whom PA widened the zone of reentry and caused repetitive reentry in small doses and abolished it in larger doses establish the dose-dependent effect of PA on reentry, and exclude the possibility that the effects of the drug on reentry were simply related to the difference between the patient groups. Furthermore, the groups in both studies are clinically similar and in each group the results were uniform.
The effects of PA on electrophysiologic parameters at 5 and 20 minutes were similar although the plasma levels were different, suggesting that there is a discrepancy between plasma levels and tissue content after acute intravenous administration of the drug. When administered intravenously, the effects of PA on electrophysiologic parameters are demonstrable only when serum levels are rather high. It has been reported previously that the plasma levels of PA after intravenous administration are only of limited value in studying drug effects.

Clinical Implications

Evidence from studies in patients with chronic recurrent ventricular tachycardia indicates that bundle branch reentry is a very rare mechanism of ventricular tachycardia. However, since the requisite conditions for microreentry which is assumed to be the mechanism of many cases of ventricular tachycardia, are the same as for macroreentry, it is tempting to postulate that PA abolishes these arrhythmias by mechanisms similar to the ones observed in this study. Wellens et al. found that in patients with chronic recurrent ventricular tachycardia, PA either abolished or modified the tachycardia zone, increased the ERP of right ventricle and lengthened the interval between the tachycardia, initiating premature beat and the first QRS complex of tachycardia. The latter observation strongly suggested reentry as the underlying mechanism of ventricular tachycardia. However, the mechanisms by which PA abolished reentry were not defined, since site of conduction delay and block could not be localized or measured. The results of this study suggest possible mechanisms by which PA can abolish various types of reentry in the HPS.

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