Procaine Amide Against Re-Entrant Ventricular Arrhythmias

Lengthening R-V Intervals of Coupled Ventricular Premature Depolarizations as an Insight into the Mechanism of Action of Procaine Amide

By Elsa-Grace V. Giardina, M.D., and J. Thomas Bigger, Jr., M.D.

SUMMARY

Nine patients with coupled ventricular premature depolarizations (VPDs) were treated with intravenous procaine amide to abolish the arrhythmia. The effect of procaine amide on the electrocardiogram was carefully observed. Seven patients were treated with intermittent intravenous therapy—100 mg of procaine amide was injected every five minutes—and two were treated by constant intravenous infusion—200 μg/min/kg body weight; blood for plasma procaine amide concentration was obtained 4.5 to 5 min after each dose. As the cumulative dose of procaine amide increased, plasma drug concentration increased and the frequency of coupled VPDs progressively decreased. Moreover, in every patient an interesting electrocardiographic phenomenon was observed: as plasma drug concentration increased, the coupling interval progressively increased until the arrhythmia was completely abolished. A hypothesis for procaine amide's antiarrhythmic action is offered based on this new observation. This hypothesis suggests that procaine amide prolongs conduction in the depressed portion of a re-entrant pathway such that conduction is further delayed and block finally occurs, thereby terminating the arrhythmia.

Additional Indexing Words:
Plasma procaine amide concentration Antiarrhythmic drugs Two compartment drug model
Computer analysis of arrhythmias

Although procaine amide has been in clinical use for more than 20 years,1,2 its mechanism of action against human re-entrant ventricular arrhythmias is not completely understood. Insufficient knowledge of the pharmacodynamics and the electrocardiographic effect of therapeutic drug concentrations and the lack of a satisfactory model for an arrhythmia have limited our understanding of the mode of drug action. Electrophysiologic properties of procaine amide have been studied in both the intact animal and isolated muscle,3,4 and antiarrhythmic effect has been explained in terms of laboratory studies demonstrating decreased automaticity, prolonged refractoriness, and decreased conduction velocity.5,6 To some extent, these properties have been inferred in man by the electrocardiographic changes resulting from procaine amide therapy.

Recently we documented the safety and clinical usefulness of an intravenous method of procaine amide administration which predictably produces therapeutic plasma drug concentrations and progressively alters the electrocardiogram as the frequency of ventricular premature depolarizations (VPDs) decreases.7 We now report an interesting electrocardiographic phenomenon induced by procaine amide: as the plasma procaine amide concentration increases, the coupling interval of the
VPDs becomes progressively longer until the arrhythmia is abolished. We believe this electrocardiographic observation results from procaine amide's electrophysiologic properties, and in turn, is responsible for its antiarrhythmic effect. Our goal is to characterize the phenomenon of an increasing coupling interval with procaine amide therapy and to provide a hypothesis for procaine amide's mechanism of action against human re-entrant ventricular arrhythmias.

Methods and Materials

Nine patients with coupled VPDs admitted to the Cardiac Intensive Care Unit were studied (table 1). Three patients had arteriosclerotic heart disease with acute myocardial infarction, two had arteriosclerotic heart disease associated with angina or previous myocardial infarction, three had heart disease of unknown etiology and one had rheumatic heart disease. Three patients were on maintenance digoxin but the cause of their arrhythmia was not felt to be digitalis induced; all had normal plasma potassium and calcium; two patients had an elevated blood urea nitrogen. In each case the patient's physician elected to treat the arrhythmia based on electrocardiographic evidence for frequent VPDs and clinical status of the patient and selected treatment with procaine amide. No patient received any other antiarrhythmic drug during this study.

All patients were continuously monitored for a period of three to ten hours. Based on analysis of this period, the presence of coupled VPDs was determined. Strict criteria were used to define constant coupling of VPDs—the coupling interval varied by no more than 60 milliseconds in any patient; nor was there evidence for fusion beats in any record. Electrocardiographic records from 32 other patients with VPDs were examined but rejected for study because these criteria were not met.

In addition to continuous monitoring of the surface electrocardiogram on an oscilloscope, arrhythmia was recorded continuously on instrumentation magnetic tape. A control period of at least 20 minutes and the entire period of procaine amide therapy was analyzed. Magnetic tape recording was later transcribed to paper at a speed of 100 mm/sec. At least ten of each of the electrocardiographic intervals, i.e., P-R, QRS, and Q-T, were measured by hand during the 4.5 to 5 minutes following each drug dose and the average duration of each determined. A digital computer was utilized to measure every R-R interval of the electrocardiogram allowing a large amount of electrocardiographic data to be rapidly and accurately measured. All sinus cycles and the coupling interval of each VPD were measured in milliseconds, printed, and plotted during the control period and drug therapy. In addition, the number of VPDs confirmed by hand count. At a later date, the average coupling interval for the VPDs and average sinus cycle length for each five minute period was determined.

Intravenous procaine amide was administered to insure delivery of a known amount of procaine amide and to gain rapid control of the arrhythmia. An indwelling polyethylene needle with a tight fitting obturator was placed in the brachial (or antecubital) vein for plasma sampling, an intravenous infusion in the other arm was used for drug injection. For seven patients a 100 mg dose of procaine amide hydrochloride was injected every five minutes through the intravenous tubing over a one minute period and then the tubing flushed with 5% dextrose and water; for two patients a constant intravenous infusion, 200 μg/min/kg body weight, was administered by Harvard Pump. The infusion rate was selected so that therapeutic plasma procaine amide concentrations would be attained within an hour. We planned to repeat 100 mg

Table 1

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<td>3) JK</td>
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<td>4) WM</td>
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<td>7) JI</td>
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<td>9) LS</td>
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*New York Heart Association Classification determined by symptoms on day prior to admission.
†Normal range 10–24 mg%; blood urea nitrogen.
‡Effective concentration measured 4½ min after PA dose that abolished arrhythmia.
§Maintenance digoxin.

Abbreviations: ASHD = arteriosclerotic heart disease; EH = enlarged heart; AMI = acute myocardial infarction; LVF = left ventricular failure (determined by physical examination and/or chest X-ray); RHD = rheumatic heart disease; MS = mitral stenosis; UHD = unknown heart disease; NSH = normal sized heart; OMI = old myocardial infarction; VPDs = coupled premature ventricular depolarizations.

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doses every five minutes or to maintain constant intravenous infusion and only discontinue the drug if 1) the arrhythmia was abolished, 2) 1,000 mg cumulative dose had been given, or 3) undesirable drug effects were encountered. In patients receiving infusions, the infusion rate was reduced or discontinued as soon as arrhythmia was abolished in order to avert untoward drug effects. Throughout the study a blood sample for procaine amide plasma concentration was obtained during the 4.5 to 5 minute period after each drug dose for the seven patients who received 100 mg every five minutes; and during every 4.5 to 5 minutes for the first 30 minutes and every ten minutes thereafter for those who received constant infusion. Arterial blood pressure was determined by cuff sphygmomanometer at the same time plasma samples were taken.

Two methods of drug administration were used because we had considered the possibility that the method of drug administration might alter the drug disposition and thereby the pattern of therapeutic response. Drug disposition in the body often satisfactorily fits a two compartment model.\textsuperscript{8,9} Figure 1 shows the procaine amide concentration time curves of the central and peripheral compartments predicted by a two compartment model for the two methods of administration used in this study. In order to determine which of the possible patterns of behavior of drug effect and concentration shown in figure 2 were applicable after a rapid intravenous injection, the first five-minute interval in which the number of VPDs was reduced by at least 50\% was analyzed. This interval was divided into five one-minute periods and the average coupling interval was determined for each minute. Three models are possible for the behavior of VPDs depending on whether the arrhythmic site in the myocardium is in the central (panel A), a slowly equilibrating peripheral

![Figure 1](http://circ.ahajournals.org/)

The theoretical plasma procaine amide-concentration time curve predicted after the rapid intermittent intravenous injection, Panel A, and the constant intravenous infusion, Panel B, the two methods of drug administration used in this study. C is drug concentration in the central compartment which is conceived as being composed of blood, a portion of the extracellular fluids, and highly perfused tissues. P is drug concentration in the peripheral compartment when equilibration is slow and the half life (t\%2) of transfer from the central to the peripheral compartment is 8 minutes. P\textsubscript{1} is drug concentration in the peripheral compartment when equilibration is rapid and the 1\% of transfer from the central to peripheral compartment is 1.5 minutes. Panel A: When 100 mg procaine amide is injected every five minutes there are marked saw-toothed fluctuations in the drug concentration measured in the central compartment (C); a smooth, progressive increase in the drug concentration occurs in the total peripheral compartment (P); and a smooth oscillating pattern in a compartment (P\textsubscript{1}) that equilibrates more rapidly with the central compartment than does P. Panel B: When 200\mu g/min/kg body weight procaine amide is delivered by constant intravenous infusion, the central (C), total peripheral (P), and rapidly equilibrating compartment (P\textsubscript{1}) all show a smooth progressive increase in concentration.
(panel B), or a rapidly equilibrating peripheral compartment (panel C) (fig. 2). If the myocardium equilibrates with the central compartment (C in fig. 1) at the same rate as the total peripheral compartment its concentration time course would be described by line P (in fig. 1). If, however, the myocardium equilibrates more rapidly than the average peripheral compartment it could be described by the theoretical line $P_1$ (fig. 1). Since we could not sample the concentration of procaine amide in the myocardium, we attempted to determine whether the arrhythmic site in the myocardium is in the central compartment or in the slower or faster equilibrating peripheral compartment by observing the effect of procaine amide on the frequency and the coupling interval of coupled VPDs.

Plasma procaine amide concentration was determined by the method of Mark et al. Procaine amide was extracted from alkalinized plasma into benzene, returned to dilute hydrochloric acid, then diazotized, coupled with (1 naphthyl) ethylene diamine, and the resulting color read in a Zeiss spectrophotometer at an optical density of 550 mg. Each patient’s control plasma was used to prepare a blank and standard. Each determination was done in duplicate and the procaine amide plasma concentration expressed as plasma procaine amide μg/ml base.

**Results**

*Cumulative Dose and Procaine Amide Concentration*

In all nine patients plasma procaine amide concentration rose as a function of dose. There was a progressive rise in plasma procaine amide concentration as the total dose increased although the rate of rise of plasma drug concentration varied. The plasma drug concentration obtained 4.5 minutes after the dose which abolished arrhythmia was termed the “effective plasma procaine amide concentration.” The range of effective plasma

**Figure 2**

Possible behavior of the VPD coupling interval in three models of drug concentration and effect at the site of origin of the arrhythmia after a rapid intravenous injection. A) If the procaine amide concentration at the arrhythmic focus in the heart follows drug concentration in the central compartment, changes in coupling interval would be greatest almost instantly following drug injection and become less marked during the following five minute interval. B) If drug concentration at the arrhythmic focus follows drug concentration in the slower equilibrating total peripheral compartment, the coupling interval should progressively increase over the five minute time course following drug injection. C) If the arrhythmic focus behaves like a compartment that equilibrates faster than the total peripheral compartment, changes in coupling interval increase but then decrease during the five minute interval. A rapid phase of distribution to the heart (if the fast phase has a t½ of one and a half minutes rather than eight minutes) would produce early myocardial changes. These alterations might decrease once an equilibrium between the heart and central compartment was established and drug distribution to the slower equilibrating total peripheral compartment takes place.
procaine amide concentration was 5.1 to 8.1 μg/ml. No patient became toxic and each arrhythmia was abolished on less than one gram dose. There was no difference in effective plasma concentration achieved with incremental dosage compared with constant intravenous infusion.

**Effect of Procaine Amide on VPDs and Coupling Intervals**

Counting every ectopic depolarization by hand and by computer analysis during the control period and during drug therapy validated the finding that VPDs were completely suppressed by procaine amide. Figure 3, a computer print out from a typical patient, shows two minute periods before drug administration and after 600 mg procaine amide had been administered. This print out recorded just prior to arrhythmia abolition documents the reduced frequency of VPDs. However, from the initiation of drug therapy a graded decrease in number of VPDs was observed (table 2). Moreover, a newly observed procaine amide induced electrocardiographic alteration was documented: the coupling interval of the VPDs progressively increased as the frequency of VPDs decreased (table 2).

For all patients, there was definite pattern of increasing coupling interval to decreasing number of VPDs as plasma drug concentration rose until arrhythmia was abolished. In eight patients a decrease in number of VPDs and an increase in coupling interval was noted just after 100 mg (six patients) or 1 mg/kg (two patients) procaine amide had been delivered. In the remaining patient (J.M.), an increase in coupling interval occurred after 200 mg cumulative dose procaine amide and a decrease in frequency of VPDs during the 10 to 15 minutes following initiation of therapy. With further drug therapy this patient’s arrhythmia

![Figure 3](http://circ.ahajournals.org/)

A typical computer print out and below, a representative portion of the simultaneously recorded surface electrocardiogram. Each black point in the graph represents one R-R interval in msec before administration of drug (A), and after 600 mg of procaine amide (B) for patient J.K. The sinus cycle length (R-R) (middle series of black points), coupling interval of VPD (R-V) (bottom series of black points) and compensatory pause (V-R′) (top series) from the surface electrogram are shown in the top two panels. The intervals also measured by hand agree with the values from the print out. In panel A, before drug treatment, the R-R interval is 820 msec; followed by a ventricular premature depolarization, R-V of 480 msec; and a compensatory pause, V-R′, of more than 1000 msec. The thin vertical line at the end of the graph in panel A is a reference point and is the mean control coupling interval determined for this time interval. In panel B, at a drug concentration of 6.5 μg/ml the coupling interval on the surface ECG had increased to 580–590 from 480 msec. From the graph it is apparent that ventricular premature depolarizations are less frequent and more variable and that sinus rate has not been significantly altered. The dashed horizontal line indicating a new mean coupling interval for all ventricular extrasystoles in this five minute period is 90 msec longer than the control.

*Circulation, Volume XLVIII, November 1973*
Table 2

Coupling Interval and Frequency of Ventricular Premature Depolarizations During Procaine Amide Therapy

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<tr>
<th>Patient*</th>
<th>R-R (msec)†</th>
<th>CI (msec)</th>
<th>VPD (no.)</th>
<th>CI (msec)</th>
<th>VPD (no.)</th>
<th>CI (msec)</th>
<th>VPD (no.)</th>
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Cumulative Dose of Procaine Amide (mg/kg) (constant infusion)

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Abbreviations: CI = coupling interval; VPD = ventricular premature depolarization.

*Patients 1-7 received 100 mg procaine amide intravenously every five minutes; patients 8 and 9 received 200 μg/kg/min by constant intravenous infusion.
†Range of sinus cycle length before procaine amide therapy.
‡The average coupling interval and frequency of premature ventricular depolarizations was determined for at least ten consecutive minutes before drug started.
§**The average coupling interval and frequency of ventricular premature depolarizations determined in each five minutes interval after drug therapy started.
progressively diminished, suggesting that a critical myocardial drug concentration must be achieved before an increase in coupling interval or decrease in VPDs is observed.

For another patient (W.F.), after 8 mg/kg procaine amide, the coupling interval decreased from 649 to 616 msec and the number of VPDs in that time interval increased from seven to sixteen. Although it is impossible to be certain what is occurring at the myocardium, one might expect that the myocardial drug concentration was progressively increasing this late in the time course of drug administration. The observation of decreasing coupling interval with an increase in the number of VPDs suggests there may have been inhomogeneity of drug concentration or unequal sensitivity to drug in the tissues causing the arrhythmia. In any case, this observation suggests that the frequency of VPDs follows more closely the length of the coupling interval than either cumulative drug dose or plasma concentration.

No difference in magnitude of change of the coupling interval could be discerned at the termination of arrhythmia as a result of different methods of drug administration (fig. 4). For the seven patients treated with repeated intravenous injections of procaine amide, the maximum average coupling interval increased by 37 to 100 msec; for the two treated with constant intravenous infusion, the maximum average coupling interval increased by 70 to 100 msec. The average change for all patients was 66 msec (P < 0.001) (table 3).

**Compartmental Analysis after Intravenous Procaine Amide**

We considered the possibility that sudden intravenous injection of procaine amide might alter drug disposition in such a way that drug is presented to the heart differently than after a constant intravenous infusion (fig. 2). Two distinct patterns of change in coupling interval after sudden intravenous injection were observed (fig. 5). For five patients, there was a clear progressive increase in the average coupling interval in each one minute period following the intravenous injection. For two patients, the coupling interval after procaine amide injection first lengthened but then shortened before the next dose. For the two patients who received procaine amide by constant intravenous infusion, the coupling interval became progressively longer over each one minute period in the five minute interval. The two patterns of response seen may be affected by the method of drug administration; however, further data will be required to confirm these observations. Regardless of the method of administration, for the majority of patients the myocardial response is that expected for a fairly slowly equilibrating peripheral compartment (fig. 2 panel B). In two patients behavior compatible with a rapidly equilibrating peripheral compartment was observed. No patient exhibited a pattern suggesting that the arrhythmia-generating site in the myocardium is in the central compartment. An alternate explanation might be that there is rapid equilibration of drug between plasma and myocardium and a delayed onset of effect.

**Effect of Procaine Amide on Sinus Cycle Length and ECG Intervals**

**Sinus Cycle Length.** Measurements of every R-R interval showed that each patient had sinus arrhythmia before and during drug therapy (table 2). The range of sinus cycle length varied by only ±0 to 30 msec after procaine amide therapy. Neither this change nor the slight change in average sinus rate was statistically significant. To validate

<table>
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**ECG Intervals Before and After Administration of Procaine Amide**

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<th>QRS msec</th>
<th>Q-T msec</th>
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<tr>
<td>Mean ± SEM</td>
<td>160 ± 8.5</td>
<td>166 ± 9.9</td>
<td>84 ± 3.8</td>
<td>91 ± 3.4</td>
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**Abbreviations:** CI = coupling interval; PA = procaine amide.
The progressive increase in coupling interval as a function of plasma procaine amide concentration for seven patients treated with incremental intravenous procaine amide (100 mg every five minutes), panel A; and for two patients who received a constant intravenous infusion (200 µg/min/kg body weight), panel B. Each symbol represents the change in mean coupling interval for all the premature ventricular depolarizations in a five minute period compared to the control. Each line connecting the individual symbols is continued until just prior to termination of arrhythmia. The data shows that each patient had a progressive increase in coupling interval of premature ventricular depolarization as a function of increasing plasma drug concentration. While the slope of each line varies, each patient showed a maximum average increase in coupling interval ranging from 37 to 100 msec.

that the increase in coupling interval was not due to changes in sinus rate, the coupling interval was normalized, i.e., the average coupling interval per five minutes was divided by the average sinus cycle per five minutes and the result expressed as a percentage. Each patient's normalized coupling interval increased by 8 to 23% before arrhythmia termination. This result indicates that the increase

in coupling interval was greater than variability in sinus cycle length and suggests that lengthening of

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coupling interval is not solely dependent on change in sinus cycle length.

**ECG Intervals.** The drug effect on the P-R, QRS, and Q-T intervals was variable and did not appear related to pre-existing abnormalities of these intervals (table 3).

**P-R Interval.** In five patients, P-R interval increased by a maximum of 5 to 20 msec; in four patients there was no change. One patient had a normal control P-R which became abnormally prolonged after procaine amide. Mean increase in P-R interval of 6.6 msec was statistically significant (P < 0.05).

**QRS Interval.** In three patients there was no change in duration of QRS and in six patients QRS increased by a maximum of 10 to 15 msec. The mean increase in QRS of 6.6 msec was statistically significant (P < 0.001). No patient developed QRS widening more than 30% of control.

**Q-T Interval.** Q-T interval increased in six patients by 20 to 30 msec and in three patients was not changed after drug therapy. The mean increase in Q-T interval of 14.4 msec was not statistically significant.

**Discussion**

Although procaine amide has been in clinical use for more than 20 years,1 2 its mechanism of action against ventricular arrhythmias in man is not completely understood. One reason for this is that often the mechanism for the arrhythmia is not entirely clear. Understanding the mode of action of an antiarrhythmic drug requires knowledge of the mechanism by which the arrhythmia in question is initiated and maintained as well as an awareness of the cardiac effects of the drug.5

In simple terms, arrhythmias are caused by either disorders of conduction or automaticity or a combination of these.10 Well-established electrocardiographic criteria have been used to differentiate the origin of arrhythmias. Traditionally a premature depolarization which bears a consistent temporal relationship to the sinus depolarization preceding it, i.e., a coupled premature depolarization, is thought to be a passive phenomenon precipitated by the preceding depolarization.11 12 This general thesis is supportable on both experimental and theoretical grounds. It is based on the historical observation that a single mechanical or electrical stimulus applied to the heart may elicit one or more subsequent contractions13 14 and that such forced beats bear a similar configuration to a spontaneous extrasystole.15 That re-entry of excitation or circus movement might be responsible for this phenomenon was considered by Mines,17 and Lewis argued that if flutter is precipitated by circus movement then single premature depolarizations might be caused by the same mechanism.18 Schmitt and Erlanger demonstrated unidirectional conduction and re-entry in isolated cardiac muscle strips.18 They proposed a model that depicted re-entry occurring in an ultimate twig of the conducting system as the explanation for coupled VPDs (fig. 6). The usefulness of this model has received further support from recent electrophysiologic studies on depressed cardiac Purkinje fibers which have demonstrated that under appropriate circumstances the properties of very slow conduction and one-way block can produce re-entry.19 20 Although we recognize that mechanisms other than simply re-entry, e.g., afterpotentials or oscillations, could generate coupled VPDs, we will assume for the purposes of this analysis that coupled VPDs are due to re-entry and will attempt to explain the effect of procaine amide on coupled VPDs in man using the Schmitt-Erlanger model.

Continuous computer analysis of the ECG before and during drug therapy allowed the frequency of VPDs and every R-R interval to be measured. In addition, we measured plasma procaine amide concentrations during drug therapy. As a result of this analysis, we observed an interesting electrocardiographic phenomenon. In every patient, as plasma procaine amide concentration increased not only did the frequency of the VPDs decrease but their coupling interval increased as well (fig. 4). The change in coupling interval was progressive and noted as soon as five or ten minutes after therapy was started—at the same time VPDs began to decrease in frequency. This increase in coupling interval occurred before and more consistently than any other change in electrocardiographic intervals. We further observed that the reduction in the number of VPDs correlated better with the increase in the coupling interval than the increase in cumulative dose or plasma procaine amide concentration (table 2). This suggests that the progressive increase in coupling interval or the decrease in VPDs is a useful tool to evaluate drug concentrations at the site of origin of the arrhythmia. Recurrence of arrhythmia may be a consequence of inadequate myocardial drug levels despite apparently adequate plasma drug concentrations. This impression is supported by an observation in one of our patients in whom VPDs increased and coupling
interval decreased despite a therapeutic plasma drug concentration.

While the observation that procaine amide increases the coupling interval is a new one, progressive lengthening of the coupling interval before termination of arrhythmia had been observed in the past. Scherf observed that after administration of quinine the coupling interval of VPDs gradually increased until the arrhythmia disappeared, only to recur once quinine effect subsided.\(^{21}\) Spontaneous increase of the coupling interval of VPDs during ventricular bigeminy until one ventricular depolarization was dropped has been observed as well.\(^{11,21}\) The underlying mechanism for prolongation of the coupling interval prior to arrhythmia termination has never been fully explained. We sought to translate the electrophysiologic properties of procaine amide into corresponding electrocardiographic data in order to explain this phenomenon and offer a hypothesis for procaine amide's mechanism of action.

That re-entry of excitation within the ventricle or the ventricular conducting system might cause coupled VPDs has been a widely held hypothesis for a number of years. Electrophysiological studies support the view that procaine amide's mechanism

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**Figure 6**

A model of re-entry presented as the possible cause of coupled ventricular premature depolarizations\(^{18}\) and as an explanation for procaine amide's effect on the coupling interval of VPDs for a typical patient. The model to the left represents a peripheral Purkinje fiber and adjacent ventricular muscle. There is a depressed segment which exhibits slow conduction and unidirectional block, Branch 2 (Br 2). An impulse spreading from the central Purkinje fiber into this region of Branch 2 is blocked, but conducts at normal velocity through Branch 1 (Br 1) to excite ventricular muscle. Activity entering Branch 2 from its ventricular end, however, is not blocked, but spreads very slowly back to the bifurcation. Given a proper balance between the time required for retrograde spread and for repolarization of Purkinje fibers proximal to the region of decrement, re-entry will occur.

The diagram to the right fits data from patient T.Z. to the model. The distance between the black lines of Purkinje fiber, that is, 560 msec, is a representative sinus cycle length. Control data is indicated by the solid black lines. As an impulse progresses from Purkinje fiber, it is blocked in Branch 2 but conducts at normal velocity through Branch 1 to the ventricle to produce a normal sinus beat on the surface electrocardiogram. The impulse may enter Branch 2 distally and conduct retrograde to re-enter Branch 1 to produce a premature ventricular depolarization with a coupling interval of 440 msec.

After the addition of procaine amide, indicated by the dashed lines, conduction time through Branch 2 is delayed. At a concentration of 7.6 μg/ml, the coupling interval has increased to 550 msec. With further dosing, conduction is so slowed that complete retrograde block occurs in Branch 2 and the arrhythmia is terminated.
of action may be related to alterations in membrane responsiveness induced by the drug. In mammalian Purkinje fibers procaine amide depresses the maximum rate of rise and amplitude of the action potential as well as slightly increasing its duration and effective refractory period. This action would cause slowing of the re-entrant impulse particularly in abnormal tissue exhibiting slow conduction and unidirectional block. The reduction in responsiveness caused by the drug could interrupt a re-entrant rhythm by converting unidirectional to bidirectional block. The effect of procaine amide on other ECG intervals. Therapeutic concentrations of procaine amide decrease conduction velocity in the fibers of the atrium, ventricle, and His-Purkinje system. Antiarrhythmic plasma concentrations of procaine amide produce some prolongation of the P-R, QRS, and Q-T intervals in man. These electrocardiographic changes show that procaine amide produces conduction delay outside the site of origin of the arrhythmia, in man (table 3). Procaine amide should produce even more profound effects on focal depressed zones responsible for the VPDs.

Given the Schmitt-Erlanger model, the mechanism of action of procaine amide proposed in figure 6 is the only reasonable explanation for our observation. Other geometric situations which would generate a VPD on a re-entrant basis reduce to a similar model. One alternate model could explain the response of VPDs to procaine amide observed in this study. An ectopic automatic focus beating at a rate nearly identical to the sinus, but asynchronous to sinus firing, could produce VPDs with fixed coupling. This model presumes entrance block and exit delay. If procaine amide increased exit conduction delay without affecting either sinus or ectopic focus automaticity, fixed coupling with long coupling intervals would result. Thus, if as procaine amide concentration increased, exit delay increased and then blocked, the electrocardiographic change we observed would be produced. It should be pointed out, however, that in studies performed in isolated mammalian Purkinje fibers, automaticity is usually suppressed at lower procaine amide concentrations than those required to alter conduction. If automaticity in a ventricular ectopic focus was decreased by procaine amide and the sinus rate did not change, then the VPD coupling interval would become quite variable. Therefore, if the assumption that coupled VPDs are due to re-entry is correct, the analysis based on this assumption shown in figure 6 is the most reasonable way to account for lengthening of the coupling interval of coupled VPDs and to explain procaine amide's mode of action against human re-entrant ventricular arrhythmias.

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Correction

Eckberg DL et al.: Circulation 47: 1252, 1973. On page 1253, the formula should read

\[
\text{wall stress} = P \cdot r_1 \left( 1 - \frac{2r_1^2}{L^2} \right) \times h
\]

where \(P\) = intracavitary pressure in g/cm², \(r_1\) = internal left ventricular cavity radius, \(h\) = wall thickness at the minor left ventricular circumference, and \(L\) = long axis of the left ventricle.
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