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THE USE OF EVOKED ENDOCARDIAL RESPONSE FOR ASSESSMENT OF ANTIARRHYTHMIC DRUG EFFECTS ON MYOCARDIUM

BY

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ABSTRACT

The technique "asymmetric biphasic stimulation" which paces the heart and neutralizes the post-stimulus polarization at the electrode-tiessue interface allows for the recording of the entire evoked endocardial response via a single electrode for both pacing and recording. Using this system the effects of antiarrhythmic drugs, procainamide and **N**-acetylprocainamide, on the myocardium were studied in 20 dogs. Before and during the five-step drug infusion, the evoked endocardial responses were recorded during bipolar and unipolar at the rates of 120, 150 and 200/min. The plasma concentration of the procainamede ranged from 1.7 to 32.5 mg/l and that of **N**-acetylprocainamide ranged from 8.1 to 116.1 mg/l. Procainamied significantly prolonged both the depolarization duration and the repolarization duration at a low plasma concentration (Class I antiarrhythmic drug property). **N**-acetylprocainamide significantly prolonged the repolarization duration at a low plasma concentration, while the depolarization duration was not significantly changed at a low or therapeutic plasma concentration (Class III antiarrhythmic drug property). The prolongacion of the depolarization duration by procainamide and **N**-acetylprocainamide was rate-dependent; the faster the rate the greater the prolongation. This simple and accurate assessment of the antiarrhythmic drug effects on the myocardium may provie a future means for the pharmacologic antiarrhythmic therapy.

Key words: Evokde endocardial response, Asymmetric biphasic stimulation, Procainamide, **N**-acetylprocainamide.

INTRODUCTION

Following the delivery of a pacing stimulus above the stimulation threshold, an electrical response is evoked in the ventricular myocardium whic is called "post-stimulus-evoked endocardial response"[1]. Donaldson and Rickards[2] utilized the evoked endocardial response to assess the drug-induced changes in the myocardial repolarization. In the past, however, it has not been possible to record the depolarization phase of the evoked endocardial response, because an ordinary pacemaker stimulus creates post-stimulus polarization effects at the electrode-tissue interface. Delivery of an asymmetric biphasic pulse promptly neutralizes the post-stimulus polarization and makes it possible to record the entire evoked endocardial response via the same electrode used for pacing[3]. The purpose of this study was to examine whether the evoked endocardial response obtained by asymmetric biphasic stimulation could be used to assess the antiarrhythmic drug effect of the myocardial depolarozation as well as the repolarization in situ.

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METHOD

General procedure Twenty mongrel dogs weighing from 13 to 20 kg were anesthetized with morphine sulphate 2 mg/kg subcutaneously followed by a continuous infusion of sodium thiopental 0.2 mg/kg/min. The animals were intubated and ventilated with the Bennet MA-I volume limited respirator. The right jugular vein was exposed and under fluoroscopic control a bipolar pacing catheter was positioned in the apex of the right ventricle. The brachial veins and the femoral vein were cannulated, the former for anesthetic and antiarrhythmic drug administration and the latter for obtaining the blood samples to determine the drug plasma concentrations. A catheter was placed in the femoral artery to periodically obtain the blood samples for the arterial blood gas measurements. Throughout each experiment, the ventilation was adjusted to maintain the arterial P_{02} between 80 and 100 mmHg and the pH between 7.35 and 7.45.

Recording of the evoked endocardial response An asymmetric biphasic pulse (Figure 1) was used. The initial negative phase of the pulse stimulates the heart and the following positive phase neutralizes the post-stimulus polarization. The stimulus amplitude is programmed to 10 mA and the pulse duration can be varied from 20 to 1000 μs in 1 μs steps. The amplitude of the neutralizing pulse is pre-programmed to one-tenth of the amplitude of the stimulus (1 mA). Because the impedance of the electrode-tissue interface is variable every moment, the ratio of the amplitude of the stimulus and neutralizing pulse actually delivered to the heart is never exactly 10:1. To completely neutralize the post-stimulus polarization at the electrode-tissue interface, the delivered electrical charge is integrated into the on-line system. When the integral of the delivered charge returns to zero, the delivery of the neutralizing pulse is automatically terminated (Figure 1). Thus, the process for neutralizing the post-stimulus polarization at the electrode-tissue interface is automatically accomplished and the high fidelity-evoked endocardial response can be recorded as close as approximately 1 ms post-stimulation with a single electrode for both pacing and recording. Typical bipolar and unipolar recordings of the evoked endocardial response are shown in Figure 2.

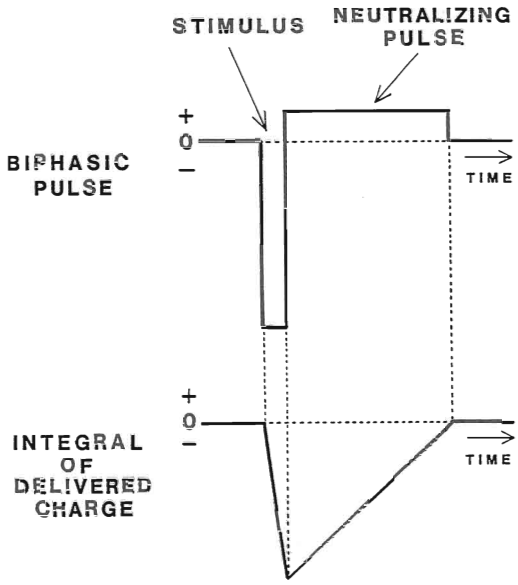

Fig. 1. Asymetric Biphasic Pulse
The stimulating-neutralizing pulse is depicted. The stimulation portion of the pulse is negative and the amplitude is programmed to 10 mA and the duration is variable from 20 to 1000 μs in 1 μs steps. The positive neutralizing portion of the pulse is pre-programmed to 10 percent of the amplitude of the stimulus (1 mA) and is self-terminated when the sum of the electrical charges delivered to the heart equals zero

During each experiment the evoked endocardial response was displayed on an oscilloscope (HP model 1741A) and was

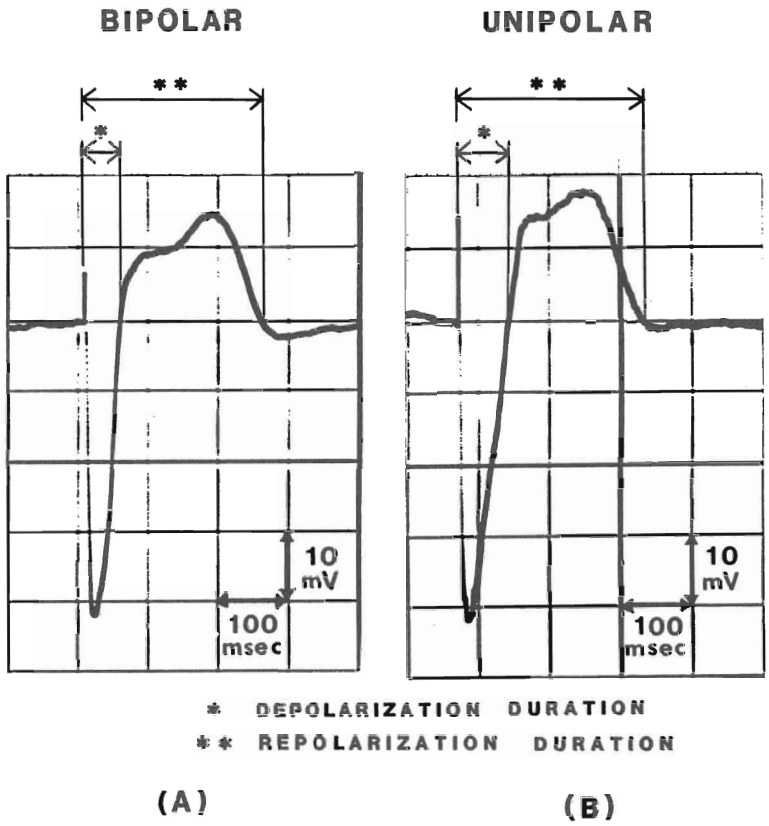

Fig. 2. (A) Typical Bipolar Recording of Evoked Endocardial Response
The depolarization duration (*) was measured as the time interval from the stimulus artifact to the second crossing point to the isoelectric line and the repolarization duration (**) from the stimulus artifact to the third crossing point to the isoelectric line. (B) Typical Unipolar Recording of Evoked Endocardial Response
The measurements of the depolarization and repolarization durations were the same as in Figure 2A

recorded on a multichannel tape recorder (HP model 3268A) at a gain of 100 and filter settings of 0.5–700 Hz. After completion of each experiment, the recorded evoked endocardial responses were digitally processed using a data precision digital computer (model Data 6000) and the computerized measurements of the depolarization and repolarization duration were made. The depolarization duration was measured as the time interval from the stimulus artifact to the second crossing point to the isoelectric line and the repolarization duration was measured from the stimulus artifact to the third crossing point to the isoelectric line (Figure 2).

Drug study protocol The effects of procainamide were studied in nine dogs and the effects of N-acetylprocainamide in six dogs. The doses of procainamide and N-acetylprocainamide (Table 1) were chosen using the kinetics data of Baer *et al.* [4] to reach rapidly the five plasma concentrations of either procainamide or N-acetylprocainamide in each dog and to maintain each concentration nearly constant during the time (approximately 10–15 minutes) necessary to make a com-

Table 1. Doses of Procainamide and N-acetylprocainamide Used for 5-Step Sequence of Bolus Injections and 45-minute Infusions

STEP	1	2	3	4	5
PA (n=9)					
Bolus injection (mg/kg)	2.8	2.8	5.6	11.2	22.4
Infusion (μg/kg/min)	14	28	56	112	224
NAPA (n=6)					
Bolus injection (mg/kg)	8.5	8.5	17	34	68
Infusion (μg/kg/min)	25	50	100	200	400

PA=procainamide; NAPA=N-acetylprocainamide

plete set of recordings of the evoked endocardial response. Thus, each animal received five successive sequences of either procainamide or N-acetylprocainamide, and each sequence included an intravenous bolus injection (loading dose) immediately followed by a slower intravenous infusion for over 45 minutes (Figure 3). All infusions were made by a constant speed Harvard infusion pump. In the control group of five dogs, saline was injected instead of the drugs using the same five successive sequences of intravenous bolus and infusion. Recordings of the evoked endocardial responses were made before the first drug or saline injection (control value) and between 30–45 minutes of each of the five intravenous infusions. At each recording step, the evoked endocardial responses were recorded for a minimum of one minute during both bipolar and unipolar pacings at three different paced rates of 120, 150, and 200/min. The blood for drug plasma concentration determination was drawn at 30 and 45 minutes of each of the five infusions.

Data analysis The percent changes in the depolarization duration and repolarization duration from the control value at each of the five drugs or saline infusion steps were averaged for each group (control, procainamide or N-acetylprocainamide group) and were expressed as mean ± one standard deviation. The paired test was used for comparisions, and the level of significance was $p<0.05$. Although the shape of the evoked endocardial response was different between the unipolar recording and bipolar recording and the depolarization duration was greater by the unipolar recording than by the bipolar recording, the magnitude of the changes in during both the depolarization duration and repolarization duration after the drug administration was identical between these two recording modes. Therefore, only the data obtained by bipolar recording are presented.

Results

Control dogs The five control experiments in which saline was administered in the five-step protocol, the same as that used for the drug studies, showed that prolonged anesthesia (285 minutes) had no significant effect on the depolarization duration and repolarization duration. The mean percent changes from the control value in the depolarization duration and repolarization duration at any step were less than 2%.

Procainamide and N-acetylprocainamide plasma concentrations The five-step dosing schedule resulted in a progressive increase in the procainamide or N-acetylprocainamide plasma concentration. The plasma concentration of procainamide ranges from 1.6 to 32.5 mg/*l* and that of N-acetylprocainamide ranged from 8.1 to 116.1 mg/*l*. In no case was there a significant difference between the 30-minute and 45-minute drug concentrations. This confirmed that each set of the recordings of the evoked endocardial re-

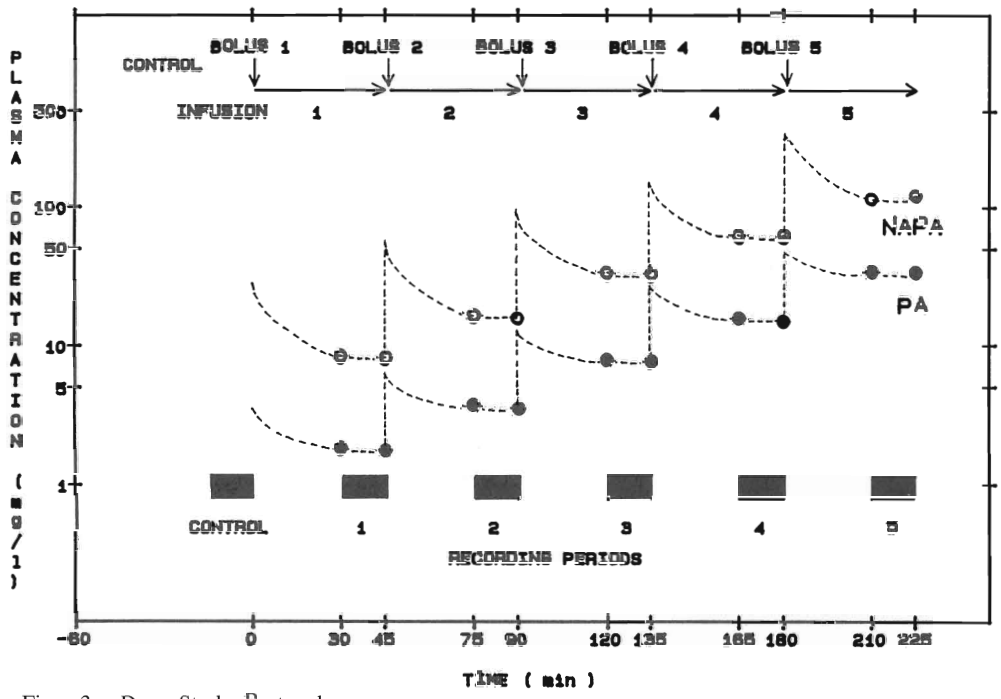

Fig. 3. Drug Study Protocol

Five successive steps of either procainamide or N-acetylprocainamide were utilized and each step included an intravenous bolus injection immediately followed by a slower intravenous infusion over 45 minutes. Plasma concentrations of procainamide (filled circles) and N-acetylprocainamide (open circles) are shwon as a function of time after five successive bolus injections and 45-minute infusions. The timing of the evoked endocardial response recording is shown at the bottom of the figure. PA=procainamide; NAPA=N-acetylprocainamide

sponse had been made at a time when the plasma concentrations of the drug were reasonably stable. The mean plasma concentrations of procainamide and N-acetylprocainamide at 30 minutes and 45 minutes for each of the five infusions are shown in Figure 3 and are listed in Table 2. The arithmetic mean of the plasma concentration at 30 minutes and 45 minutes was calculated for each infusion in each dog and was used to establish the concentration-response curves.

Effects of procainamide and N-acetylprocainamide on the evoked endocardial response The effects of procainamide on the evoked endocardial response were studied in nine dogs and those of N-acetylprocainamide in six dogs. Figure 4 depicts a typical example of the effect of procainamide on the voked endocardial response. At a procainamide plasma concentration of 14.6 mg/*l*, both the depolarization duration and repolarization duration were significantly prolonged (Class I antiarrhythmic drug property[5]). Figure 5 depicts a typical example of the effect of N-acetylprocainamide on the evoked endocardial response. At an N-acetylprocainamide plasma concentration of 15.0 mg/*l*, the repolarization duration was significantly prolonged, while the depolarization duration was not significantly effected (Class III antiarrhythmic drug property [5]). Concentration-response curves for the depolarization duration (Figure 6) and for the repolarization duration (Figure 7) were generated by plotting the logarithms of the drug plasma concen-

Table 2. Mean Plasma Concentrations of Procainamide and **B**-nacetylprocainamide (mg/l) at 30 Minutes and 45 Minutes of Each of Five Infusion Steps

STEP	1	2	3	4	5
PA (n=9)					
Cp 30 min	1.8±0.1	3.6±0.2	7.7±0.4	15.2±1.2	32.8±2.9
Cp 45 min	1.7±0.1	3.4±0.1	7.5±0.4	14.9±1.2	32.1±2.6
Cp mean	1.7±0.1	3.5±0.2	7.6±0.4	15.0±1.2	32.5±2.6
NAPA (n=6)					
Cp 30 min	8.2±0.7	16.0±1.6	32.2±1.6	60.4±2.5	116.3±3.8
Cp 45 min	8.0±0.8	15.7±1.6	31.7±2.4	60.4±2.0	115.9±4.6
Cp mean	8.1±0.8	15.9±1.6	32.0±2.0	60.4±0.8	116.1±3.5

PA=procainamide; NAPA=**N**-acetylprocainamide; Cp=plasma concentration of drugs; Cp mean=arithmetic mean of Cp at 30 minutes and 45 minutes of each of the 5 infusion steps.

trations on the abscissa and the corresponding changes in the depolarization duration or repolarization duration on the ordinate. Procainamide showed a dose-dependent increase in the depolarization duration. Of the three heart rates tested, the depolarization duration significantly and progressively increased from the second through the fifth increment of the procainamide dosage, at plasma concentrations ranging from 3.5±0.2 to 32.5±2.6 mg/*l*. At a rate of 120/min, the mean percent increases in the depolarization duration for each of the five plasma concentrations of procainamide were 0±1% (NS), 2±2% ($p<0.05$), 5±3% ($p<0.01$), 12±4% ($p<0.01$) and 28±7% ($p<0.01$) (Figure 6). In contrast, **N**-acetylprocainamide had a minimal effect on the depolarization duration. There was a significant increase from the control value in the depolarization duration only after the fifth and last dosage increase, at a plasma concentration of 116.1±3.5 mg/*l*. At the rate of 120min the mean percent increase in the depolarization duration for each of the five plasma concentrations of **N**-acetylprocainamide were 0±1% (NS), 1±1% (NS), 1±2% (NS), 2±2% (NS) and 7±6% ($p<0.05$) (Figure 6).

The effects of procainamide and **N**-acetylprocainamide on the depolarization duration were rate-dependent. At a constant plasma concentration of the drugs the depolarization duration exhibited a progressive prolongation as the rate was increased from 120 to 150 and from 150 to 200/min (Figure 6). After the fifth drug infusion the mean percent changes in the depolarization duration at the heart rates of 120, 150 and 200/min were 28±7%, 36±11% and 50±14% for procainamide and 7±6%, 9±5% and 17±8% for **N**-acetylprocainamide (Figure 8).

The repolarization duration showed dose-dependent responses to both procainamide and **N**-acetylprocainamide; the repolarization duration significantly increased by each of the five—dose increments of both procainamide and **N**-acetylprocainamide. At the rate of 120/min the mean percent changes in the repolarization duration for each of the five plasma concentrations of the drugs were 5±2% ($p<0.01$), 8±3% ($p<0.01$), 13±3% ($p<0.01$), 20±6% ($p<0.01$), and 32±7% ($p<0.01$), for procainamide and 5±2% ($p<0.01$), 10±6% ($p<0.01$), 16±8% ($p<0.01$), 32±8% ($p<0.01$), and 27±7% ($p<0.01$), for **N**-acetylprocainamide (Fi-

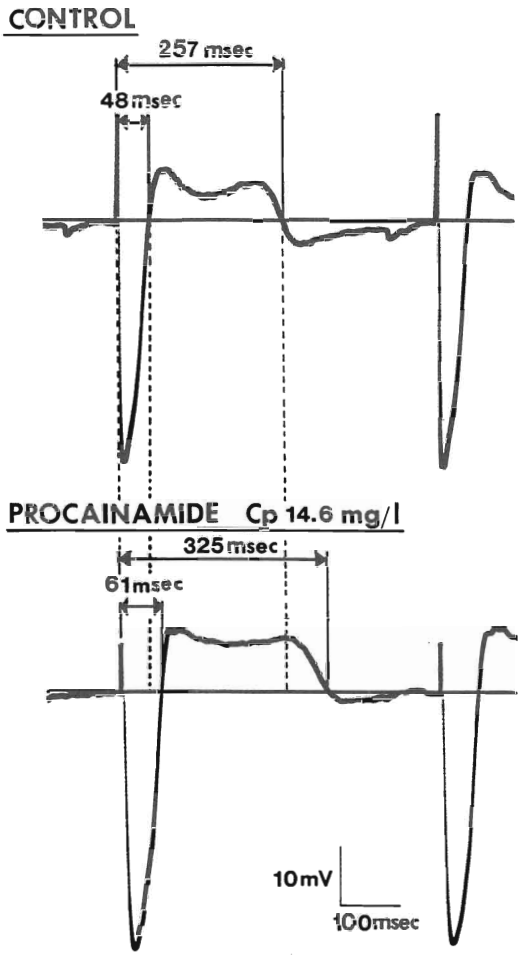

Fig. 4. Typical Example of Procainamide Effects on Evoked Endocardial Response
At a procainamide plasma concentration of 14.6 mg/l, the depolarization duration was prolonged from 48 ms to 61 ms and the repolarization duration from 257 ms to 325 ms (Class I antiarrhythmic drug properties). Cp=plasma concentration of the drug

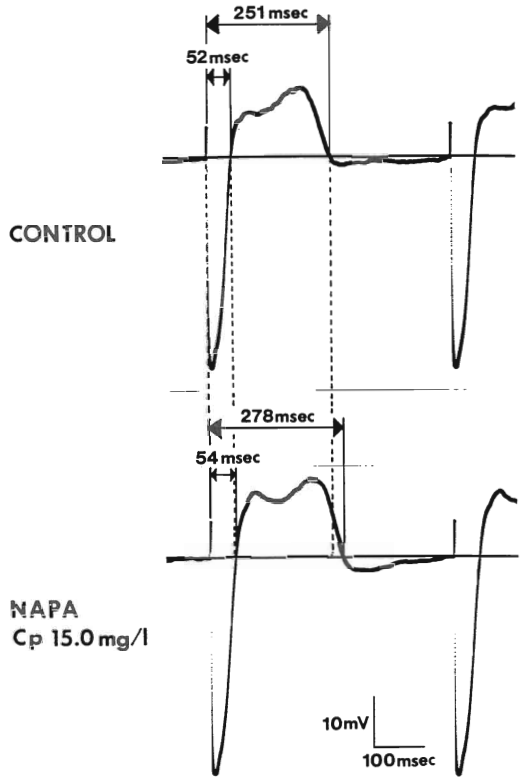

Fig. 5. Typical Example of N-acetylprocainamide Effects on Evoked Endocardial Response
At the N-acetylprocainamide plasma concentration of 15.0 mg/l, the repolarization duration was prolonged from 251 ms to 278 ms, while the depolarization duration was not significantly changed (Class III antiarrhythmic drug properties). Cp=plasma concentration of the drug; NAPA=N-acetylprocainamide

gure 7).

Discussion

In 1979 Auerbach and Furman[6] originally reported on the obtaining of a post-stimulus-evoked endocardial response in an open chest canine model using a single electrode for both pacing and sensing. Shortly thereafter, in 1981 Rickards and Donaldson[7] successfully recorded an evoked endocardial response in the human and utilized it to regulate the discharge rate of the rate-responsive pacemaker[8,9], to detect early myocardial ischemia[10] and to evaluate the drug-induced changes in myocardial repolarization[2]. These investigators created a sensing window relatively late in the evoked endocardial response and measured the repolarization duration as the time interval between the pacemaker sti-

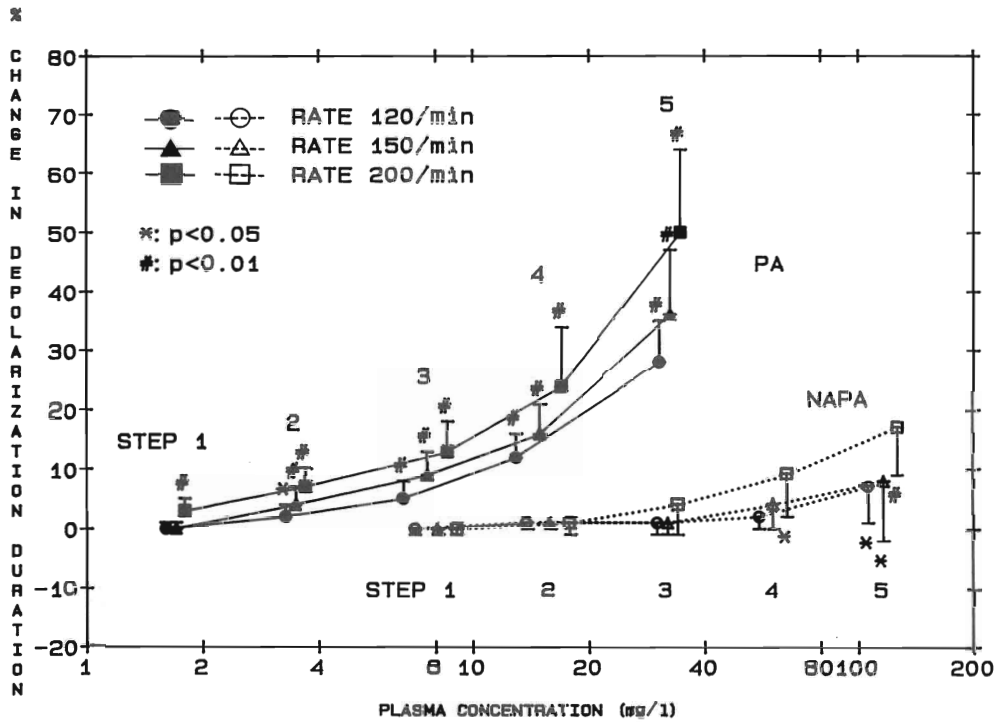

Fig. 6. Concentration-response Curves of Depolarization Duration
The logarithms of the plasma concentrations of procainamide and N-acetylprocainamide at each of the 5 infusion steps are plotted on the abscissa and the percent changes in the depolarization duration from the control value are plotted on the ordinate. Procainamide showed a progressive prolongation in the depolarization duration from the second through the fifth infusion step, the plasma concentration ranging from 3.5±0.2 to 32.5±2.6 mg/l. N-acetylprocainamide prolonged the depolarization duration only at the fifth infusion step, the plasma concentration being 116.1±3.5 mg/l. The circles show the values for the paced rate of 120/min, the triangles for the rate of 150/min and the squares for the rate of 200/min. The filled markers and solid lines represent the effects of procainamide, while the open markers and dotted lines represent the effect of N-acetylprocainamide. PA=procainamide; NAPA=N-acetylprocainamide

mulus and the peak of the repolarization wave. Thus, they were able to utilize the evoked endocardial response even though they could not eliminate the post-stimulus polarization at the electrode-tissue junction. In the past, however, it has not been possible to record the depolarization phase of the evoked endocardial response bacause of the post-stimulus polarization at the electrode-tissue junction. The technique, asymmetric biphasic stimulation, allows for obtaining the depolarization phase of the evoked endocardial response by delivering the neutralizing pulse following the stimulus. The method of asymmetric biphasic stimulation which we used in this study has a major advantage in the method of obtaining an evoked endocardial response with a single electrode system. The impedance of the electrode-tissue junction is variable every moment and a pre-programmed neutralizing pulse would not perfectly neutralize the post-stimulus polarization effect. Therefore, to precisely neutralize the stimulating phase of the biphasic pulse and to be able to obtain the entire and high fidelity evoked endocardial response, the delivered elec-

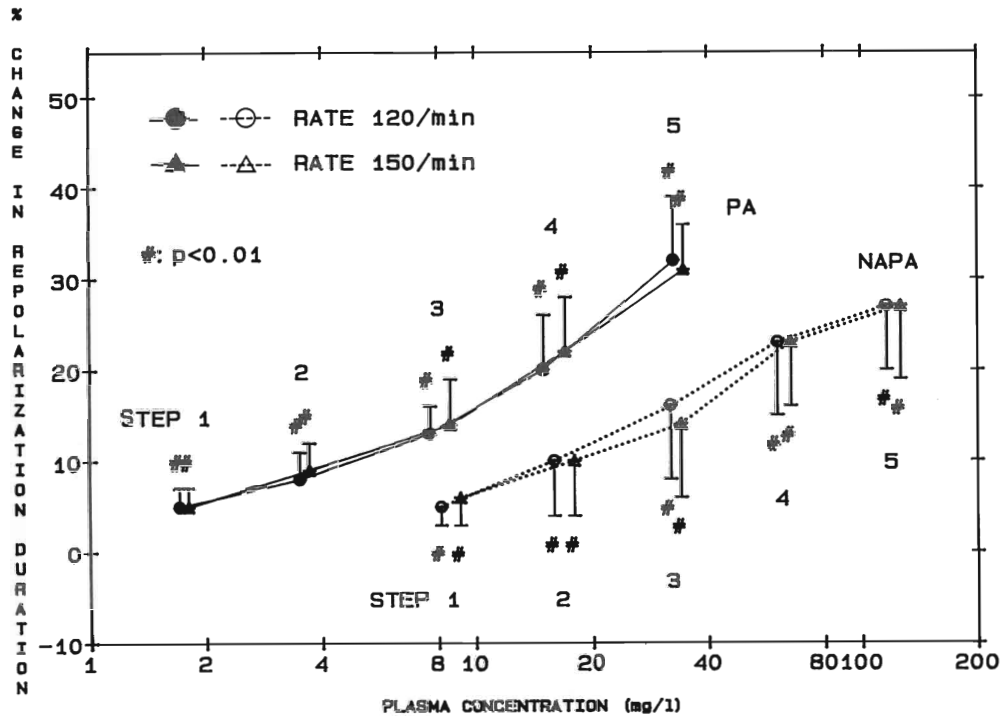

Fig. 7. Concentration-response Curves of Repolarization Duration
The logarithms of the plasma concentrations of procainamide and N-acetylprocainamide at each of the 5 infusion steps are plotted on the abscissa and the percent changes in the repolarization duration are plotted on the ordinate. Both procainamide and N-acetylprocainamide significantly prolonged the repolarization duration from the first through the fifth infusion step, the plasma concentration ranging from 1.7±0.1 to 32.5±2.6 mg/l for procainamide and from 8.1±0.8 to 116.1±3.5 mg/l for N-acetylprocainamide. Values for the rate of 200/min are not presented because at the two highest drug plasma concentrations the repolarization durations were greater than the R-R interval (300 ms). The circles show the values for the paced rate of 120/min and the triangles for the rate of 150/min. The filled markers and solid lines represent the effects of procainamide, while the open markers and dotted lines represent the effects of N-acetylprocainamide. PA=procainamide; NAPA=N-acetylprocainamide

trical charge was integrated in an on-line system and the neutralizing pulse was automatically terminated when the sum of the charges of stimulating and neutralizing the pulses attained zero. Thus, the high fidelity-evoked endocardial response could be recorded as close as approximately 1 ms post-stimulus. In this study, we examined the utilization of this system to assess the electrophysiologic effects of procainamide (Class Ia antiarrhythmic agent[5]) and N-acetylprocainamide (Class III antiarrhythmic agent[11,12]) on the myocardial depolarization and repolarization in situ.

To study the mechanism of action of the antiarrhythmic drugs, their effect on the action potential of the myocardial cells has to be assessed[5,13]. Most of this information has been obtained by in vitro studies, recording the transmembrane action potential of the heart muscle strips using capillary microelectrodes. Knowledge of the electrophysiological effects on the intact beating heart can be obtained by recording the monophasic action potential using a suction electrode[14,15] or contact

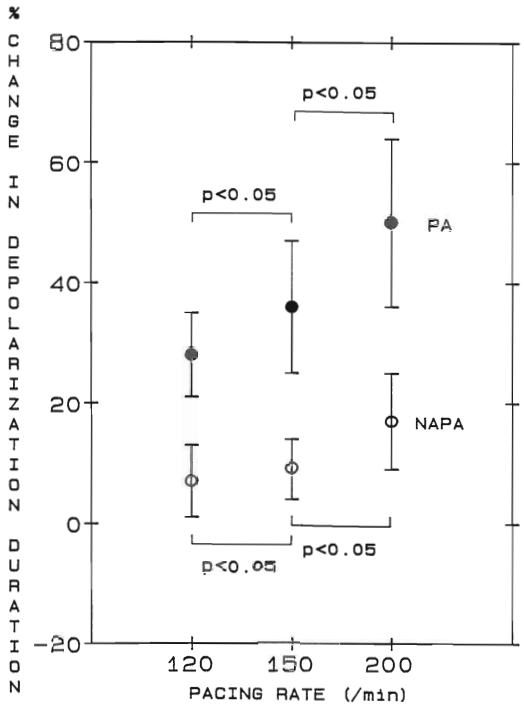

Fig. 8. Rate-dependent Prolongation of Depolarization Duration by Procainamide and N-acetylprocainamide
The percent increase in the depolarization duration at the paced heart rates of 120, 150, and 200/min after the fifth procainamide and N-acetylprocainamide infusion is shown. The filled circles represent the values for procainamide, while the open circles for N-acetylprocainamide. The percent increase in the depolarization durations was significantly greater at the rate of 150/min than at 120/min and at 200/min than at 150/min for both procainamide and N-acetylprocainamide. PA=procainamide; NAPA=N-acetylprocainamide

electrode[16]. However, it is not widely available because it requires a special catheter electrode. Furthermore, although antiarrhythmic drugs show a different magnitude of their effects at different heart rates, the recording of the monophasic action potential cannot correct the rate-induced phenomenon. In contrast, the recording of the stable evoked endocardial response can be readily obtained with a single standard electrode over a long period[17,18] and the drug effects can be compared as matched heart rates before and after the drug administration.

Donaldson *et al.*[2] utilized the repolarization duration of the evoked endocardial response to assess the effect of the Class III antiarrhythmic drugs, amiodarone and bethanidine. These drugs effect primarily the repolarization and have relatively little effect on depolarization. Therefore, for these drugs the repolarization duration alone is a reliable indicator of the drug effect. Class Ia antiarrhythmic drugs, however, have major effects on both the myocardial depolarization and repolarization. Our study revealed that the measurements of the depolarization duration and repolarization duration of the evoked endocardial response could be used to reliably assess the electrophsiologic effects of both the Class Ia antiarrhythmic agent and Class III antiarrhythmic agent. Procainamide (Class Ia antiarrhythmic drug) prolonged both the depolarization duration and repolarization duration from its low plasma concentration. In contrast, N-acetylprocainamide (Class III antiarrhythmic agent) prolonged only the repolarization duration at its low plasma concentration and slightly prolonged depolarization duration only at its very high plasma concentration. Our study also showed that the prolongations in the depolarization duration by procainamide and N-acetylprocainamide were rate-dependent; the faster the rate the greater the prolongation. This finding is consistent with their use-dependent sodium channel-blocking effect established by the recording of the transmembrane action potential of the myocardial cell using the capillary microelectrodes[19,20].

Many investigators have believed that the plasma level of the antiarrhythmic drugs, especially after the intravenous administration of drugs, does not precisely

reflect their myocardial content and electrophysiologic effects[21,22]. Drug-induced changes in the depolarization duration and repolarization duration of the evoked endocardial response may provide a new means of evaluating the antiarrhythmic drug effects on the myocardium. On-line analysis of the hi-fidelity-evoked endocardial response by telemetry transmission or hard wire connection may, in the future, be used to initiate, terminate and modify the pharmacologic antiarrhythmia therapy.

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REFERENCES

1) Donaldson, R.M., and Rickards, A.F.: The ventricular endocardial paced evoked response. PACE, 1983; 6: 253–9.
2) Donaldson, R.M., and Rickards, A.F.: Evaluation of drug-induced changes in myocardial repolarization using the paced evoked response. Br. Heart J., 1982; 48: 381–7.
3) Herscovici, H.: Biphasic cardiac pacer. US patent 4543956, Oct. 1, 1985.
4) Baer, D.T., and Barkus, J.C., Jr.: Procainamide pharmacokinetics in beagles: Urinary pH dependency and comparison with N-acetylprocainamide. Res. Com. Chem. Pathol. Pharmacol., 1977; 17: 333–6.
5) Vaughan Williams, E.M.: Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olsen KH eds. Symposium on cardiac arrhythmias. Södertälje, Sweden: AB Astra, 449–72, 1970.
6) Auerbach, A.A., and Furman, S.: The autodiagnostic pacemaker. PACE, 1979; 2: 58–68.
7) Rickards, A.F., and Norman, J.: Relation between QT interval and heart rate. New design of physiologically adaptive cardiac pacemaker. Br. Heart J., 1981: 45: 56–61.
8) Donaldson, R.M., Fox, K., and Rickards, A.F.: Initial experience with a physiological, rate responsive pacemaker. Clin. Res., 1983; 286: 667–71.
9) Donaldson, R.M., and Rickards, A.F.: Rate responsive pacing using the evoked QT principle. A physiological alternative to atrial synchronous pacemakers. PACE, 1983; 6: 1344–9.
10) Donaldson, R.M., Taggart, P., Swanton, H., Fox, K., and Rickards, A.F.: Intracardiac electrode detection of early ischemia in man. Br. Heart J., 1983; 50: 213–21.
11) Jaillon, P., and Winkle, R.A.: Electrophysiologic comparative study of procainamide and N-acetylprocainamide in anesthetized dogs: concentration-response relationships. Circulation, 1979; 60: 1385–94.
12) Okumura, K., and Waldo, A.L.: Effects of N-acetylprocainamide on experimental atrial flutter and atrial electrophysiologic properties in conscious dogs with sterile pericarditis: comparison with effects of quinidine. J. Am. Coll Cardiol., 1987; 9: 1332–8.
13) Rosen, M.R., and Hoffman, B.F.: Mechanisms of action of antiarrhythmic drugs. Clin. Res., 1973; 32: 1–8.
14) Hoffman, B.F., Cranefield, P.F., Lepeschkin, E., Surawicz, B., and Herrlich, H.C.: Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. Am. J. Physiol., 1959; 196: 1297–301.
15) Olsson, B., Varnauskas, E., Korsgren, M.: Further improved method for measuring monophasic action potentials of the intact human heart. J. Electrocardiol., 1971; 4: 19–23.
16) Franz, M.R.: Long-term recording of monophasic action potentials from human endocardium. Am. J. Cardiol., 1983; 51: 1629–34.
17) Platia, E.V., and Brinker, J.A.: Time course of transvenous pacemaker stimulation impedance, capture threshold, and electrogram amplitude. PACE, 1986; 9: 620–5.
18) Boute, W., Derrien, W.B.Y., and Wittkampf, F.H.M.: Reliability of evoked endocardial T-wave sensing in 1,500 pacemaker patients. PACE, 1986; 9: 948–53.
19) Courtney, K.R.: Interval-dependent effects of small antiarrhythmic drugs on excitability of guinea-pig myocardium. J. Mol. Cell. Cardiol., 1980; 12: 1273–86.
20) Ehring, G.R., and Hondeghem, L.M.: Structural similarities and cardiac electrophysiological differences between lidocaine and procainamide. Proc. West. Pharmacol. Soc., 1980; 23: 163–6.
21) Wellens, H.J.J., Bar F.W.H.M., Lie K.I., Duren, D.R., and Dohmen, H.J.: Effect of procainamide, propranolol and verapamil on mechan-

ism of tachycardia in patients with chronic recurrent ventricular tachycardia. Am. J. Cardiol., 1977; 40: 579–85.
22) Morady, F., Kou, W.H., Schmaltz, S., Annesley, T., Buitleir, M.D., Nelson, S.D., and Kushner, J.A.: Pharmacodynamics of intravenous procainamide as used during acute electrophysiologic testing. Am. J. Cardiol., 1988; 61: 93–8.