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Electrophysiologic Actions of High Plasma Concentrations of Propranolol in Human Subjects

HENRY J. DUFF, MD, DAN M. RODEN, MD, FACC, LEIF BRORSON, MD, ALASTAIR J. J. WOOD, MB, ALBERT K. DAWSON, PhD, R. KIRBY PRIMM, MD, FACC, JOHN A. OATES, MD, RAPHAEL F. SMITH, MD, FACC, RAYMOND L. WOOSLEY, MD, PhD

Nashville, Tennessee

The authors have previously shown that 40% of patients whose ventricular arrhythmias respond to propranolol require plasma concentrations in excess of those producing substantial beta-receptor blockade (> 150 ng/ml). However, the electrophysiologic actions of propranolol have only been examined in human beings after small intravenous doses achieving concentrations of less than 100 ng/ml. In this study, the electrophysiologic effects of a wider concentration range of propranolol was examined in nine patients. Using a series of loading and maintenance infusions, measurements were made at baseline, at low mean plasma propranolol concentrations (104 ± 17 ng/ml) and at high concentrations (472 ± 68 ng/ml). Significant ($p < 0.05$) increases in AH interval and sinus cycle length were seen at low concentrations of propranolol, with no further prolongation at the high concentrations; these effects are typical of those produced by beta-blockade. However, progressive shortening of the endocardial monophasic action potential duration and QTc interval were seen over the entire concentration range tested ($p < 0.05$). At high concentrations, there was significant ($p < 0.05$) further shortening of both the QTc and monophasic action potential duration beyond that seen at low propranolol concentrations, along with a progressive increase in the ratio of the ventricular effective refractory period to monophasic action potential duration. No significant changes were seen in HV interval, QRS duration or ventricular effective refractory period.

In summary, the concentration-response relations for atrioventricular conductivity and sinus node automaticity were flat above concentrations of 150 ng/ml. On the other hand, the durations of the monophasic action potential and the QTc interval shortened at high concentrations. It is concluded that propranolol, in addition to blocking beta-receptors, produces other beta-receptor independent electrophysiologic effects in human beings.

The beta-receptor blocking agent propranolol has long been known to suppress some ventricular arrhythmias (1–3). Recent work in our laboratory (4) showed that more than 70% of unselected patients with chronic ventricular arrhythmias responded to propranolol, but that a very wide plasma concentration range (10 to 1,000 ng/ml) was required to produce this effect. In addition, whereas substantial beta-receptor blockade is evident at plasma concentrations of 25 to 150 ng/ml (5–9), 40% of our patients required concentrations in excess of 150 ng/ml for arrhythmia suppression. We hypothesized that the antiarrhythmic responses seen at high plasma concentrations might be related to electrophysiologic actions other than beta-receptor blockade. However, the electrophysiologic actions of propranolol in human beings have only been examined after relatively small intravenous doses that achieved low plasma propranolol concentrations (5 to 29 ng/ml) (10,11). We now report our evaluation of concentration-response relations for the electrophysiologic actions of propranolol over the wide range of concentrations required for the antiarrhythmic effects in our previous study.

From the Divisions of Clinical Pharmacology and Cardiology, Departments of Pharmacology and Medicine, Vanderbilt School of Medicine, Nashville, Tennessee and the Veterans Administration Medical Center, Nashville, Tennessee. This study was supported by United States Public Health Service Grants 5MO1 RR-95, GM15431 and HL 26782 and by the Canadian Heart Association Ottawa, Canada. Dr. Duff is a scholar of the Alberta Heritage Foundation for Medical Research, Edmonton, Canada. Dr. Roden is a recipient of the Clinical Scientist Award of the American Heart Association, Dallas, Texas. Dr. Wood is a recipient of a Pharmaceutical Manufacturers Association Foundation (New York, New York) Faculty Development Award in Clinical Pharmacology. Dr. Oates is the Joe and Howard Werthan Professor of Investigative Medicine. Manuscript received February 1, 1983; revised manuscript received July 5, 1983, accepted July 8, 1983.

Address for reprints: Raymond L. Woosley, MD, PhD, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232.

Methods

Study patients. Ten patients with stable ventricular arrhythmias (nonsustained ventricular tachycardia in five and

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ventricular couplets in nine) without known reversible cause participated in this study. There were nine men and one woman, aged 30 to 58 years (mean 52). Four had ischemic heart disease, and two each mitral valve prolapse, cardiomyopathy and no structural heart disease. None had unstable angina, chronic obstructive lung disease, congestive heart failure (New York Heart Association [NYHA] functional class III or IV), preexisting abnormalities in conduction or unstable concurrent illness. Patients with very high frequency ventricular arrhythmia were not candidates for study because the presence of numerous ectopic beats could interfere with reliable measurement of the electrophysiologic variables.

The patients were admitted to the Clinical Research Center of Vanderbilt University Hospital, and all medications were withdrawn for a period sufficient to allow their elimination (at least four half-lives). The study was approved by the Committee for the Protection of Human Subjects of Vanderbilt University (initial approval June 9, 1976), and all patients gave informed written consent.

Establishment of propranolol infusion rates. A standard series of loading and maintenance infusions of propranolol was administered (Fig. 1) to achieve the desired pseudo-steady state levels. Before the infusions, each patient was given a test dose of intravenous propranolol, 0.1 mg/min for 10 minutes. Previous experience suggested that this test dose would safely determine if a patient could tolerate high dosages of intravenous propranolol. The infusion rates were an initial loading dose of 1.0 mg/min for 20 minutes, a maintenance infusion of 0.1 mg/min, a second loading dose of 3.0 mg/min for 25 minutes and a second maintenance infusion of 0.6 mg/min. These rates were designed to achieve plasma propranolol concentrations of 100 ng/ml (first maintenance infusion) and then 500 ng/ml (second maintenance infusion). Because of the marked interindividual variability in propranolol pharmacokinetics, this series of infusions was tested in each patient approximately 1 week before the electrophysiologic study and modified if necessary to achieve plasma concentrations in the desired range.

Electrophysiologic studies. No medications were administered for at least 72 hours before the electrophysiologic study. Electrophysiologic measurements were recorded at baseline and 20 minutes after the beginning of each maintenance infusion of propranolol. Plasma propranolol concentrations, serum potassium and lidocaine concentrations (from local anesthesia) were measured before and just after the electrophysiologic recordings.

Using sterile technique, a bipolar ventricular pacing electrode, a tripolar electrode for obtaining a His bundle electrogram and a suction bipolar electrode for recording monophasic action potentials were inserted via through the femoral veins. The ventricular monophasic action potential recordings (12) were made using a bipolar endocardial suction

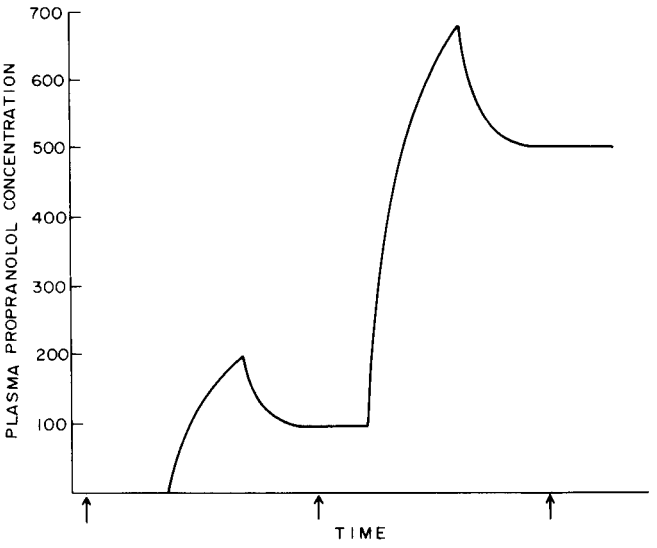

Figure 1. Projected time course of plasma propranolol concentrations as a result of the infusion protocol. The **arrows** designate the times when electrophysiologic measurements were obtained. Plasma propranolol was measured just before and after the recordings of electrophysiologic data.

electrode (ABO trading, Tullv. 1138:S-430 41 Kullavik, Sweden) using techniques developed by Olsson, Brorson and co-workers (13,14). From the right atrium, the catheter was advanced across the tricuspid valve and brought in contact with the endocardium of the right ventricular septum. When a monophasic waveform appeared, suction was applied (-100 mm Hg) for not more than 3 minutes. An intracavitary electrocardiogram was obtained by using an electrode at the tip of the suction catheter and a reference electrode on the right leg. If this signal showed an injury current, simultaneous monophasic action potential signals were not included in the analysis.

Monophasic action potential duration. This interval was determined during ventricular pacing at a constant cycle length of 500 ms. After each recording, the suction electrode catheter was withdrawn slightly and advanced again to contact endocardium when further recordings were required. The monophasic action potential signal and the unipolar electrogram were amplified with a direct current-coupled Electronics for Medicine differential amplifier (model PHD) and recorded using an Electronics for Medicine model DR-8 recorder with frequency response of 0 to 1,000 Hz at 100 mm/s. The duration of at least three monophasic action potentials was measured at 90% repolarization and then averaged. The typical monophasic action potential recording shown in Figure 2 illustrates the method of measuring at 90% repolarization. After the measurements of monophasic action potential duration had become stable, recordings were made after 30 beats paced from the right ventricle. Mea-

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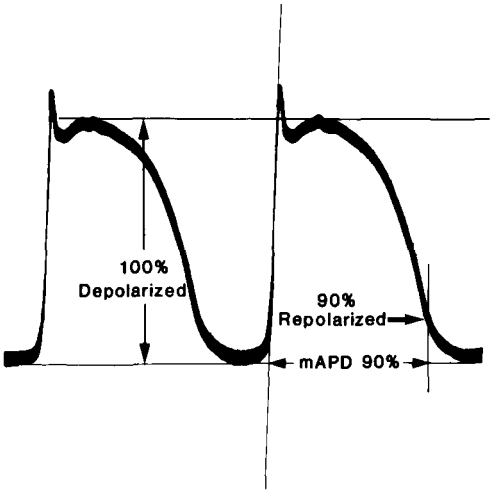


Figure 2. Typical monophasic action potential which illustrates the method used to measure 90% repolarization. mAPD = monophasic action potential duration.

surements were made by two observers and agreed to by consensus.

Right ventricular effective refractory period. This period was measured by the extrastimulus technique with the electrode catheter in constant position at the right ventricular apex. A Medtronic model 5352 programmable stimulator was used to pace the right ventricle at a cycle length (S_1S_1) of 500 ms and introduce a premature extrastimulus (S_2) (all at twice diastolic threshold). The premature stimulus (S_2) was introduced late in diastole and the S_1S_2 interval progressively shortened at 2 ms intervals until ventricular refractoriness was encountered. The premature stimulus was delivered every 20 to 25 paced beats.

Electrocardiographic intervals. Surface electrocardiographic leads II and V_1 and the His bundle electrogram were recorded on the Electronics for Medicine DR-8 recorder. The PR, QRS, QT and RR intervals were measured for each recording; the rate-corrected QT interval (QTc) was calculated from the formula: $QTc = QT/\sqrt{RR}$.

Propranolol assay. Blood samples were drawn into heparinized glass tubes with ground glass stoppers and aliquots of plasma were separated. The plasma was stored at $-15°$ until assayed for propranolol using a high performance liquid chromatographic procedure (16). The extent of protein binding was determined by equilibrium dialysis using ^{3}H-propranolol (16,17).

Statistical analysis. Analysis of variance was used to assess the significance of changes from control observed during the two maintenance propranolol infusions. The Neuman-Keuls test was used to assess the significance of multiple comparisons. A probability (p) less than 0.05 was sufficient to reject the null hypothesis. Data are presented as mean ± standard error.

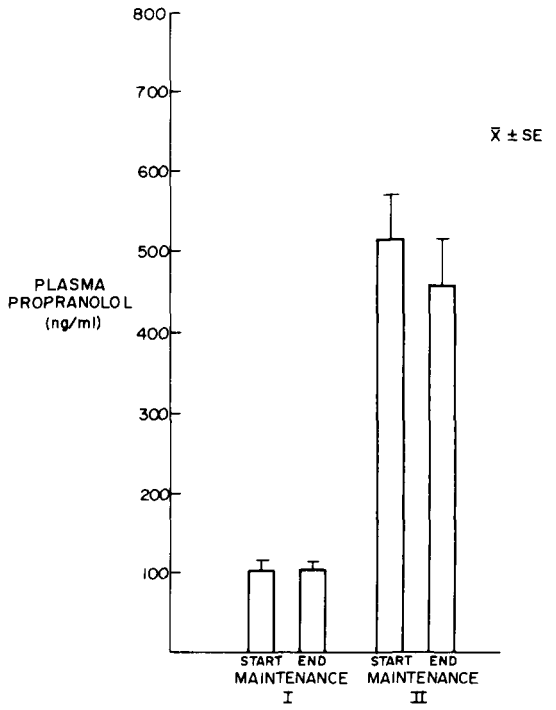
Results

Plasma propranolol concentrations attained during the electrophysiologic studies (Fig. 3). The first maintenance infusions achieved a mean concentration of 104 ± 17 ng/ml before the electrophysiologic measurements and 104 ± 11 ng/ml after these measurements. The second maintenance infusions achieved concentrations of 518 ± 28 ng/ml before and 472 ± 68 ng/ml after the electrophysiologic measurements. A mean total of 116 ± 12 mg of intravenous propranolol was administered without side effects in any of the patients. The rate of the second maintenance infusion was increased to 0.8 mg/min in two patients as a result of the initial propranolol infusion before the study. There was no difference in the extent of propranolol plasma binding at low (15 ± 2.7% unbound) and at high (15.5 ± 3.4% unbound) concentrations. In one patient, a plasma lidocaine level above 1 μg/ml was recorded; this patient's data have been excluded from analysis. There was no significant change in serum potassium concentration during the serial propranolol infusions.

Electrophysiologic actions of propranolol. Significant increases in AH interval and sinus cycle length were seen at the lower concentrations of propranolol (compared with control) (Table 1). No further prolongation in these intervals was observed at the higher concentrations of propranolol.

The QTc interval and the monophasic action potential duration were significantly shortened at low concentrations

Figure 3. Plasma propranolol concentrations achieved by the maintenance infusions.



of propranolol. However, at high concentrations of propranolol there was further small but significant shortening ($p < 0.05$) in both the QTc interval and monophasic action potential duration (Fig. 4). A superimposition of monophasic action potentials of one patient at baseline and at low and high concentrations of propranolol is shown in Figure 5. The ventricular effective refractory period was unchanged at both low and high concentrations of propranolol. There was a significant increase in the ratio of the ventricular effective refractory period to monophasic action potential duration at low concentrations of propranolol and a further increase ($p < 0.05$) in this ratio at high concentrations of propranolol. Figure 6 contrasts the increases in this ratio that occurred over the whole range of propranolol concentrations to the increase in AH interval that occurred at low concentrations. No significant changes from control were observed in the HV interval or QRS duration at either low or high concentrations of propranolol.

Because these patients had a low frequency of ventricular arrhythmias while ambulatory and the infusions were performed for relatively short durations (less than 4 hours) under conditions of supine bed rest, assessment of the antiarrhythmic efficacy of intravenous propranolol was not attempted.

Discussion

Plasma propranolol concentrations of 40 to 150 ng/ml in human beings are sufficient to produce substantial beta-receptor blockade (5–9), whose major electrophysiologic action is prolongation of the AH interval and sinus slowing (10,11,18). Our data show that at high plasma concentrations of propranolol, electrophysiologic effects apart from those associated with beta-receptor blockade can be detected. These additional effects, a decrease in monophasic action potential duration and QTc interval and an increase in the ratio of ventricular effective refractory period to monophasic action potential duration, occurred over the range of concentrations required by some patients for suppression of ventricular arrhythmias (4).

Table 1. Electrophysiologic Actions of Low and High Concentrations of Propranolol in Nine Patients

	Baseline	Maintenance I	Maintenance II
Plasma propranolol (ng/ml)	0	104 ± 17	472 ± 68
Sinus RR interval§	826 ± 19	947 ± 31*	991 ± 29
AH interval§	109 ± 18	125 ± 20†	124 ± 20
HV interval§	47 ± 13	48 ± 14	49 ± 15
VERP§	222 ± 17	229 ± 13	228 ± 15
mAPD§	272 ± 31	267 ± 33*	225 ± 22‡
QTc interval§	418 ± 31	390 ± 44*	380 ± 45‡
VERP/mAPD ratio	0.80 ± 0.07	0.86 ± 0.07*	0.90 ± 0.06‡

*$p < 0.05$, † $p < 0.01$ = maintenance I compared with baseline ‡$p < 0.05$ = maintenance II compared with maintenance I.

§Electrophysiologic data in milliseconds.

mAPD = monophasic action potential duration; VERP = ventricular effective refractory period.

Previous studies on electrophysiologic properties of propranolol. Few studies systematically examined the effects of propranolol on repolarization (QTc and monophasic action potential recordings). In agreement with our results, Seides et al. (11) and Stern and Eisenberg (19) found significant QTc shortening with propranolol. However, Echt et al. (20) showed only nonsignificant shortening of QT and monophasic action potential duration with intravenous propranolol. The explanation for this discrepancy may relate to the manner in which propranolol was administered in their study. In that study, propranolol was infused over 15 minutes and electrophysiologic recordings were started only after discontinuing the infusion. Therefore, these measurements were taken at a time when plasma concentrations would be falling rapidly (distribution phase), a factor that may explain the lack of significant changes. Furthermore, Pruett et al. (21) showed that high concentrations (500 ng/ml) of d,l-propranolol in vitro also produced action potential duration shortening. They also found this effect with d-propranolol, a much weaker beta-receptor blocking agent than the levo isomer (22). Similarly, Harrison et al. (23) reported that 6-hydroxydopamine pretreatment did not alter propranolol-induced shortening of action potential duration, again suggesting this to be a nonbeta-mediated effect. Although local anesthetic properties have been ascribed to propranolol in vitro, these require much higher concentrations than those achieved clinically (24,25). Furthermore, when propranolol shortened action potential duration in vitro (21), it had no effect on phase O upstroke, suggesting that action potential duration shortening was not a reflection of this local anesthetic property. The mechanism of the action potential duration shortening produced by propranolol therefore remains uncertain.

Data from animal studies also suggest that high concentrations of propranolol may alter the electrophysiologic properties of ventricular tissue. Jaillon et al. (26) reported no change in ventricular refractoriness after intravenous propranolol (1.2 mg/kg). However, Brorson et al. (27) and Dawson et al. (28) reported that propranolol (500 to 1,000 ng/ml) prolonged refractoriness, action potential duration and AH interval in anesthetized dogs. The latter two changes were reversible by isoproterenol although the alteration in refractoriness was not, again raising the possibility that high concentrations of propranolol exerted nonbeta-mediated effects. These results are at variance with those we found in patients; the explanation probably lies in the use of general anesthesia in the dog studies. General anesthesia can substantially increase ventricular refractoriness (29,30) and al-

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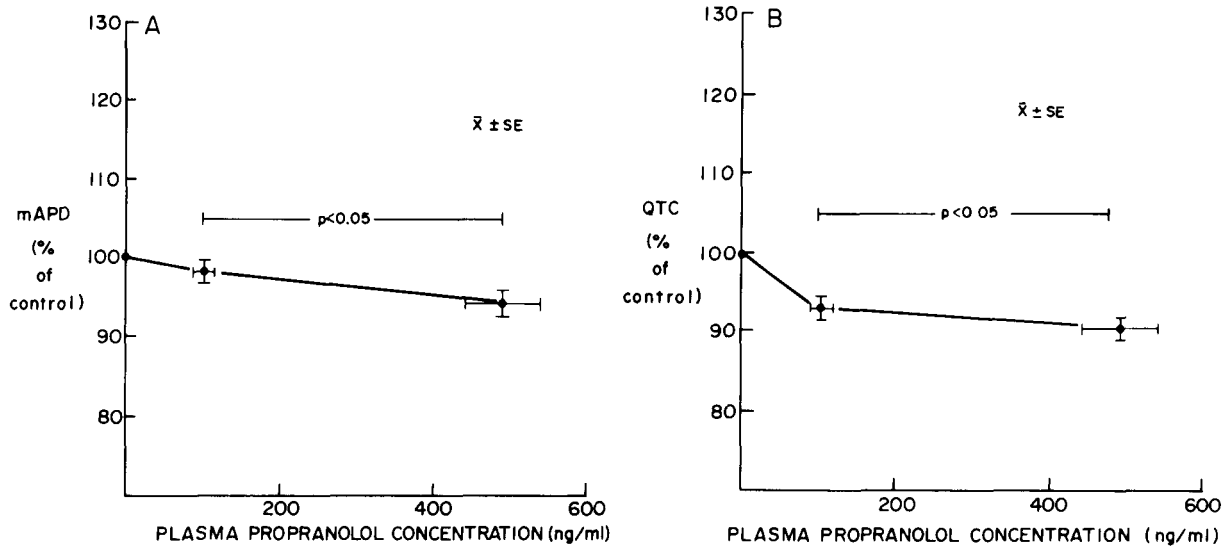
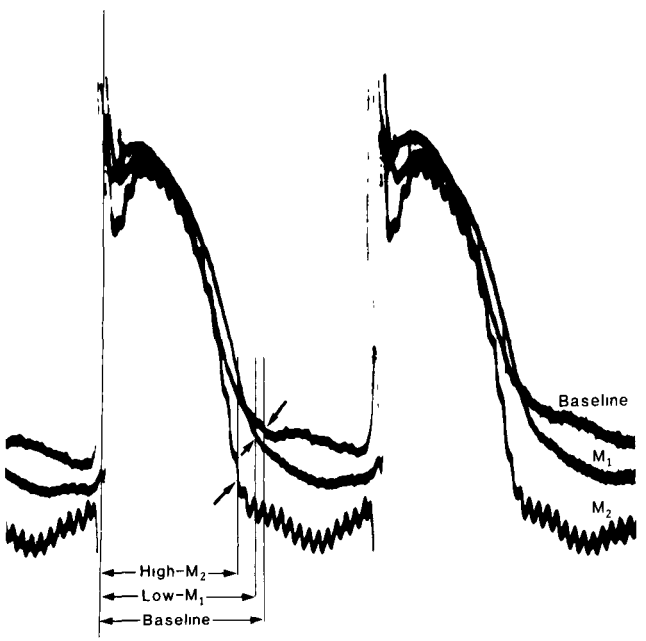


Figure 4. The relation between plasma propranolol and durations of monophasic action potential (mAPD) (**A**) and QTc interval (**B**).

ter action potential duration by changing sympathetic tone (31,32). In vitro work suggests that the dependence of the action potential duration on catecholamines may be a result of the interplay between alpha- and beta-receptor effects: propranolol usually shortens action potential duration but in the presence of excess catecholamines propranolol is reported to prolong action potential duration (33).

Figure 5. Superimposition of monophasic action potentials of one patient at baseline, low and high concentrations of propranolol. M_1 and M_2 = maintenance infusions I and II, respectively.



Relation to antiarrhythmic efficacy of propranolol. This study was not designed to assess whether the progressive shortening of action potential duration is responsible for the antiarrhythmic efficacy seen in some patients at these high concentrations. Theoretically, shortening of action potential duration in the absence of a change in ventricular refractoriness could have antiarrhythmic effects, because the conduction velocity of a premature beat may be influenced by the degree to which surrounding tissue has repolarized (34,35). Acceleration of repolarization by propranolol may minimize the decremental conduction of a premature ventricular beat and so alter the conditions predisposing to reentry. The phenomenon of preventing local and graded responses by propranolol has already been demonstrated in Purkinje fibers by David and Tempte (25).

Another theoretical mechanism for antiarrhythmic efficacy at high concentrations in some patients may relate to the progressive increase in the ventricular effective refractory period/monophasic action potential duration (ERP/mAPD) ratio seen at these concentrations. A change in the ERP/mAPD ratio generally reflects a change in membrane responsiveness and raises the possibility of a sodium channel effect. Although it is plausible that these electropharmacologic changes may be responsible for antiarrhythmic efficacy, we have no direct data to support a cause-effect relation.

In this study, the pharmacologic actions of propranolol were assessed after its short-term administration; these actions may not be identical to those seen during prolonged oral therapy with propranolol. Raine and Vaughan Williams (36) showed that during long-term treatment of rabbits with propranolol, alterations in sympathetic nervous system tone may occur and so alter the effect of propranolol on repolarization. In keeping with these data, Edvardsson and Olsson (37) reported that although acute metroprolol treatment

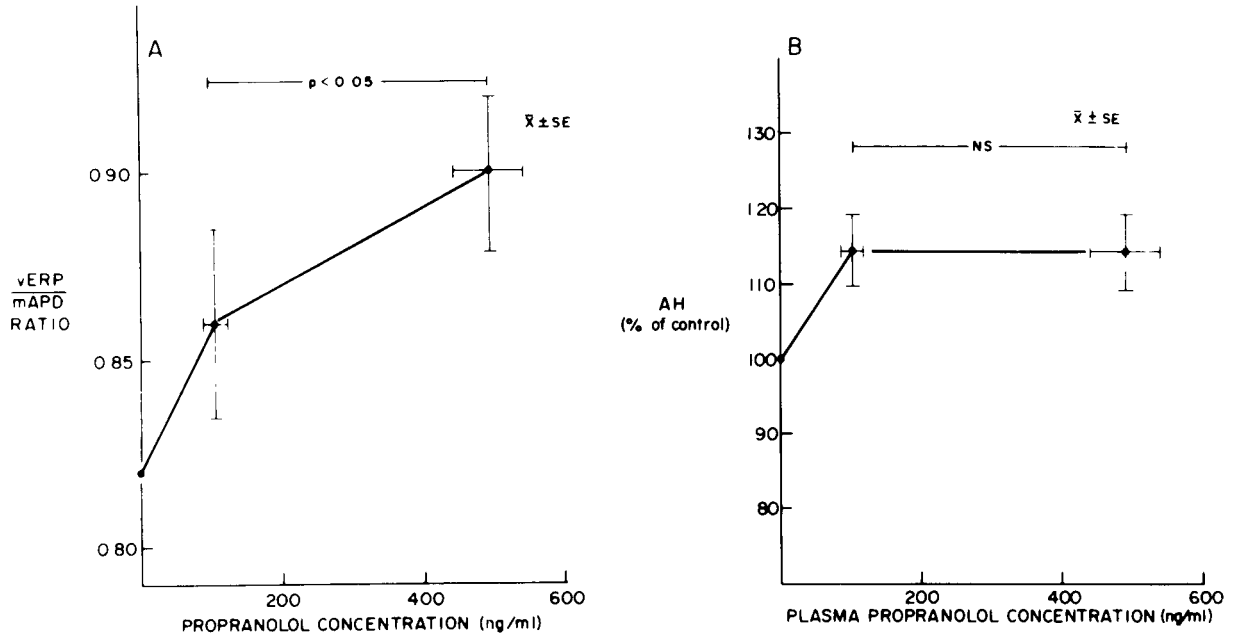


Figure 6. Relation between plasma propranolol concentration and changes in ratio of ventricular effective refractory period to monophasic action potential duration (vERP/mAPD) (**left panel**) and changes in AH interval (**right panel**).

did not affect repolarization, chronic treatment was associated with prolongation of monophasic action potential duration and ventricular refractoriness.

In summary, in our study, propranolol exerted two types of effect. The first, seen at low concentrations, was typical of beta-blockade (AH prolongation and sinus slowing). However, at higher concentrations, action potential duration shortening became evident, while no increment in beta-blocking action was noted. Propranolol, therefore, exerts electrophysiologic effects in human beings by two mechanisms, one related to beta-blockade and the other independent of beta-blockade.

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