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Effects of Procainamide and *N*-Acetylprocainamide on Myocardial Contractility in Ischemic Isolated Rabbit Hearts (41285)

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Abstract. While many antiarrhythmic drugs depress myocardial function, *N*-acetylprocainamide, the major metabolite of procainamide, appears to improve myocardial performance *in vivo*. The present study compared the effect of procainamide with *N*-acetylprocainamide on the isolated, perfused, globally ischemic rabbit heart. Procainamide depressed *dP/dt* at infusion rates of 2 mg/min or greater. *N*-Acetylprocainamide depressed *dP/dt* at infusion rates of 40 mg/min or greater and may have increased *dP/dt* at low rates of around 1 mg/min. Pretreatment of the rabbits with reserpine abolished any increase in *dP/dt* produced by *N*-acetylprocainamide. We conclude that *N*-acetylprocainamide does not have intrinsic direct positive inotropic activity in this model.

Recent studies have shown the association of complex ventricular arrhythmias and left ventricular dysfunction in patients recovering from myocardial infarcts who die suddenly (1, 2). Many antiarrhythmic agents currently available to treat these patients are associated with significant myocardial depression and may precipitate and/or exacerbate congestive heart failure (3, 4). *N*-Acetylprocainamide, (NAPA), the major metabolite of procainamide, is currently undergoing clinical trials as an antiarrhythmic agent (5, 6). Several reports have suggested that NAPA improves cardiac performance in man, as judged by systolic time interval measurements from carotid pulse tracings (5, 6). Studies in healthy dogs have also shown an increase in contractile force in response to NAPA administration, in contrast to the depressant effect seen following administration of procainamide (7). Since patients requiring antiarrhythmic therapy often have concomitant left ventricular dysfunction, this study was undertaken to assess the direct effects of procainamide and NAPA on myocardial contractility in a hemodynamically depressed isolated heart model.

Materials and Methods. The apparatus used was a modification of the standard Landendorf retrograde perfusion system described by Kligfield *et al.* (8). Coronary arterial perfusate entered the cannulated aortic root either at a fixed hydrostatic pressure from a reservoir set at a fixed height above the cannula, or at a fixed flow rate through a Holter variable extracorporeal pump.

Male, New Zealand White rabbits, weighing 1.5 to 2.0 kg, were anticoagulated intravenously with 500 U of sodium heparin, fastened to a dissection board, and sacrificed by a blow to the head. Hearts were then rapidly removed and arrested in ice-cold, modified Krebs–Ringer bicarbonate solution (KRB) with the following composition: 120 m*M* NaCl, 4.75 m*M* KCl, 2.01 m*M* $CaCl_2$, 1.10 m*M* KH_2PO_4, 1.19 m*M* $MgSO_4$, 25.0 $NaHCO_3$, and 5.5 m*M* dextrose. Beating was reinitiated by securing the aorta to a stainless-steel perfusion cannula and perfusing the heart, at a constant pressure of 100 cm of water, with KRB maintained at 27° and bubbled continuously with 95% O_2, 5% CO_2 gas mixture to provide a partial pressure of oxygen of 550–600 mm Hg and a pH of 7.3–7.4. The interval between cardiectomy and perfusion was never more than 3 min.

After a 5-min period of perfusion, the left atrium was opened and a latex balloon, made from a mold of the left ventricle (LV) and tied around a catheter-tip transducer with sampling lumen, was inserted through

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the mitral valve into the LV to allow measurement of isovolumic pressure development. The balloon was filled with saline until an end-diastolic pressure (EDP) between 0 and 4 mm Hg was obtained. A pressure–volume curve was determined for the balloon prior to insertion to insure that its final volume would be on the flat part of the curve and no pressure artifact was introduced. The first derivative of the LV pressure curve, *dP/dt*, was obtained directly from a calibrated derivative computer.

Following establishment of a steady LVEDP, hearts were perfused for a 15-min *control period*. At the end of this time, control values for heart rate (HR), peak systolic pressure (PSP), and peak systolic *dP/dt* were determined by averaging data from five successive beats. Control, autoregulated coronary flow rates were determined by collecting total venous effluent over 15-sec intervals. Following these measurements, coronary flow was globally reduced until a 50% reduction in *dP/dt* was achieved. This flow rate was then measured and maintained for the duration of a subsequent *ischemic flow period*. Heart rates were maintained at the control period rate, during ischemic perfusion, by right ventricular pacing. After 10 min of ischemic perfusion hemodynamic parameters were again recorded and groups of six hearts were then infused with four successive doses in the low range or five successive doses in the high range of procainamide or NAPA. A fifth group of six control hearts were perfused with KRB alone as placebo.

The low-dose procainamide group (LP) received successive doses of 0.02, 0.05, 0.1, and 0.2 mg/min. This dose range was calculated, on the basis of ischemic coronary flow rates, to cover the 1.6 to 16.4 μg/ml concentration range encountered clinically. The high-dose procainamide group (HP) received doses of 1, 2, 4, 8, and 16 mg/min, resulting in perfusate drug concentrations approximately 50 to 80 times that occurring in patient plasma.

The low-dose NAPA group (LN) received successive infusions of 0.1, 0.25, 0.5, and 1/0 mg/min, calculated to achieve 7.6 to 77 μg/ml, exceeding the range of NAPA plasma concentrations observed in patients receiving NAPA or some patients with renal failure receiving procainamide. The high-dose (HN) group received 50 to 80 times this amount of drug during infusions of 5.0, 10.0, 20.0, 40.0, and 80.0 mg/min.

The protocol for drug or placebo administration was identical for all five of the groups above. Each dose indicated was infused in a constant volume of 1 ml/min for a period of 3 min during which steady state was reached with a 2-min washout period (no drug) between dose levels. Control group hearts were infused with 1.0 ml/min of the KRB vehicle during each "drug" period with a 2-min washout period in between.

The responses of *dP/dt* to the doses of procainamide and NAPA tested were assessed by comparing the data recorded at the end of each drug period, when the hemodynamic responses to drug or vehicle infusion had stabilized, to data obtained during stable function at the end of the previous washout period. Differences in performance during drug infusion were then expressed as percentage change from the previous washout period compared to the changes observed in hearts infused with vehicle only. Statistical comparisons were done using the unpaired Student *t* test.

The influence of endogenous catechols on NAPA-induced changes was studied in two additional experimental groups of six hearts each. Animals in both of these groups were injected with reserpine (1 mg/kg) ip 24 hr prior to sacrifice and perfusion, as described above. Following the 15-min control and 10-min ischemic perfusion periods one group received successive doses of 0.1, 0.25, 0.5, 1.0, and 5.0 mg/min of NAPA in a volume of 1 ml/min. The second group received 1 ml/min of the KRB vehicle as control. The effectiveness of reserpinization was tested by infusion of tyramine just prior to the ischemic perfusion period (3 μg/min) and after the final washout period (10 μg/min) in the manner as the procainamide was infused. The responsiveness of these preparations to exogenous catechols was documented by infu-

sion of epinephrine (1 μg/ml) at the termination of each experiment. Hemodynamic data from these hearts was expressed and compared.

Results. *Predrug "ischemic baseline."* Prior to ischemia, the left ventricular pressure values (mean ± SE) were 90 ± 7, 99 ± 7, 97 ± 10, 98 ± 4, and 114 ± 7 mm Hg and the *dP/dt* were 1030 ± 100, 1379 ± 181, 1233 ± 162, 1289 ± 57, and 1425 ± 109 for the control, low-dose NAPA, high-dose NAPA, low-dose procainamide, and high-dose procainamide groups, respectively.

Parameters of percentage reduction of left ventricular systolic pressure, *dP/dt*, and the absolute values of coronary flow rates and left ventricular end-diastolic pressure were not significantly different among the study groups during the baseline ischemic period (Fig. 1).

Effect on dP/dt: NAPA vs Control. At low doses of NAPA (0.1 to 1 mg/min) there was a small, but persistent, difference in *dP/dt* between the NAPA group and the controls. The NAPA group had slightly higher values that achieved statistical significance when the entire sets of measurements were compared using a group comparison *t* test (NAPA 3.62 ± 4.75% vs Control 0.44 ± 7.1, $P < 0.02$). High-dose NAPA infusion (5–80 mg/min) did not have a significant effect on *dP/dt* below a dose of 40 mg/min. At 40 mg/min, *dP/dt* was decreased by 14.6 ± 4.5% ($P < 0.02$, NAPA vs Control). At the maximum dose of 80 mg/min, NAPA depressed *dP/dt* by 40.4 ± 3.1% ($P < 0.001$, NAPA vs Control) (Fig. 2).

Procainamide vs Control. Procainamide had no significant effect on *dP/dt* at low doses (0.02 to 0.2 mg/min). However, high doses (1–16 mg/min) of procainamide caused a dose-related depression of *dP/dt* from −8.9 ± 6.1% at 1 mg/min to −79 ± 32.7% at 16 mg/min with four of the six hearts exhibiting complete depression of

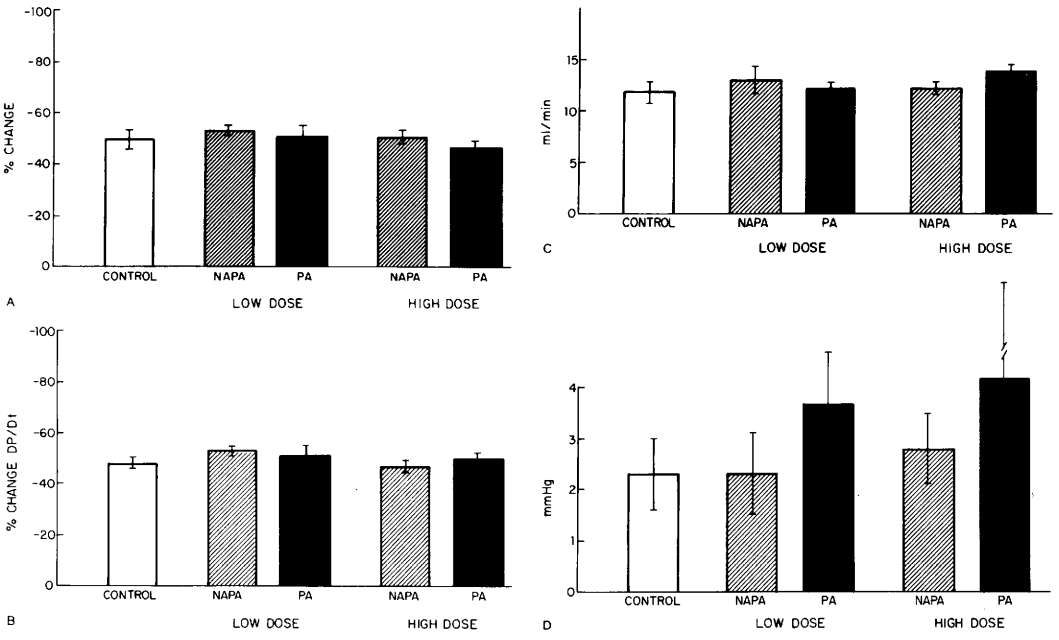

FIG. 1. The ischemic predrug period (baseline). Left ventricular pressure and *dP/dt* are compared to preischemic control periods (A, B). Coronary perfusion rate and LVEDP are given as absolute values during ischemic perfusion (C, D). (A) Percentage decrease in LVP in ischemic predrug period at 10 min (mean ± SE). (B) Percentage decrease in *dP/dt* in ischemic predrug period at 10 min (mean ± SE). (C) LVEDP in ischemic predrug period at 10 min (mean ± SE). (D) Coronary perfusion rates, ml/min (mean ± SE).

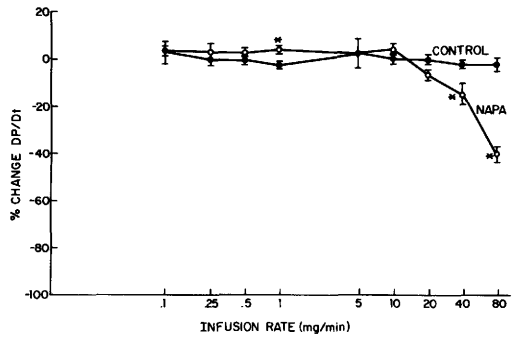

FIG. 2. Effect of NAPA on *dP/dt* in the isolated ischemic rabbit heart. Asterisks indicate statistically significant differences between groups. The *P* value for 40 mg/min is <0.02 and for 80 mg/min, it is <0.001.

dP/dt at the maximum dose (Fig. 3). The differences between Control and procainamide groups was statistically significant ($P < 0.05$) at 2 mg/min or greater infusion rates.

NAPA vs procainamide. At low antiarrhythmic doses, NAPA had a small positive effect on mean hemodynamic responses compared to low-dose procainamide (3.6 ± 4.8% vs −1.7 ± 5.9%, $P < 0.002$) using a group comparison of all doses in the lower dose range. At high doses procainamide was consistently more depressant of the contractility when compared to NAPA, despite a fivefold higher dose of the latter.

Reserpinized hearts. An infusion of tyramine (3 μg/min) prior to the ischemic control period caused little or no change in ventricular function. Five of the twelve reserpinized animals showed a small transient increase in peak *dP/dt* following a tyramine infusion, however, a similar change was evoked by an infusion of the KRB vehicle. The lack of response to high-dose tyramine infusion (10 μg/min) at the end of the final washout period, is shown in Fig. 4A. In contrast to this is the dramatic response to epinephrine infusion (1 μg/min) 5 min later in the same heart (Fig. 4B).

NAPA had no significant effect in reserpinized hearts, at doses of 0.1 to 5 mg/min when compared to reserpinized hearts treated with KRB alone (Control, Fig. 5).

Discussion. Several recent reports have suggested that NAPA has a positive inotropic effect. In two separate clinical trials of NAPA, Atkinson *et al.* (5) and Kluger *et al.* (6) have reported significant increases in preejection period index (PEPI) and decreases in preejection period/left ventricular ejection time ratios using carotid pulse tracings. These changes are consistent with improved contractility, however, systolic time intervals are also influenced by peripheral resistance and positive changes do not necessarily reflect direct inotropic effects (10). That NAPA has an indirect effect on myocardial contractility has been proposed by Lertora *et al.* (14) to explain their observations of a failure of NAPA to improve normal systolic time intervals. Lertora and colleagues compared the effects of NAPA and procainamide on myocardial contractile force in dogs using the Walton–Brodie arch strain gauge, which controls for the influences of preload and peripheral resistance (7). They reported that NAPA (at doses of 10 to 40 mg/kg) improved contractile force by 5–22%, compared to a decrease of 14–17% with equal doses of procainamide. Despite the de-

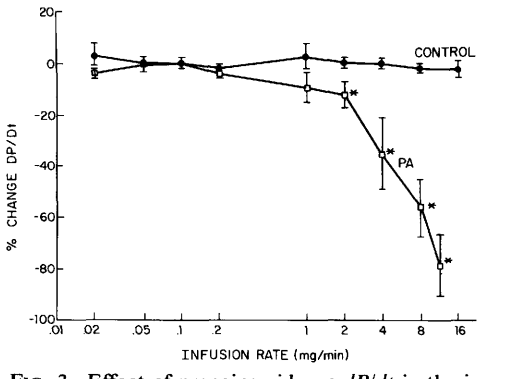

FIG. 3. Effect of procainamide on *dP/dt* in the isolated ischemic rabbit heart. Asterisks indicate statistically significant differences between groups. The P value is <0.05 for 2 mg/min and <0.01 or smaller for all others.

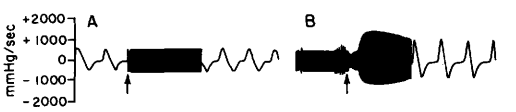

FIG. 4. Effect of infusion of tyramine (A) and epinephrine (B) on ventricular function of a representative heart from a reserpinized animal.

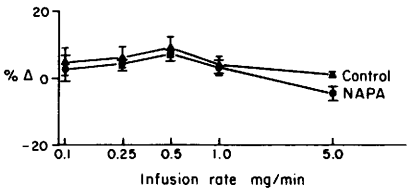

FIG. 5. Effect of NAPA on *dP/dt* in reserpinized isolated ischemic rabbit hearts.

creased influence of preload and peripheral vascular effects on measurement of contractile force in this model, there still remains the confounding extracardiac effects of autonomic function and catecholamine release. Ellis and colleagues have also shown improvement in contractility, as measured by *dP/dt* at a common developed pressure using an acutely infarcted dog model. They found that at the end of a 2-hr infusion of NAPA, at a rate of 2–10 mg/min, there was an increase in *dP-dt* over a 2-hr observation period compared to a decrease in saline-infused controls (11). Again, this model is not free from extracardiac influences. Refsum has reported increased rate and contractile force with NAPA infusions in isolated rat atria. These findings may reflect catecholamine release from intracardiac adrenergic nerve terminals since no reserpinized controls were studied (12) nor was the influence of heart rate controlled.

Our study used a model of controlled global ischemia which resulted in hemodynamic depression as often occurs in the clinical situation in which antiarrhythmic therapy is frequently administered. This model permitted study of changes in LV contractility under conditions of fixed preload and peripheral resistance as well as fixed heart rates. It also permitted elimination of systemic neural and hormonal influences. In these ways, our study differed from the studies of these drugs in intact dogs.

Low dose NAPA apparently caused a small increase in *dP/dt* that was far less in this model than that reported *in vivo* (7, 11). Furthermore, this small effect was eliminated when endogenous myocardial catecholamines were depleted by prior reserpinization. This finding suggests that NAPA's small positive effect on contracility in this model is secondary to its ability to release catecholamines from intracardiac sources. The increased contractility seen *in vivo*, in response to NAPA administration, may be due to this effect as well as other extracardiac neural, hormonal, and vascular effects.

At doses of 0.1 to 20 mg/min NAPA demonstrated no significant depressant effect on the myocardium. It was only at calculated perfusate levels 80–200 times those measured in patients that NAPA became significantly depressant. Blocking endogenous catecholamine release with reserpine did not unmask a depressant effect of NAPA in the 0.1 to 5 mg/min dose range.

In contrast, procainamide had no significant depressant effect at low doses but was significantly depressant at doses of 2–16 mg/min. Although the exact antiarrhythmic ratio of procainamide to NAPA is not agreed upon (5, 6, 13), procainamide was consistently depressant compared to NAPA at one-fifth the dose level.

In summary, NAPA had no intrinsic positive inotropic effect in this model, nor was it significantly depressant below doses that were 80–200 times that necessary for antiarrhythmic activity in man. This property may make it safe to use in patients with arrhythmias and left ventricular dysfunction.

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