Effect of Procainamide on Myocardial Contractile Function and Digoxin Inotropy

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The effect of procainamide and digoxin, singly and together, on peak active force and rate of force development of isolated right ventricular papillary muscles from adult cats was examined. Procainamide (1.5 x 10^{-5}M) increased force and rate of force development in each muscle with further increments in performance up to 2.4 x 10^{-4}M in most muscles. The maximal increases in force (± SEM) averaged 75 ± 13% above control values. Essentially no response to procainamide was observed when basal levels of contractile state were increased by increasing stimulus frequency or calcium concentrations of the bathing solution. Propranolol (10^{-6}M) markedly reduced and verapamil (10^{-7}M) abolished the inotropic effect of procainamide. Exposing muscles to procainamide (1.5 or 3 x 10^{-5}M) before or after the administration of digoxin (2 or 4 x 10^{-7}M) did not alter the inotropic action of either drug.

Thus, procainamide in concentrations that are in the therapeutic range in human patients has potent positive inotropic effects that may be masked at high levels of contractile state. This action of procainamide appears to be due to an effect on calcium channels, which in part may be due to beta-adrenergic receptor stimulation. These concentrations of procainamide do not alter the inotropic response to digoxin.

Methods

Preparation of papillary muscles. Right ventricular papillary muscles were removed from anesthetized adult cats and placed immediately in a muscle bath containing a solution of the following concentration (mM): sodium 143, potassium 4.5, magnesium 0.5, calcium 1.25, chloride 124, H_2PO_4^- 1.2, HCO_3^- 24 and glucose 5.6. The solution was bubbled vigorously with 95% oxygen and 5% carbon dioxide, which produced a (P O_2) partial pressure of oxygen greater than 500 mm Hg and a pH of 7.4. Temperature was maintained at 30°C and the muscle was stimulated at a frequency of 12/min using field electrodes parallel to the long axis of the muscle. Stimulus voltage was maintained at 10% above threshold values and was checked frequently during each experiment. The nontendinous end of the muscle was held by a clip that was secured to the bottom of the bath. The tendinous end was attached by a short silk suture to a force transducer. The transducer was fixed to a micrometer that permitted muscle length to be altered by known amounts while the muscle contracted isometrically.

The muscle was stretched to 0.5 g of resting tension and allowed to contract isometrically for 45 to 60 minutes, at which time contractile force was stable. The muscle was then stretched slowly until peak active force was obtained. Muscle length was fixed at this point and peak active force...
and the maximal rate of force development (dF/dt) were recorded, the latter determined electronically.

**Studies with procainamide and digoxin.** Muscles from nine cats were exposed to increasing concentrations of procainamide ranging from $1.5 \times 10^{-5}$ to $2.4 \times 10^{-4} M$. After each increment in concentration, adequate time was allowed for contractile force to become stable before the concentration was increased further. Seven additional muscles were exposed to $1.5 \times 10^{-5} M$ and another seven muscles were exposed to $3 \times 10^{-5} M$ procainamide, after which each group was exposed to $2 \times 10^{-5} M$ digoxin. After these observations were made, the concentration of digoxin was increased to $4 \times 10^{-7} M$ in those muscles exposed initially to $3 \times 10^{-5} M$ procainamide.

Thirteen muscles were exposed to digoxin alone initially at a concentration of $2 \times 10^{-7} M$, which subsequently was increased to $4 \times 10^{-7} M$. Five additional muscles were exposed initially to $4 \times 10^{-7} M$ digoxin, followed by increasing concentrations of procainamide. We selected these digoxin concentrations on the basis of our earlier observation that $2 \times 10^{-3} M$ digoxin produced approximately half the maximal inotropic effect obtainable with the glycoside, whereas $4 \times 10^{-7} M$ digoxin produced a near maximal effect.

**Procainamide studies after propranolol or verapamil.** After our observations on the effect of procainamide alone, we exposed six muscles to $10^{-6} M$ propranolol and then to increasing concentrations of procainamide. We also exposed nine muscles to $10^{-7} M$ verapamil, followed by increasing concentrations of procainamide.

**Procainamide studies at higher stimulus frequency and calcium concentration.** In five other muscles, the frequency of stimulation was increased from 12 to 30/min, after which the muscles were exposed to increasing concentrations of procainamide. In seven muscles, the calcium concentration of the bathing solution was increased to 2.5 mM, and the studies with procainamide alone were repeated.

Procainamide was dissolved in distilled water. The muscle bath contained 30 ml of modified Krebs solutions, and the largest volume of procainamide-containing solution added during any experiment was 1.28 ml.

**Developed force and dF/dt were normalized for differences in muscle size by expressing these variables in units per cross-sectional area. Cross-sectional area of the muscle was determined from its weight wet and length at peak active force development as measured with a calibrated reticle.**

**Statistical calculations.** Statistical analyses were performed using Student’s paired and unpaired t test when comparing respective values in individual animals or between groups, respectively. Analysis of variance was used when comparing values among groups (10).

## Results

Cross-sectional area of the muscles (mean ± standard error of the mean) in the various groups averaged $1.2 ± 0.1 \text{ mm}^2$ (range 0.94 to 1.3). Differences among groups were not statistically significant.

In all studies, changes in rate of force development were quantitatively similar to the changes in developed force. Therefore, we elected to present only the developed force data.

**Procainamide effect.** The effect of increasing concentrations of procainamide on contractile force is given in Table 1. An increase in force occurred in each muscle exposed to the lowest concentration of procainamide (p < 0.01). In two muscles, force increased to a maximal value at a procainamide concentration of $6 \times 10^{-5} M$, with no further change up to a concentration of $2.4 \times 10^{-4} M$. In five muscles, maximal values occurred at a concentration

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### Table 1. Developed Force with Various Interventions

<table>
<thead>
<tr>
<th>Developed Force</th>
<th>Procaainamide</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Group A (n = 9)</td>
<td>g/mm²</td>
</tr>
<tr>
<td></td>
<td>% control</td>
</tr>
<tr>
<td>Group B (n = 5)</td>
<td>g/mm²</td>
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<tr>
<td></td>
<td>% control</td>
</tr>
<tr>
<td>Group C (n = 7)</td>
<td>g/mm²</td>
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<tr>
<td></td>
<td>% control</td>
</tr>
<tr>
<td>Group D (n = 5)</td>
<td>g/mm²</td>
</tr>
<tr>
<td></td>
<td>% control</td>
</tr>
</tbody>
</table>

*Values significantly different from control (p < 0.05). Data are reported as mean values ± standard error of the mean. Group A = procainamide at a stimulus frequency of 12/min; Group B = procainamide at a stimulus frequency of 30/min; Group C = procainamide with a calcium concentration of 2.5 mM; Group D = procainamide after $4 \times 10^{-7} M$ digoxin.
of $1.2 \times 10^{-4}M$, with no further change at the highest concentration. In the remaining two muscles, maximal values occurred at a procainamide concentration of $1.2 \times 10^{-4}M$, with a decrease in function at $2.4 \times 10^{-4}M$. The maximal increase in force averaged $75 \pm 13\%$ above control values. Resting tension did not change at any concentration of procainamide.

**Procainamide effect with increased calcium concentration.** Doubling the concentration of calcium in the bathing solution to $2.5 \text{ mM}$ before the addition of procainamide resulted in a marked increase in active force development (Table 1). Under these conditions, addition of procainamide resulted in no significant increment in mechanical performance.

**Procainamide effect at higher stimulus frequency.** Increasing stimulus frequency from 12 to 30/min increased developed force by an average of $57 \pm 13\%$. Procainamide then produced no increase in force (Table 1).

**Procainamide effect after propranolol or verapamil.** The positive inotropic effect of each concentration of procainamide was significantly less after pretreatment with $10^{-6}M$ propranolol and was abolished by pretreatment with $10^{-7}M$ verapamil (Fig. 1).

**Procainamide-digoxin interaction.** The effect of $2 \times 10^{-7}$ and $4 \times 10^{-7}M$ digoxin alone and after $1.5 \times 10^{-5}$ and $3 \times 10^{-5}M$ procainamide on active force development is illustrated in Figure 2. Increments in force development with digoxin after exposure to both concentrations of procainamide were not significantly different statistically from that produced with digoxin alone. Pretreatment with $4 \times 10^{-7}M$ digoxin also did not alter the positive inotropic response to procainamide (Table 1).

**Discussion**

**Comparison with previous studies.** Our observation that procainamide exerted a positive inotropic effect over a wide range of concentrations is at variance with other studies that have reported that procainamide has a negative (2,7) or no (3,9) effect on myocardial mechanical performance. However, others (6,8) reached conclusions similar to ours.

A number of factors, such as the use of atrial versus ventricular myocardium, intact anesthetized versus unanesthetized animals and human subjects, in vivo versus in vitro studies as well as species differences may contribute to these disparate results. Clearly, the use of different concentrations of procainamide is an important variable and high concentrations of the drug do produce negative inotropic effects as we observed in several muscles exposed to $2.4 \times 10^{-4}M$ procainamide.

**Effect of basal contractile state on procainamide inotropic.** An additional factor that we believe contributes to the variable response to procainamide is the level of mechanical performance before drug exposure. When we doubled the calcium concentration of our bathing solution, active force development increased by approximately $130\%$ and procainamide then produced no significant increment in force. Increasing force development by increasing stimulus frequency also resulted in no inotropic response to
contractile state, the inotropic action of procainamide may not be apparent. However, there are exceptions as will now be discussed.

**Digoxin-procainamide interaction.** Our results with a near maximal concentration of digoxin and procainamide demonstrate that neither drug alters the inotropic action of the other. This implies that their inotropism is mediated by different mechanisms. The latter implication is supported by studies that demonstrated that procainamide does not alter membrane sodium-potassium-adenosine triphosphatase (ATPase) activity (11), inhibition of which is believed to result in the inotropic action of digitalis (12,13).

**Mechanism of procainamide effects.** The normal inotropic response to procainamide after the contractile state was increased by digoxin is unlike the blunted effect of procainamide after increasing the contractile state by increasing extracellular calcium or more rapid rates of stimulation. The lack of inotropic effect of procainamide under these latter conditions suggests a similar mechanism of inotropic action. Increased extracellular calcium increases intracellular calcium by directly enhancing slow channel influx. The mechanism of action responsible for the force-frequency effect is less clear, although increased slow channel influx may be involved (14).

Our observations with propranolol indicate that procainamide exerts at least part of its inotropic effect by stimulation of beta-adrenergic receptors either directly or indirectly. Our results with verapamil are compatible with either a direct effect of procainamide on slow channel influx or a beta-adrenergic receptor agonist action. Others (15) demonstrated that beta-adrenergic receptor stimulation augments slow channel influx of calcium and that this effect and its accompanying increase in force development can be blocked by calcium antagonists. An argument against the concept that procainamide stimulates beta-adrenergic receptors is the observation that concentrations of procainamide similar to those we employed did not increase tissue cyclic adenosine monophosphate (AMP) levels (16). However, these studies were performed in atrial tissue.

**Clinical implications.** This study and our previous study (1) indicate that procainamide possesses distinct advantages over quinidine, but the clinical significance of these observations is conjectural. The concentrations of procainamide used in the digoxin studies (4 and 8 µg/ml) are well within the therapeutic range for human beings and these concentrations did exert a positive inotropic effect albeit under unphysiologic conditions. However, procainamide has hemodynamic effects other than those due to its direct myocardial action, and the former may modify the cardiac response to the drug in vivo. Our study also was done using normal muscles, and the response of depressed myocardium may not be similar. Furthermore, N-acetylprocainamide is a major metabolite of procainamide and has significantly different hemodynamic effects from those of its parent compound (17,18). In any event, we have demonstrated that drugs grouped together as class I antiarrhythmic agents on the basis of their electrophysiologic effects have strikingly different effects on mechanical performance and interact differently with the cardiac glycosides.

We are indebted to Jeanne Arceneaux for expert assistance in the preparation of this manuscript.

**References**