Comparison of the Peak Inotropic Effects of a Catecholamine and a Digitalis Glycoside in the Intact Canine Heart

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SUMMARY
The relative peak effects of isoproterenol and ouabain on myocardial contractility and cardiac output were compared by infusing increasing amounts of these two drugs into seven open-chest anesthetized dogs until toxicity developed. Just prior to the development of toxicity isoproterenol increased contractile force an average of 149% and the peak rate of force development (df/dt) an average of 278% of control values, compared to an increase of only 49% and 35%, respectively, with the administration of ouabain. Cardiac output and stroke volume were also significantly greater with the catecholamine than the glycoside. The combination of isoproterenol and ouabain produced essentially the same contractile force and stroke volume achieved by isoproterenol alone. Suppression of ouabain-induced arrhythmias by ventricular pacing allowed additional glycoside to be infused until ventricular fibrillation terminated the study. With pacing and ouabain, contractile force increased 131% above control, a level similar to that achieved by isoproterenol; peak df/dt increased to 200% above control, a value significantly lower than that obtained with isoproterenol. However, stroke volume decreased despite a substantial increase in left ventricular end-diastolic pressure. It is concluded that maximal doses of isoproterenol produce significantly greater increases in myocardial contractility and cardiac output compared to ouabain, even when the toxicity produced by the latter is suppressed by electrical stimulation.

Additional Indexing Words:
Isoproterenol Ouabain Myocardial contractility Contractile force
Inotropic state Ventricular pacing Digitalis Strain-gauge arch
Cardiac glycosides Peak dp/dt

Two classes of drugs, catecholamines and digitalis glycosides, are commonly used to improve myocardial contractility in clinical practice.1,2 Little information is available, however, as to their interaction and their relative efficacy.3 Moreover, it previously has been shown that further increases in the contractile force of the intact heart can be achieved when ouabain-induced arrhythmias are suppressed by KCl, and additional amounts of glycoside are administered.4 Whether or not this enhancement of the performance of the heart as a muscle leads to an improvement in its performance as a pump is not known.

We sought to answer these questions by measuring changes in myocardial contractility and cardiac output produced by increasing concentrations of isoproterenol and by a continuous infusion of ouabain. The responses to the maximum dose of each drug that did not produce toxicity were compared. Also, the effects of additional doses of ouabain, which

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could be administered when the toxic arrhythmia induced by the glycoside was suppressed by ventricular pacing, were studied.

Methods

Seven mongrel dogs, weighing between 19 and 21 kg, were anesthetized with sodium pentobarbital (average dose, 35 mg/kg) and ventilated with a Harvard respiratory pump with a mixture of room air and 100% O₂. The heart was exposed through a median sternotomy and suspended in a pericardial cradle. Isometric contractile force was measured by means of a Walton-Brodie strain-gauge arch sutured to the right ventricle. Relative changes in contractile force and in the peak rate of force development (dF/dt) were determined from high resolution tracings of contractile force. To minimize the effect of changes in right ventricular dimensions on the contractile force developed by the fibers attached to the gauge, the segment of myocardium between the 2 feet of the arch was stretched approximately 50% beyond its diastolic length. Under these conditions a threefold increase in cardiac output caused by a shunt from aorta to right atrium resulted in increases in contractile force and dF/dt averaging less than 5%.

Heparin, 5 mg/kg, was administered intravenously. Mean arterial pressure was maintained constant by means of a compressed air-blood reservoir connected to both femoral arteries through large bore cannulae. Body temperature was monitored with a thermistor probe placed in the rectum and maintained within normal range with heating pads. Systemic arterial pressure was measured through a cannula placed in the subclavian artery. Left ventricular pressure was measured with a pressure transducer attached to a large bore metal cannula inserted through the ventricular apex. Left ventricular end-diastolic pressure was determined from high sensitivity recordings and the maximum rate of rise of left ventricular pressure, peak dp/dt, was measured from high speed recordings of left ventricular pressure at a lower sensitivity and expressed in mm Hg per second. A flow transducer was placed around the ascending aorta and the flow was monitored with a gated sien wave electromagnetic flowmeter.* Mean flow was obtained by electrical integration of the phasic flow signal. Pacing wires were sutured to the right ventricle for pacing the heart with an electronic stimulator during selected parts of the experiment. Frequent determinations were made of serum potassium and arterial pH, Po₂, and Pco₂; no significant deviation from the normal range of these measurements was noted.

Experimental Protocol

After control measurements were made, isoproterenol was infused intravenously at rates of 0.03, 0.10, 0.30, and 1.0 µg/kg/min until either a decrease in contractile force or, more rarely, ventricular ectopic activity supervened. Measurements were again obtained after return to the control state and during reinfusion of the dose of isoproterenol that caused the maximal increase in contractile force without producing an arrhythmia; this dose was termed "the peak dose." Ventricular pacing was also performed during the peak response to isoproterenol at a rate just above the catecholamine-induced sinus tachycardia. After all values returned to control levels, ouabain, 20 µg/kg, was administered intravenously in a bolus injection, and measurements were made 40 min later. An infusion of ouabain, 50 µg/kg/hr, was then started and continued until the development of toxicity, as manifested by ventricular ectopic activity. Measurements were made every 5 min, and data obtained just prior to the appearance of arrhythmias were considered to represent the maximal responses to the glycoside and were termed the "pre-toxic" ouabain effect. When the first ectopic beats were observed, heart rate was transiently increased by ventricular pacing to the same frequency achieved earlier during the peak isoproterenol infusion so that the peak effects of isoproterenol and pre-toxic levels of ouabain could be compared at the same heart rate. In addition, the peak dose of isoproterenol was infused for a brief period to determine the additive effects of pre-toxic doses of the catecholamine and glycoside. The ouabain-induced arrhythmias were successfully suppressed by ventricular pacing; additional ouabain was then infused at a rate of 100 µg/kg/hr until ventricular fibrillation terminated the experiment. Measurements obtained just before the onset of ventricular fibrillation were considered to represent the peak cardiac response to ouabain and were referred to as the "peak" ouabain effect. During the infusion of supra-toxic doses of ouabain, ventricular pacing at rates comparable to those observed during isoproterenol infusion resulted in either ventricular fibrillation or a decrease in contractility and cardiac output. A lower frequency was therefore used which averaged 159 ± 5 beats/min at the peak dose of ouabain compared to 180 ± 6 beats/min during the peak effect of isoproterenol (P < 0.05). In two additional dogs peak doses of isoproterenol were repeatedly infused over a 2 to 3-hour period and

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no deterioration was observed in the contractile force or cardiac output responses.

All data were analyzed statistically using Student's paired t test.

Results

Effects on Myocardial Contractile Force

The average effects in the seven dogs of isoproterenol and ouabain on myocardial contractile force and on the maximal rate of force development (df/dt) as measured by the strain-gauge arch are summarized in figure 1. Infusion of the peak dose of isoproterenol increased contractile force an average of 149 ± 14% (standard error of the mean difference) and increased df/dt 278 ± 22% (P < 0.001). During peak isoproterenol infusion ventricular pacing (at a rate just above that caused by isoproterenol) produced small, statistically insignificant decreases in contractile force and df/dt to 140 ± 14% and 260 ± 18% of control, respectively. Right ventricular contractile force and its first derivative then returned to control levels (fig. 1).

Forty minutes after the initial dose of ouabain (20 μg/kg) was administered, contractile force had increased by an average of 33 ± 5% (P < 0.001), and df/dt rose 28 ± 5% (P < 0.02). Infusion of ouabain to just short of toxicity raised contractile force to 49 ± 7% and df/dt to 35 ± 10% above control (P < 0.001). After the first appearance of ectopic activity, the heart rate in five of the animals was increased by ventricular pacing to the same frequency that had been observed in them during the infusion of peak dose of isoproterenol. This increase in heart rate from an average of 111 to 180 beats/min produced no significant change in the isometric contractile force but increased df/dt by an average of 24 ± 4% (P < 0.001) above the pre-pacing level to values still considerably lower than those achieved by peak isoproterenol. In addition, infusion of the peak dose of isoproterenol just after the appearance of ouabain-induced arrhythmias increased contractile force and df/dt to levels which did not differ significantly from the levels previously achieved with isoproterenol alone (fig. 1). Of note, the peak dose of isoproterenol that was administered did not increase the frequency of ectopic beats nor precipitate any new ventricular arrhythmias despite the fact that rather large amounts of ouabain had already been infused.

After the glycoside-induced arrhythmias were suppressed by ventricular pacing, ouabain infusion was continued until ventricular fibrillation supervened. Prior to the terminal arrhythmia, contractile force increased to a peak level of 131 ± 11% above control, a level that was not significantly different from the increase above control level achieved with isoproterenol during ventricular pacing (fig. 1). Although df/dt increased to an average of 200 ± 17% above control, this value was significantly lower than the peak response to isoproterenol during pacing (P < 0.001).

The relative effects of isoproterenol and ouabain on left ventricular dp/dt are shown in figure 2. Comparisons were made using data in which differences in observed dp/dt could
not be attributed to changes in preload as reflected in the left ventricular end-diastolic pressure. Changes in afterload as a potential influence on dp/dt were also excluded since arterial pressure was maintained at a constant level throughout each experiment. Control dp/dt averaged 1,890 ± 150 mm Hg/sec; peak dp/dt during isoproterenol infusion averaged 3,420 ± 230 mm Hg/sec compared to an average of 2,310 ± 160 mm Hg/sec with infusion of ouabain to the pre-toxic level, a difference of 32 ± 7% (P < 0.001, fig. 2A). This greater effect of isoproterenol on dp/dt persisted even when the heart rates during the pre-toxic infusion of ouabain were increased in five animals by ventricular pacing to the same frequencies as the sinus tachycardia produced by isoproterenol (fig. 2B). Since ventricular pacing per se may alter dp/dt, comparisons were made with isoproterenol data obtained during ventricular pacing. Finally, dp/dt at peak doses of both drugs (ventricular pacing again was employed during both ouabain and isoproterenol studies) was 25 ± 7% greater with the catecholamine than with the glycoside (P < 0.02, fig. 2C).

**Effects on Cardiac Output**

Comparison of the Effects of Isoproterenol with Pre-toxic Doses of Ouabain

The control values of cardiac output and stroke volume averaged 1.60 ± 0.38 L/min and 12.8 ± 3.3 ml, respectively. As shown in figure 3, contractile force, stroke volume, and cardiac output were all significantly greater with isoproterenol than with an infusion of ouabain to the pre-toxic level. In order to eliminate the possibility that the greater cardiac output and stroke volume achieved by isoproterenol could have been due to the Starling effect, that is, due to a higher ventricular preload, we used peak isoproterenol data only if the left ventricular end-diastolic pressure was equal to or below the value measured during ouabain infusion; otherwise, we used the data from a lower dose of isoproterenol at which the Starling effect

**Figure 2**

The effect of isoproterenol (isoprot.) and ouabain on the mean peak rate of rise of left ventricular pressure (LV dp/dt) in seven dogs. (A) Comparison of isoproterenol with pre-toxic levels of ouabain. (B) Comparison at the same drug doses as A but with heart rate at the pre-toxic level of ouabain increased by ventricular pacing to the rate observed during isoproterenol infusion (five dogs). Ventricular pacing was also performed during isoproterenol infusion for this comparison. (C) Comparison of isoproterenol with peak doses of ouabain achieved after suppression of toxic arrhythmias by ventricular pacing which was also performed during the isoproterenol infusions.

**Figure 3**

The effects of isoproterenol (isoprot.) and pre-toxic levels of ouabain on the mean values of contractile force, cardiac output, and stroke volume. The mean values for left ventricular end-diastolic pressure (LVEDP) are also shown. On the right, the heart rates at the pre-toxic level of ouabain were increased in five animals by ventricular pacing to rates obtained with isoproterenol infusion.
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Figure 4

The effect of peak doses of isoproterenol alone and in combination with pre-toxic levels of ouabain on the same hemodynamic parameters as described in figure 3.

could not be implicated as a cause for the observed differences. Thus, it should be noted that the data in the left portion of figure 3 were obtained at comparable end-diastolic pressures for each drug. Heart rates, however, were considerably more rapid during the catecholamine infusion than during the ouabain infusion (average, 175 ± 9 versus 109 ± 7 beats/min, P < 0.001). When heart rates were equalized by ventricular pacing in five of the seven dogs, cardiac output and stroke volume were still considerably higher during peak doses of isoproterenol than with pre-toxic doses of ouabain (P < 0.05, fig. 3).

Comparison of the Effects of Peak Doses of Isoproterenol Administered Alone or after Pre-toxic Doses of Ouabain

When isoproterenol followed the administration of a pre-toxic dose of ouabain, the levels of right ventricular contractile force and stroke volume were not significantly different from those achieved by isoproterenol alone (figs. 1 and 4). However, after the infusion of ouabain to pre-toxic levels, peak doses of isoproterenol consistently caused less cardiovascular acceleration, and the cardiac output was significantly lower than when isoproterenol was given prior to ouabain. Heart rate during peak isoproterenol infusion averaged 183 ± 4 beats/min prior to the administration of ouabain and 166 ± 8 beats/min after its administration (P < 0.05).

Comparison of the Effects of Pre-toxic and Peak Levels of Ouabain

The infusion of ouabain to the pre-toxic level produced a significant increase in contractile force, essentially no change in stroke volume, and a small but significant decrease in cardiac output (fig. 5). The decrease in cardiac output was associated with a fall in heart rate from an average of 117 ± 8 to 106 ± 7 beats/min (P < 0.001). When arrhythmias were suppressed by ventricular pacing, additional infusion of ouabain to peak effect resulted in a further increase in contractile force; however, stroke volume fell significantly (from an average of 12.9 ± 2.5 ml with the pre-toxic dose to 6.0 ± 0.4 ml with

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the peak dose, \( P < 0.05 \) despite an increase in left ventricular end-diastolic pressure from an average of \( 5.1 \pm 0.3 \) to \( 11.1 \pm 1.2 \) mm Hg \( (P < 0.001) \). Cardiac output also fell, but this change did not achieve statistical significance. When the effects of peak doses of isoproterenol during ventricular pacing were compared with those of peak doses of ouabain, it was found that the cardiac output and stroke volume responses to the catecholamine were much greater than those in response to the glycoside (average, 4.17 versus 0.95 L/min and 23 versus 6 ml, \( P < 0.001 \)). The greater cardiac output and stroke volume responses achieved by peak isoproterenol could not be explained by the Starling mechanism, since left ventricular end-diastolic pressure tended to be, if anything, somewhat lower with isoproterenol than with ouabain (8.7 versus 11.1 mm Hg, \( P < 0.01 \)).

Discussion

One of the major purposes of the present investigation was to determine the relative inotropic effects of isoproterenol and ouabain in the normal intact canine heart. When the effects of isoproterenol and ouabain were compared just prior to the development of toxicity, right ventricular contractile force (measured by a strain-gauge arch) was considerably greater during infusion of the catecholamine than the glycoside. Ventricular pacing successfully suppressed the ouabain-induced arrhythmias that subsequently appeared, permitting additional amounts of the glycoside to be infused. This resulted in a further increase in contractile force until ventricular fibrillation supervened and, prior to the onset of the terminal arrhythmia, contractile force reached a level comparable to that attained by peak doses of isoproterenol.

It would therefore appear that if the arrhythmic effects of ouabain are suppressed, the inotropic ceiling reached by ouabain is similar to that of isoproterenol. However, contractile force is not a primary index of the contractile state of the myocardium, since it depends on both the rate of force development, \( df/dt \), which reflects the intensity of the active state of the contractile elements, and on the time available to reach peak tension, which is directly proportional to the duration of the active state.\(^7\)\(^8\) When the effects of peak doses of ouabain and isoproterenol on \( df/dt \) of the isometric muscle segment and the left ventricular \( dp/dt \) were compared, both \( df/dt \) and \( dp/dt \) were significantly lower at the peak levels of ouabain. Since these two indices of myocardial contractility more closely reflect the intensity of the active state than does contractile force alone, the results suggest that not only is the augmentation of myocardial contractility produced by isoproterenol greater than that attained by pre-toxic amounts of ouabain, it is also of greater magnitude than the inotropic level that can be achieved by further administration of ouabain after arrhythmias are suppressed by ventricular pacing.

Since it has been shown that increases in heart rate increase the rate of development of tension, we attempted to determine whether or not the differences in the contractile response produced by isoproterenol and ouabain could be explained by the differences in heart rate which existed with the two drugs. When attempts were made to pace the ventricle at comparable rates during infusion of supra-toxic levels of ouabain, either ventricular fibrillation occurred, or contractility and cardiac output fell precipitously. However, at pre-toxic levels of ouabain, the ventricle was paced at a rate similar to that observed during peak, pre-toxic doses of isoproterenol. Although \( df/dt \) increased significantly, the level reached was still considerably lower than that achieved with isoproterenol. Despite the increase in \( df/dt \), no further increase in isometric force developed. Thus, an increase in heart rate under these conditions caused an increase in the mean rate of tension development and, presumably, a proportionate decrease in the time to reach peak tension, so that developed tension was not altered. These findings are similar to those observed in man by Sonnenblick and co-workers\(^8\) who studied the effects of increasing

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heart rate on the development of contractile force utilizing a strain-gauge arch sutured to the right ventricle of patients undergoing cardiac operations. In several other studies, however, alterations in frequency of contraction produced changes in the magnitude of force development as well as the velocity of contraction, and it would appear that the effects of frequency on force development depend on the frequency range employed, the species studied, and whether atrial or ventricular myocardium is examined. Moreover, it has been shown that digitalis glycosides prevent frequency-dependent increases in force development when administered in high doses.

In addition to determining the relative capacities of isoproterenol and ouabain to increase myocardial contractility, we also examined the effects of combined administration of the two drugs. When isoproterenol was administered to an animal that had already received a pre-toxic dose of ouabain, right ventricular force equalled, but did not exceed, the level it achieved from isoproterenol alone. Similar results were obtained in an earlier study in our laboratory in which peak doses of isoproterenol were infused into dogs after suppression of digitalis-induced arrhythmias by potassium chloride or diphenylhydantoin. This finding suggests that the peak inotropic effect achieved by the catecholamine approaches a ceiling above which the muscle cannot respond, even when its contractility has been improved with a large dose of a cardiac glycoside. It was also observed that the peak dose of isoproterenol produced less cardio-acceleration after the administration of ouabain. These findings are consistent with the observations of Mendez and associates, who found that the prior administration of cardiac glycosides reduced the positive chronotropic response of the intact canine heart to intravenous epinephrine and to stimulation of the cardio-accelerator nerve.

Since the inotropic response to the combination of isoproterenol and ouabain did not differ appreciably from that obtained with isoproterenol alone, it is possible that under appropriate clinical conditions the prior administration of digitalis to a patient with cardiac failure may allow larger doses of isoproterenol to be infused without causing excessive tachycardia. The use of a combination of isoproterenol and a cardiac glycoside should be approached with caution, however, to avoid potentially serious arrhythmias. Nevertheless, it is of interest that this combination of drugs, each in sub-toxic doses, did not precipitate any arrhythmias in this study. Since isoproterenol produces an appreciable tachycardia, it is possible that any tendency for glycoside-induced arrhythmias to emerge would be partly counteracted by the increase in heart rate in a manner similar to that observed with rapid ventricular pacing.

Another major purpose of this investigation was to determine the relative effects of isoproterenol and ouabain on the performance of the heart as a pump. Stroke volume and cardiac output were considerably greater with peak doses of isoproterenol alone than with pre-toxic levels of ouabain. These differences existed even when the heart rate at the pre-toxic doses of ouabain was increased by pacing to the rate observed during isoproterenol infusion (fig. 3). Since ventricular pacing per se may alter cardiac output, comparisons were made using data obtained with ventricular pacing during the action of both drugs. Moreover, when a peak dose of isoproterenol was given after the administration of ouabain, the resultant cardiac output and stroke volume were no greater than with the same dose of isoproterenol administered alone.

Since alterations in afterload may influence ventricular performance, mean arterial pressure was maintained at a constant level with the compressed air-blood reservoir bottle. Maintenance of the same arterial pressure also prevented baroreceptor-mediated changes in myocardial contractility and ensured adequate coronary perfusion pressure throughout the experiment. This latter point is of importance in light of the finding of Daniell and associates who reported that a decrease in coronary perfusion due to the vasodilator
action of isoproterenol may limit the augmentation of myocardial contractility produced by this drug.

In addition to their inotropic actions both ouabain and isoproterenol directly alter systemic vascular resistance; the glycoside causes vasoconstriction during acute administration,\textsuperscript{18} and the catecholamine causes vasodilatation through stimulation of the beta receptors located in the peripheral arterioles.\textsuperscript{1} Liedtke and co-workers\textsuperscript{19} have postulated that these contrasting effects on peripheral resistance could account for the difference in the magnitude of the cardiac output responses to these two drugs. However, under the experimental conditions employed in this study, it was possible to exclude the differing effects of the two drugs on peripheral resistance by maintaining arterial pressure constant with a "pressure-bottle" connected to the arterial bed. This allows a comparison of the direct effects on the performance of the heart as a pump.

The point to be emphasized in this study is that while both agents exert a positive inotropic effect, isoproterenol produces a greater stroke volume than ouabain, at the same left ventricular end-diastolic pressure and heart rate, a finding that can only be interpreted as demonstrating that isoproterenol exerts a greater effect on the pumping capacity of the heart. In other words, at the same preload, afterload, and heart rate the difference in the stroke volume responses to the two drugs appears to be due entirely to a difference in their capacities to displace the ventricular function curves upward and to the left.

A previous study demonstrated that a further increment in myocardial contractile force could be achieved when ouabain-induced arrhythmias were suppressed by KCl and additional amounts of glycoside were administered.\textsuperscript{4} These findings suggested that under appropriate clinical conditions it might be advisable not to discontinue treatment with digitalis if the arrhythmia could be controlled by KCl. In the present investigation it was observed that as with KCl, toxic arrhythmias can be suppressed with ventricular pacing, allowing the administration of additional amounts of glycoside and a further increment in contractile force. However, this was associated with what must be interpreted as an impairment in the capacity of heart to function as a pump, since stroke volume and cardiac output both fell despite a substantial increase in left ventricular end-diastolic pressure.

The cause of this deterioration in ventricular performance despite an apparent increase in myocardial contractility is unclear. It is possible that these doses of ouabain impaired myocardial relaxation, altering the relationship between left ventricular end-diastolic pressure and left ventricular end-diastolic fiber length. Thus, with these doses of ouabain the ventricle might be ejecting from a shorter end-diastolic fiber length, even though end-diastolic pressures were the same or higher than during the control period.

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