Effect of Digitalis on Left Ventricular Function in Exercising Dogs

LAWRENCE D. HORWITZ, JAMES M. ATKINS, AND MUNEYASU SAITO

SUMMARY The effect of ouabain on left ventricular function in nonfailing hearts was assessed in 14 chronically instrumented dogs during graded treadmill exercise. At rest, ouabain increased the maximum first derivative of the left ventricular pressure (dp/dtmax) and stroke volume by 38% and 16%, respectively. No change occurred in end-diastolic left ventricular diameter or peak systolic left ventricular pressure. During exercise, ouabain reduced maximum running speed and limited the increments in heart rate and systolic pressure but did not alter dp/dtmax, stroke volume, or end-diastolic diameter. When atropine and ouabain were given and severe exercise was performed, there were no differences from controls in running speed, heart rate, dp/dtmax, or other parameters. When ouabain and propranolol were given, dp/dtmax increased at rest and during exercise, compared with results with propranolol alone. It is concluded that the inotropic effect of ouabain is negligible during strenuous physical activity because of the presence of high levels of sympathetic stimulation. However, during exercise in the presence of β-adrenergic blockade, increases in myocardial contractility do occur in response to ouabain.

Digitalis glycosides induce an increase in myocardial contractile force in isolated cardiac muscle,1-3 open-chest or intact anesthetized animals,4-6 conscious resting animals,6-7 and anesthetized or conscious resting man.8-11 However, it has not been clear whether this inotropic effect improves ventricular pump performance in the nonfailing heart. It is difficult to draw conclusions about this question in the resting or anesthetized states because digitalis-induced reduction in venous return may obscure a tendency for a rise in stroke volume.5

Acute volume loading and exercise substantially increase venous return12, 13 and cardiac work loads. Although it might be expected that, under these conditions, beneficial influences of inotropic agents on ventricular pump performance would be more clearly evident than in less stressful situations, stroke volume and cardiac output are not increased by digitalis during rapid, intravenous infusions in conscious dogs14 or exercise in man.15-16 The significance of these findings is uncertain for two major reasons. Although a modest inotropic response to digitalis has been observed in resting conscious dogs,6, 7 there have been no measurements of its effect on myocardial contractile force during stresses such as volume loading or exercise. Without knowing whether an inotropic effect has occurred, it is difficult to interpret a lack of change in pump function. Second, because of the potential role of the Frank-Starling mechanism, information about end-diastolic myocardial fiber length is a crucial prerequisite in an evaluation of the relationship between myocardial contractile state and stroke volume. Because this information was not obtained in previous studies of digitalis and volume loading or exercise, it is impossible to exclude the possibility that with administration of the drug the same stroke volume was obtained from a lower preload, a finding which would be indicative of enhanced cardiac function.

To define more clearly the effects of digitalis glycosides on myocardial contractile force and ventricular pump performance in nonfailing hearts, we administered ouabain to dogs studied at rest and during a graded regimen of treadmill exercise. In addition to cardiac output and systolic pressure, we measured an index of myocardial contractile force, the maximum first derivative of left ventricular pressure,17, 18 and an index of left ventricular muscle fiber length and volume, left ventricular internal diameter.19, 20 This is the first study of exercise stress which assesses the effects of digitalis on either myocardial contractile force or left ventricular dimensions. Our most striking finding was that, although ouabain augmented myocardial contractility at rest, there was no discernible inotropic effect during exercise. A hypothesis to explain this unexpected finding is proposed.

Methods

Fourteen mongrel dogs weighing 14-24 kg were trained to run on a level treadmill. Subsequently, each dog underwent a sterile thoracotomy under sodium pentobarbital anesthesia (30 mg/kg, iv). Using techniques described previously,19, 20-22 two sonocardiometer transducers were attached to the endocardial surface of the anterior and posterior walls of the left ventricle, a Konigsberg P18 high-fidelity solid state pressure transducer was inserted into the left ventricle near the apex, an electromagnetic flow probe was placed around the proximal ascending aorta, and 18-gauge polyvinyl catheters were placed in the left atrium and a jugular vein. In some dogs, either sonar transducers or flow probes were not implanted. At least 3 weeks were allowed for recovery from surgery and retraining. At the time of experiments all...
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...dogs were free of infection or electrocardiographic abnormalities and could exercise at the same levels attained prior to surgery.

As described previously, measurements were made of ascending aortic flow with a Zepeda EDP2 square wave, electromagnetic flowmeter, left ventricular transverse, internal diameter with a sonocardiometer, left ventricular pressure with a Konigsberg P18 solid state pressure transducer, and left atrial and aortic pressures with Statham P23Db manometers via catheter systems. All signals were inscribed on a Beckman RM oscillograph and an Ampex FR 1300A magnetic tape recorder. The flow signals were limited in frequency response by the oscillograph (signal amplitude decreased 5% at 80 Hz). The resolution of the sonocardiometer was approximately 0.07 mm and the output amplitude decreased 5% at 20 Hz. The solid state pressure transducers had a natural frequency in excess of 3000 Hz. The first differential of the left ventricular pressure (dp/dt) was obtained with an active circuit which decreased 3 dB at 100 Hz.

Preexercise or resting measurements were obtained with the dogs standing quietly on the treadmill. Each dog then ran, in sequence, 3-minute periods at preselected loads of mild, moderate, and severe exercise on a level treadmill (0° grade). Mild exercise ranged from 3 to 4 mph, moderate exercise from 6 to 8 mph, and severe exercise, the maximum load at which the dog could be induced to run, from 9 to 13 mph. There were 5-minute rest periods after the mild and moderate exercise runs. After any running sequence, the dog was permitted 48-72 hours to recover prior to another experiment.

Three sets of experiments were performed:

1. In nine dogs, we first obtained one or two satisfactory exercise periods without drugs. On a subsequent experimental day, ouabain (approximately 0.035 mg/kg) was given via the jugular catheter over 10 minutes. Twenty minutes later the exercise sequence was repeated.

2. Two or three days later, in five dogs, in all of which experiment 1 had been completed, atropine (0.1 mg/kg, iv) was given and the exercise sequence performed 10 minutes later. On a subsequent day, ouabain was first administered, followed 10 minutes later by atropine administration, and 10 minutes later by the exercise sequence.

3. In a separate set of studies in six dogs, propranolol (Ayerst Laboratories) (1 mg/kg, iv) was administered and an exercise sequence studied 15 minutes later. On a subsequent day ouabain was given, followed by propranolol, and exercise was begun 20 minutes after the ouabain had been injected.

The exact dosage of ouabain was determined initially by giving each dog small intravenous doses until signs of mild gastrointestinal toxicity occurred; hypersalivation and a brief period of retching were the usual end points. If arrhythmias or recurrent vomiting resulted, the experiment was cancelled and the dose was reduced slightly when studies were performed on a later date. The efficacy of this dose, approximately 0.035 mg/kg, was confirmed by resting dose response curves, as shown in Figure 1. At doses below those at which toxic arrhythmias occurred, the maximum levels of the first differential of the left ventricular pressure (dp/dtmax), an index of myocardial contractility, were encountered at 0.03-0.04 mg/kg. Occasional electrocardiographic monitoring at rest and during exercise confirmed that lengthening of the P-R interval, or other evidence of atrioventricular block, did not appear at the dosage used.

The dosage of atropine used abolished the effects on heart rate of acetylcholine injections, 1.0 mg, iv, on repeated challenge for a 45-minute period beginning 10 minutes after atropine administration. The dosage of propranolol used abolished the effects of isoproterenol (3-5 µg/min, iv) on heart rate and dp/dtmax on repeated challenge for a 45-minute period beginning 20 minutes after propranolol administration. According to previous reports, this dosage exerts its effects purely through β-adrenergic blockade and is below levels which influence the myocardium independently of β receptors by interfering with calcium metabolism in the sarcoplasmic reticulum.

Data were analyzed by averaging eight consecutive beats to reduce the effects of respiratory variation. Random sampling confirmed that there was little or no hemodynamic variation during the last minute of each 3-minute exercise period. Statistical analyses were performed by paired t-tests using each dog as its own control.

Results

OUABAIN ALONE

In all nine dogs studied, the mild and moderate exercise loads were the same during control runs without drugs and those with ouabain. However, in eight dogs, the severe exercise level, that is the maximum speed at which the dog was able to run, was reduced by 1-3 mph with ouabain. Hemodynamic changes that occurred are summarized in Table 1.

![Figure 1: Dose-response curve for ouabain in a resting, conscious dog. The maximum first derivative of the left ventricular pressure, dp/dtmax, is the ordinate. Increments of 0.01 mg of ouabain were given iv at 20-minute intervals. Above 0.04 mg/kg, in this and other dogs, recurrent vomiting or arrhythmias occurred.](http://circres.ahajournals.org/Download.pdf)
Although in most dogs heart rate decreased slightly, this parameter was not changed significantly at rest by ouabain. During moderate and severe exercise, the increment in heart rate was less than in runs without drugs by 41 beats/min (20%) and 54 beats/min (23%) for moderate and severe loads, respectively. During mild exercise, seven of nine dogs had lower heart rates with ouabain, although the change was not statistically significant. At rest, ouabain was associated with a 16% increase in heart rate. However, due to the lower heart rates, the product of the heart rate and left ventricular peak systolic pressure, an index of myocardial oxygen consumption, was less with ouabain than without drugs during moderate and severe exercise (Table 1). Left ventricular end-diastolic pressure was not altered significantly by ouabain at rest or during exercise.

The maximum first derivative of the left ventricular pressure (dp/dtₘₐₓ) was increased significantly at rest (+38%, P < 0.01) (Table 1). No significant differences in dp/dtₘₐₓ were induced by ouabain during exercise.

**OUABAIN WITH ATROPINE**

To minimize the heart rate effect of ouabain and to delineate better the alterations in myocardial contractility, five dogs underwent additional studies with atropine alone and atropine plus ouabain. After ouabain alone, all five were able to reach the maximum speed attained previously without drugs. The decrement in maximum speed ranged from 1 to 3 mph (mean, 2.0 mph). However, with ouabain and atropine, or with atropine alone, all were able to run at the same severe exercise speed as was accomplished without drugs. Results at rest and during severe exercise are shown in Table 2.

Both atropine and the combination of atropine and ouabain increased resting heart rate. At rest, ouabain increased dp/dtₘₐₓ in four of the five dogs, although the change was not statistically significant. Atropine alone...
elevated dp/dtmax in all five dogs but, again, the change was not statistically significant. Atropine plus ouabain resulted in a significant increase (P < 0.01) in dp/dtmax over resting values without drugs.

During severe exercise there were no significant differences in heart rate, stroke volume, cardiac output, left ventricular systolic or end-diastolic pressures, or dp/dtmax when control runs were compared with runs with ouabain plus atropine. Atropine alone resulted in a slightly higher heart rate but did not alter dp/dtmax during severe exercise (Table 2). There were no differences in dp/dtmax among the various groups during mild or moderate exercise. Atropine alone resulted in significant increases in heart rate over the other states at all levels of activity.

OUABAIN WITH PROPRANOLOL

In six dogs, the effect of ouabain on dp/dtmax was studied during β-adrenergic blockade with propranolol (Table 3). Compared with runs without drugs, propranolol did not significantly change heart rate at rest but did limit the increment in heart rate during exercise. The dp/dtmax was less than in studies without drugs at all loads. Left ventricular end-diastolic pressure was higher at all loads and the increment in left ventricular systolic pressure was less during moderate and severe exercise. These findings closely resemble those reported previously at this dose of propranolol.26

Ouabain plus propranolol increased dp/dtmax over values obtained with propranolol alone in all dogs at rest and during all levels of exercise (Table 3). Increases ranged from 16% to 42% at rest, 6% to 33% with mild exercise, 14% to 21% with moderate exercise, and 10% to 16% with severe exercise. The severe loads in the propranolol-treated dogs were the same with and without ouabain. Heart rates and left ventricular end-diastolic pressures tended to be slightly lower at all loads with ouabain plus propranolol than with propranolol alone, although only at the mild exercise level was there a statistically significant difference in heart rate. There were no consistent changes in left ventricular systolic pressure. Stroke volume was measured in one dog in this group and it was increased by ouabain by 12% (3.4 ml) at rest and 12-24% during exercise, compared with results with propranolol alone. Left ventricular diameter was measured in two dogs. There were no consistent differences in end-diastolic diameter between studies with propranolol alone and with propranolol plus ouabain. However, the addition of ouabain resulted in lower end-diastolic diameters at rest and during exercise. Changes from values with propranolol alone ranged from 2.0 to 3.2 mm during exercise.

Discussion

It is generally accepted that the beneficial effect of digitalis glycosides in congestive heart failure is due primarily to their ability to enhance the force of myocardial contraction. A salutary action of these drugs on myocardial force generation has been convincingly demonstrated in isolated cardiac muscle,1-3 open-chest heart preparations,4,5 anesthetized intact animals,6 conscious resting animals,7 anesthetized man,8 and conscious resting man with or without heart disease.9,10,11 However, most previous investigations of the influence of digitalis on cardiac function have dealt with subjects with possible myocardial depression due to anesthetic agents or disease, or have lacked measurements which are reliable indices to changes in myocardial contractility or ventricular dimensions. In conscious, resting animals, increases in myocardial contractility due to digitalis also have been observed, but the changes are relatively small.9,12 The extent to which

Table 2 Effect of Atropine and Ouabain at Rest and during Severe Exercise

<table>
<thead>
<tr>
<th></th>
<th>Without drugs</th>
<th>Ouabain</th>
<th>Atropine</th>
<th>Atropine + ouabain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results at Rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/ min)</td>
<td>111 ± 6</td>
<td>96 ± 8</td>
<td>193 ± 9</td>
<td>171 ± 14</td>
</tr>
<tr>
<td>Stroke volume (ml/ beat)</td>
<td>35.1 ± 5.2</td>
<td>40.0 ± 6.6</td>
<td>25.1 ± 4.6</td>
<td>29.1 ± 5.9</td>
</tr>
<tr>
<td>Cardiac index (ml/ min-kg)</td>
<td>185 ± 33</td>
<td>180 ± 30</td>
<td>232 ± 53</td>
<td>228 ± 34</td>
</tr>
<tr>
<td>LV dp/dtmax (mm Hg/sec)</td>
<td>3,744 ± 476</td>
<td>5,195 ± 634</td>
<td>4,568 ± 525</td>
<td>5,522 ± 681</td>
</tr>
<tr>
<td><strong>Results during Severe Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/ min)</td>
<td>228 ± 9</td>
<td>164 ± 1</td>
<td>258 ± 4</td>
<td>215 ± 19</td>
</tr>
<tr>
<td>Stroke volume (ml/ beat)</td>
<td>42.1 ± 7</td>
<td>49.0 ± 8.3</td>
<td>42.0 ± 7.2</td>
<td>45.2 ± 7.2</td>
</tr>
<tr>
<td>Cardiac index (ml/ min-kg)</td>
<td>448 ± 63</td>
<td>366 ± 34</td>
<td>509 ± 81</td>
<td>444 ± 61</td>
</tr>
<tr>
<td>LV dp/dtmax (mm Hg/sec)</td>
<td>10,185 ± 1,508</td>
<td>9,024 ± 1,167</td>
<td>10,156 ± 1,522</td>
<td>10,256 ± 1,410</td>
</tr>
</tbody>
</table>

Results in five dogs, each of which on separate days was studied without drugs, with ouabain alone, with atropine alone, and with the combination of ouabain and atropine. x = mean ± se for each group; d = mean difference from results without drugs for that state using each dog as its own control ± SEM; LV = left ventricular.

* Indicates P < 0.05 comparing atropine and ouabain to drug-free runs.
Digitalis enhances myocardial contractility in the normal, conscious animal or man during exercise or other stressful conditions has not been known. In addition, it has not been clear whether this drug benefits cardiac pump performance during exercise, since assessment of left ventricular function on the basis of changes in aortic blood flow measurements, without knowledge of changes in end-diastolic muscle fiber length or myocardial contractile state, is impossible. This study is the first to offer data on the effect of digitalis on myocardial contractility and overall cardiac function in the normal heart during a physiological stress, dynamic exercise.

At rest, the increase in contractility due to ouabain was associated with an increase in stroke volume, which maintained cardiac output despite a lower heart rate in many dogs (Table I). This increase in stroke volume was due to greater myocardial fiber shortening, as shown by the lower left ventricular end-systolic diameter. Since left ventricular end-diastolic diameter and left ventricular peak systolic pressure were unchanged, this appears to be an instance in which an increase in myocardial contractility influenced cardiac pump performance in the normal heart. In contrast, at all levels of exercise, neither dp/dt max nor stroke volume were altered by ouabain. End-systolic diameter was not affected by ouabain during mild and severe exercise; the lower end-systolic diameter with ouabain during moderate exercise may reflect reduction in afterload, rather than a change in myocardial contractility. Since left ventricular end-diastolic diameter, a reliable index of preload, was not changed significantly by ouabain at any exercise load, effects of the drugs on vascular tone did not limit venous return during exercise and this was not a mechanism which limited stroke volume.

The maximum first derivative of the left ventricular pressure (dp/dt max) is a reliable index to myocardial contractility under most conditions. Only large alterations in preload, afterload, or heart rate are likely to influence this measurement. Increases in dp/dt max in response to ouabain were present at rest but not during exercise. Although, on the basis of this observation, it appeared that ouabain did not enhance myocardial contractile force during exercise, there was reason to question this conclusion with regard to severe exercise. At this level, substantial heart rate differences and variation in exercise loads between runs with and without ouabain could have influenced dp/dt max independently of changes in myocardial contractility. Accordingly, studies were done with concomitant administration of atropine and ouabain. This eliminated the differences in heart rate and exercise load during severe exercise. Preload and afterload were similar to levels during runs without drugs. Again, there was no change in dp/dt max from control runs during severe exercise (Table II). Therefore, there is no increase in myocardial contractility due to ouabain during near-maximal exercise.

A possible explanation for the lack of discernible alteration in myocardial contractility by ouabain during moderate and severe exercise is that sympathetic tone is so high that little or no further increment in myocardial contractility by ouabain is necessary.
contractility is possible. To test this hypothesis, we studied animals during β-adrenergic blockade. When results during β-blockade with and without ouabain were compared, the ouabain group exhibited a consistently higher dp/dt<sub>max</sub> at all levels of activity. Changes in heart rate, preload, or afterload do not account for this finding (Table 3). Since the dose of propranolol was well below that which causes demonstrable direct myocardial depression through interference with calcium fluxes, it is likely that β-blockade was the major, if not the sole, effect of the drug. Therefore, it appears that when sympathetic stimulation is absent or markedly reduced, ouabain increases myocardial contractility at all levels of effort. Although not conclusive, this finding is consistent with the hypothesis that in the presence of very high levels of sympathetic stimulation, digitalis does not exert its inotropic effect on the normal heart because myocardial contractility is at or near its maximum. An alternative hypothesis, which is also consistent with these data, is that catecholamines and digitalis compete for the same pathways in causing inotropic changes. In addition, it is impossible to exclude the possibility that propranolol exerted some degree of direct myocardial depression independent of its β-blocking effect and that this depression was the primary reason for the efficacy of ouabain with propranolol pretreatment.

Although the effect of ouabain on myocardial contractility during exercise was negligible, the drug reduced the increment in cardiac output through attenuation of the heart rate response. Digitalis glycosides induce slowing of sinoatrial node discharge rates through direct effects on pacemaker cells and either increased activity of vagus nerve fibers or increased sensitivity of pacemaker cells to vagal discharge. The magnitude of this rate-limiting effect may be species-dependent, since in normal man the decrement in heart rate during exercise due to digitalis preparations appears to be small or absent. Differences in preparations and dosages also may have contributed to differences in results. Since ability to compensate by increased stroke volume seems limited, the effect of a reduction in the exercise heart rate is to reduce cardiac output. It appeared that this reduction in cardiac output impaired running ability, since most dogs could not accomplish their previous maximum running speed with ouabain. The concomitant administration of atropine with ouabain restored cardiac output to levels reached without drugs and the maximum speed again was achieved.

At rest, the increase in stroke volume that occurred with ouabain took place under conditions that permit the conclusion that the drug may have enhanced ventricular pump capacity. However, during exercise, when stroke volume, preload, and afterload were similar with and without ouabain, there was no evidence that ventricular function was altered.

Although the increase in cardiac output during exercise was limited by ouabain, it is likely that the increase in myocardial oxygen expenditure was limited as well. The heart rate-systolic pressure product, an index of myocardial oxygen consumption, was lower after ouabain at all levels of exercise. Therefore, the attenuation of the heart rate response with digitalization may permit accomplishment of submaximal exercise with greater cardiac efficiency.

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Baroreceptor Fibers and Whole Nerve Activity in the Normotensive and the Renal Hypertensive Dog

PETER SLEIGHT, JAMES L. ROBINSON, DRusilla E. BROOKS, AND PETER M. REES

SUMMARY Carotid sinus baroreceptor nerve activity was examined in eight renal hypertensive dogs with a duration of hypertension of 5 to 82 days and a mean blood pressure of 148 ± 0.5 mm Hg. These results were compared with those from 13 normotensive dogs. Whole carotid sinus nerve activity and single fiber activity were recorded in the isolated carotid sinus preparation in response to controlled static and pulsatile pressures. Stimulus-response curves were constructed. Single fiber adapted (5-second) threshold pressure under static pressure conditions increased from 104 ± 3.2 mm Hg in the normotensive dogs to 128 ± 3.9 mm Hg in the hypertensive dogs. Impulse frequency at the inflection pressure was reduced from 39 ± 2.3 impulses/sec in normotensive dogs to 32 ± 1.7 impulses/sec in hypertensive dogs. Whole carotid sinus nerve activity and single fiber activity were also significantly higher in hypertension. The resting pressure at the plateau pressure was reduced from 188 ± 0.4 mm Hg for the normotensive dogs to 166 ± 3.5 mm Hg for the hypertensive dogs. Baroreceptor resetting was not seen before 5 days of hypertension. It was possible to reverse the resetting by lowering the blood pressure in one dog which had been hypertensive for 47 days.

McCUBBIN et al. first demonstrated resetting of the carotid sinus in the renal hypertensive dog. Recording from the whole carotid sinus nerve, they observed that nerve activity occurred first at a much higher pressure than in hypertensive dogs and that a pulsatile nerve activity still was present at pressures which in normotensive dogs gave rise to continuous activity. Since these initial findings, other authors have shown a shift of the baroreceptor activity-pressure response curve by recording from whole carotid sinus nerves in dogs and whole aortic nerves in rats and rabbits. These previous observations all were made on whole nerves and did not show whether individual baroreceptor units were reset. Recently, single aortic baroreceptor fiber activity has been recorded in hypertensive rabbits and a shift of the response curve was seen in most of the fibers. There have not been any studies of the activity of individual carotid sinus baroreceptors in the hypertensive dog, and we have therefore made a quantitative examination of their characteristics. Both whole nerve activity and single carotid sinus baroreceptor activity were recorded in response to controlled static and pulsatile perfusion pressures.

Methods

PRODUCTION OF RENAL HYPERTENSION

Under sterile conditions, 23 mongrel dogs of either sex (18.5 ± 0.74 kg) anesthetized with fentanyl (0.02 mg/kg, im) and droperidol (1.2 mg/kg, im), atropine (0.04 mg/kg, im) and sodium pentobarbital (6 mg/kg, iv) underwent unilateral nephrectomy. An externally adjustable clamp was implanted around the renal artery of the remaining
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