Effect of the Ouabain-Quinidine Interaction on Left Ventricular and Left Atrial Function in Conscious Dogs

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SUMMARY The effect of the ouabain-quinidine interaction was examined in 10 conscious dogs. Left ventricular (LV) pressure, LV dp/dt, LV diameter and left atrial (LA) diameter were measured with high-fidelity micromanometers and sonomicrometer crystals. Ouabain, 0.025 mg/kg, significantly (p < 0.05) increased LV dp/dt, LV and LA fractional shortening and LV and LA velocity of circumferential fiber shortening (Vcf). In a separate experiment, quinidine was administered as a bolus dose, 3.85 mg/kg, followed by an infusion, 0.28 mg/kg/min. This resulted in steady-state quinidine concentrations that produced no change in wall motion or hemodynamics. When ouabain was given 1 hour into the quinidine infusion, only LV dp/dt increased significantly (p < 0.05). Ouabain alone increased LV dp/dt 26.4 ± 3.5%, whereas ouabain during the quinidine infusion increased it by 9.5 ± 2.3%. Similar differences were seen in the responses to ouabain in the absence and presence of quinidine: LV Vcf, 22.4 ± 4.9% vs 6.0 ± 2.1%, LV fractional shortening, 23.1 ± 4.6% vs 5.8 ± 2.1%, LA Vcf, 22.7 ± 5.9 vs 4.6 ± 2.0% and LA fractional shortening, 21.8 ± 7% vs 7.8 ± 3.3%. Thus, in the presence of quinidine the increase in inotropy usually seen with ouabain was markedly attenuated. These data suggest that the quinidine-induced increase in digoxin serum concentrations is accompanied by a decrease in the contractile response of the heart to digoxin.

DIGITALIS and quinidine have been used together for many years. However, only recently has a pharmacokinetic interaction between digoxin and quinidine been described.1–3 Serum digoxin levels have been noted to increase two- or threefold in the presence of steady-state quinidine concentrations.4 The basis of this interaction appears to be a quinidine-induced decrease in the digoxin volume of distribution and in the total body clearance of digoxin, the latter a result of a diminution in both digoxin renal and nonrenal clearance. Available data suggest that there is an increased vagal or chronotropic effect of digoxin in the presence of quinidine. The impact of this interaction on the inotropic effect of digoxin is unclear. Some case reports have implied increased inotropy,1,5 whereas assessment of left ventricular (LV) performance with systolic time intervals has suggested a decrease in inotropy.6,7 The goal of this investigation was to define the inotropic result of the digitalis-quinidine interaction in conscious dogs. The LV and left atrium (LA) were both examined because of the known differences in anatomic, biochemical, electrical and mechanical properties between atrium and ventricle. In addition, it has been shown that the LA and LV have similar wall velocities at rest, but the velocity of LV shortening was more sensitive to increases in afterload.8 Also, cholinergic control is different in the LA than in the LV.9,10 In this study, to ensure that the changes measured were changes in inotropy, the drug doses were chosen such that they did not alter heart rate, LV preload or afterload.

Methods

Experimental Preparation

The experiments were performed in 10 mongrel dogs (20–25 kg) using operative techniques described by Goldman et al.11,12 The dogs were anesthetized with halothane, nitrous oxide and oxygen and a left thoracotomy was performed in the fifth intercostal space. One set of sonomicrometer crystals (4–5 mm) was placed across the lateral dimension of the LA on the epicardial surface. One crystal was positioned just anterior to the insertion of the left pulmonary veins and the other was placed just anterior to the insertion of the right pulmonary veins. Another set of crystals was positioned across the endocardial surface of the LV to obtain measurements of its internal diameter in the minor axis. One LV crystal was placed through a diagonally directed stab wound created by a 16-gauge needle onto the posterior endocardial surface of the ventricle near the minor equator. The other endocardial crystal was placed slightly lateral to the left anterior descending coronary artery. The sonomicrometer crystals were attached to an electronics system (Triton Technology) described earlier.13 This instrumentation generates a voltage linearly proportional to the sound transit time, which is converted to length assuming a sound velocity of 1.55 mm/μsec. This results in an instantaneous and reproducible measure of internal LV diameter. The drift in the system is minimal and periodic calibrations are performed. The position of the crystals was confirmed by postmortem examination.

A high-fidelity micromanometer (P22 Königsberg Instruments) was placed into the LV cavity through a stab wound in the apex. In five dogs, a second manometer was placed in the LA cavity through the LA appen-
dage. This was done to verify the timing of the a-wave in the LA and LV pressure recordings. Atrial pacing wires (Davis and Geck) were sutured to the LA appendage. The wires were brought out underneath the skin to the dorsal surface of the neck and protected by a specially designed jacket (Alice King Chatham Co.). The dogs were treated with 400,000 U of procaine penicillin G and 500 mg dihydrostreptomycin sulfate intramuscularly daily for 3 days after operation. The dogs were allowed to recover for 14 days to achieve stable baseline values.

Measurements

The dogs were trained to lie quietly on the floor and were studied in the conscious, unsedated state. The LA diameter, LV internal diameter, ECG, LA and LV pressures and LV dp/dt were recorded continuously. A constant heart rate was maintained by atrial pacing.

Data were recorded on an oscillographic recorder (Electronics for Medicine, VR-6). Values for LV dp/dt were obtained from a differentiating circuit in the oscillographic recorder. LV velocity of circumferential fiber shortening (Vcf) was determined as the percent change in internal diameter divided by the LV ejection time (LVET). The onset of LV ejection was taken at peak LV dp/dt, which coincides with the onset of pressure increase in the aorta immediately above the aortic valve. The end of LV ejection was taken as the nadir of the ventricular diameter trace. In two dogs, this nadir was not well defined and the diameter was measured at peak negative LV dp/dt. LA Vcf was calculated in a manner similar to the ventricle: the percent change in diameter of the LA during systolic shortening divided by the LA ejection time. LA ejection time was defined as the time required for systolic shortening to occur. LA ejection was measured from the largest atrial diameter before atrial shortening to the nadir of the atrial diameter tracing (fig. 1). This approach has been used to calculate the change in LA velocity with increasing afterload, to define the extent of cholinergic sympathetic interaction in the control of LA function and to measure the effects of verapamil on inotropic responses in conscious dogs. To avoid respiratory variation, at least 10 beats were analyzed for each measurement. All experiments were performed on separate days and at least 72 hours were allowed to elapse after ouabain was used.

Experimental Protocol

Ouabain, 0.025 mg/kg, was administered over 30 seconds as a single i.v. dose and data were recorded every 10 minutes. The maximal inotropic responses occurred 30 minutes after dosing.

In six dogs, a quinidine bolus of 3.85 mg/kg was administered over 1 minute and followed by an infusion of 0.28 mg/kg/min for 1 hour with a Cormed infusion pump. Blood samples were obtained for serum quinidine measurements before and every 15 minutes for 2 hours after starting the infusion. At 60 minutes with stable hemodynamics, ouabain, 0.025 mg/kg, was administered as a bolus through a separate i.v. line and data were recorded every 10 minutes for 1 hour. The quinidine infusion was maintained during this period. In two dogs, the quinidine infusion alone was maintained for 90 minutes without administration of ouabain.

To determine if the basal heart rate altered the response to ouabain, on a separate day six dogs were given ouabain during atrial pacing at 103.3 ± 2.7 beats/min and the LV dp/dt was compared with that in six dogs paced at 125.9 ± 4.7 beats/min.

Differences between LV and LA inotropic responses were analyzed for statistical significance using the t test for paired data. When comparing the changes with ouabain to the changes with quinidine-ouabain and the changes in LV dp/dt at different heart rates, the responses were analyzed for statistical significance using the t test for unpaired data.

Results

The effects of ouabain in the control were compared with the effects of ouabain given during the quinidine infusion.

Effect of Ouabain

Ouabain resulted in an increase in LV dp/dt, and LV and LA fractional shortening but did not change LV

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** The effects of ouabain on left ventricular pressure (LVP), left atrial pressure (LAP), LV dp/dt and LV and LA wall motion. The left side of the panel is the control and the right side the response 30 minutes after ouabain administration, 0.025 mg/kg. The arrows define the start and end of LA ejection with atria systole. After ouabain, there is a marked increase in LV dp/dt, an increase in LV and LA fractional shortening and no change in heart rate or LV and LA pressure. Time lines are 0.04 second.
Effect of Ouabain in Conscious Dogs

Ouabain was infused during 70 min in conscious dogs. Atropine (0.025 mg/kg) was administered during the last 10 min of the ouabain infusion to minimize the effects of bradycardia. Ouabain produced a significant decrease in LV dP/dt (fig. 2). LV dP/dt increased 26.4 ± 3.5% in the control group, compared with 9.5 ± 2.3% after quinidine (p < 0.001). Similar differences were seen in the responses to ouabain in the absence and presence of quinidine: LV Vcf, 22.4 ± 4.9% vs 6.0 ± 2.1% (p < 0.02); LV fractional shortening, 23.1 ± 4.6% vs 5.8 ± 2.1% (p < 0.02); and LA Vcf, 22.7 ± 5.9% vs 4.8 ± 2.0% (p < 0.01); and LA Vcf.

Comparison of the Response to Ouabain in the Presence and Absence of Quinidine

The inotropic responses to ouabain in the control group were compared to the inotropic responses to ouabain given during the quinidine infusion (fig. 2). LV dP/dt increased 26.4 ± 3.5% in the control group, compared with 9.5 ± 2.3% after quinidine (p < 0.001). Similar differences were seen in the responses to ouabain in the absence and presence of quinidine: LV Vcf, 22.4 ± 4.9% vs 6.0 ± 2.1% (p < 0.02); LV fractional shortening, 23.1 ± 4.6% vs 5.8 ± 2.1% (p < 0.02); and LA Vcf, 22.7 ± 5.9% vs 4.8 ± 2.0% (p < 0.01); and LA Vcf.
TABLE 3. Quinidine Plasma Concentrations After a 3.85-mg/kg Bolus Followed by 0.28-mg/kg/min Infusion in Conscious Dogs

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Dog no.</th>
<th>Quinidine plasma concentration (μg/ml)</th>
<th>Mean ± SEM</th>
</tr>
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<tbody>
<tr>
<td>0.25</td>
<td>1</td>
<td>2.73</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.56</td>
<td>1.96</td>
</tr>
<tr>
<td></td>
<td>3</td>
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</tr>
<tr>
<td></td>
<td>4</td>
<td>2.80 ± 0.34</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>5</td>
<td>3.00</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5.34</td>
<td>2.14</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2.70 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>0.75</td>
<td>8</td>
<td>2.24</td>
<td>1.98</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2.67 ± 0.33</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>10</td>
<td>2.46</td>
<td>1.92</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>2.91 ± 0.45</td>
<td></td>
</tr>
<tr>
<td>1.25</td>
<td>12</td>
<td>5.95</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>2.45 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>1.50</td>
<td>14</td>
<td>2.97</td>
<td>1.77</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>3.36 ± 0.59</td>
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<td>1.75</td>
<td>16</td>
<td>2.91</td>
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<td></td>
<td>17</td>
<td>3.13 ± 0.60</td>
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</tr>
<tr>
<td>2.00</td>
<td>18</td>
<td>3.10</td>
<td>2.35</td>
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<td>20</td>
<td>2.46 ± 0.24</td>
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</tr>
<tr>
<td></td>
<td>21</td>
<td>2.93 ± 0.42</td>
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</tr>
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</table>

Fractional shortening, 21.8 ± 7.7% vs 7.8 ± 3.3% (p < 0.01).

Effect of Basal Heart Rate on the Response to Ouabain

Ouabain administration in six dogs paced at 103.3 ± 2.7 beats/min resulted in an increase in LV dP/dt of 685.7 ± 108.4 mm Hg/sec. This was not different from the increase of 476.7 ± 71.7 mm Hg/sec in the group paced at 125.9 ± 4.7 beats/min (p > 0.05).

Steady-state Quinidine Concentrations

Quinidine concentrations for the six dogs are shown in table 3. The mean serum quinidine concentration at 60 minutes was 2.92 ± 0.45 μg/ml, not significantly different from the concentration at 90 minutes, 3.21 ± 0.59 μg/ml (p > 0.05).

Discussion

Doses of quinidine that did not alter atrial or ventricular function in the conscious dog caused significant attenuation of the usual positive inotropic response to ouabain. Thus, the inotropic response to ouabain during the quinidine infusion was different from that to ouabain alone. For all measurements of cardiac function, there was a significantly greater percent increase after ouabain alone compared with ouabain in the presence of quinidine.

Previous clinical reports in man suggest that cardiac performance is enhanced when the serum digoxin concentration is increased during quinidine treatment. Two studies using systolic time intervals, however, have suggested a decrease in response to digoxin in the presence of quinidine. Steiness et al. followed the preejection period index after a single i.v. dose of digoxin with and without quinidine. They noted that the characteristic 20% increase in the preejection period index was significantly diminished when quinidine was coadministered. Hirsch et al. studied LVET and the QS interval in a group of normal persons before digoxin, during steady-state digoxin therapy, during steady-state digoxin and quinidine therapy, and during steady-state quinidine administration. Digoxin decreased the LVET and QS, and the addition of quinidine caused the LVET to lengthen significantly. Quinidine alone caused a small but insignificant lengthening of the LVET and QS. Despite an increase in the serum digoxin concentration with the addition of quinidine, the systolic time interval changes were consistent with a decrease in LV function.

The positive inotropic response to ouabain in the present study is similar to that reported with acute administration of ouabain11, 14 and chronic administration of digoxin. Although these previous reports focused on changes in LV function, similar responses have been documented in both the LV and LA. In the present study, the administration of ouabain resulted in a small but insignificant increase in end-diastolic diameter and LVSP (table 1). This has been reported previously20 and is probably due to the increase in peripheral resistance seen with the acute administration of digitalis preparations.

Quinidine at higher doses than used here has been reported to decrease LV function in conscious dogs.21 This response seems to be dose-related; no depression of cardiac performance has been reported at doses similar to those used in this experiment.22 Therefore, the dose of quinidine that was chosen had no effect on wall motion or hemodynamics. In two dogs the quinidine was administered for 90 minutes without ouabain to demonstrate that the lack of an inotropic response to ouabain in the presence of quinidine was not due to an independent negative inotropic effect of quinidine.

The ouabain-quinidine interaction affects both LA and LV performance in an identical manner. This is an important observation because of the frequent use of isolated atrial preparations to study cardiovascular pharmacology. In the past, investigators have extrapolated conclusions from these in vitro experiments to man. With the instrumentation used in this study, one can measure changes in LA wall velocities with pharmacologic interventions in conscious dogs.

The best explanation for the negative inotropic consequences of this interaction would be displacement of cardiac-bound ouabain by quinidine. Doherty et al. gave dogs triitated digoxin alone and with quinidine. They reported a decrease in the digoxin concentration in the heart and an increase of 50% in the digoxin in the subcortical white matter of the brain. The same group of investigators have reported that quinidine eliminated binding sites that were unoccupied by ouabain. Similar results were found in skeletal muscle binding in man.25 Using a cat papillary muscle preparation, Williams et al. demonstrated that pretreatment with quinidine inhibited the positive response to digoxin. Also, quinidine has been shown to reduce the affinity of Na, K-ATPase for digoxin. Digoxin has been reported to be bound to the peripheral autonomic cardiac nervous system as well as to the heart itself. These observations would be consistent with our hemodynamic results that suggest a displacement of ouabain from active myocardial sites by quinidine.

Increased heart rate has a positive inotropic effect itself. It has also been suggested that the greater the
contractile state of the heart, the less the subsequent inotropic response from digitalis.29, 30 Therefore, we had to establish that the attenuated response to ouabain in the presence of quinidine was not a result of the higher heart rate in the latter experiment. For this reason, the inotropic response to ouabain was measured in a group of dogs at different paced heart rates and was not different. These results are consistent with those of Horwitz et al.,30 who found that the increase in LV dP/dt after ouabain was similar in dogs at rest compared with dogs given atropine.

Assuming that these observations in conscious dogs can be translated to cardiovascular effects in man, they suggest that the digitalis-quinidine interaction results in a decreased inotropic effect in spite of the observation of increased serum digoxin concentrations after quinidine administration. This study examines only the mechanical and not the electrophysiologic effects of this interaction, but it suggests that if digitalis toxicity is increased after quinidine administration, it is not the result of an increase in the effects of digitalis on the myocardium, but may be a manifestation of increased digitalis concentration elsewhere in the body. Clinical toxicity in terms of gastrointestinal symptoms and life-threatening ventricular arrhythmias have been documented in the presence of the concomitant use of digoxin and quinidine. The severity of these toxic symptoms requires a reevaluation of the approach of increasing the dose of digoxin in the presence of quinidine to compensate for diminution in the inotropic effect of the glycoside.

References
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