Effects of Cardiac Depression and of Anesthesia on the Myocardial Action of a Cardiac Glycoside

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ABSTRACT The effects of ouabain (G-strophanthin) 20 μg/kg, on left ventricular (LV) pressure (P), diameter (D), velocity of contraction (dD/dt), and dP/dt were studied in conscious dogs instrumented with ultrasonic diameter gauges and miniature pressure gauges. The effects of ouabain were compared on separate occasions in the same dogs after cardiac depression with propranolol, 3.0 mg/kg, and also after general anesthesia with Na pentobarbital, 30 mg/kg. Maximal pressor effects were observed in the first 10 min, but maximal effects on the contractile state occurred at 30 min after ouabain. At this time, in conscious dogs, ouabain had increased LV isovolumetric systolic pressure by 5%, LV isovolumetric velocity by only 9%, and LV (dP/dt)/P by 21%, while end systolic diameter (ESD) decreased slightly and end diastolic diameter (EDD) and heart rate (HR) were unchanged. After anesthesia, ouabain increased LV systolic pressure by 8%, velocity 32%, (dP/dt)/P by 47%, and ESD decreased by 1.2 mm while EDD rose slightly and HR fell by 26 beats/min. Returning HR to control with atrial pacing decreased EDD 0.9 mm below control. After cardiac depression with propranolol, ouabain caused responses similar to those observed in the anesthetized dogs. Thus, the cardiac glycoside was found to exert only minor inotropic effects on the nonfailing heart of conscious dogs but far more striking inotropic responses in the anesthetized state.

INTRODUCTION

The classic studies of Cattell and Gold demonstrated the inotropic properties of a digitalis glycoside in the papil-

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lary muscle preparation (1) and since then it has been generally accepted that the beneficial clinical effects of these drugs in patients with heart failure and sinus rhythm results from this action (2-5). The failure of glycosides to increase cardiac output in human subjects and experimental animals without heart failure led to the suggestion that these agents exert qualitatively different effects on the normal and failing heart (6-11). It was subsequently shown in open chest, anesthetized, nonfailing dog (12-16) and human hearts (17) that the glycosides substantially augment the myocardial contractile state. Later investigations in unanesthetized subjects with trivial or mild heart disease demonstrated an inotropic action in this setting as well (18, 19). Thus the majority of evidence indicates that cardiac glycosides stimulate the contractility of the nonfailing heart. However, the previous studies utilizing isolated cardiac muscle or anesthetized open chest preparations (12-17, 20) may have been biased to the extent that anesthesia or surgical manipulations alter the myocardial contractile state (21-24) while the studies in conscious man utilized indirect means of evaluating the contractile state (18, 19, 25).

The present investigation, employing currently accepted indicators of contractility, was carried out in healthy conscious dogs instrumented for the continuous measurement of left ventricular pressure, dimensions, dP/dt, and velocity of shortening. It was designed to clarify the mechanisms of action of a cardiac glycoside by characterizing the effect of ouabain in healthy conscious dogs and comparing the effects of the glycoside in the same animals after the induction of general anesthesia with Na pentobarbital and after myocardial func-

Abbreviations used in this paper: D, diameter; dD/dt, velocity of contraction; dP/dt, time rate of change of pressure; EDD, end diastolic diameter; ESD, end systolic diameter; HR, heart rate; LV, left ventricular; P, pressure.
Figure 1 A typical record in one of the experimental animals. The instantaneous records of left ventricle diameter, velocity, pressure, dP/dt, and heart rate are shown at fast and slow paper speeds. A, in the conscious state during control and early response to ouabain on the left and 30 min after ouabain on the right. B, the same dog studied anesthetized, control and early response to ouabain on the left and response at 30 min on the right; C, same dog after propranolol, control and early response to ouabain on left, response at 30 min on right.
tion had been depressed with large doses of propranolol. In this manner the differences could be reconciled between the effects observed in this study in conscious dogs and those reported previously in nonfailing hearts, which were obtained primarily from anesthetized prepa-

METHODS

Eight mongrel dogs, weighing between 17 and 25 kg, were anesthetized with Na pentobarbital, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges were implanted within the left ventricle through a stab wound in the apex. Opposing ultrasonic diameter transducers were sutured to the epicardium of the anterior and posterior left ventricle. Stimulator electrodes were sutured to the left atrium.

The experiments were conducted 2–6 wk postoperatively, when the dogs had recovered from operation and were again vigorous and healthy. While the dogs were resting quietly or sleeping, control records of left ventricular pressure (P) and diameter (D), the time rate of change of diameter (dD/dt), the time rate of change of pressure (dP/dt), and heart rate were obtained. Ouabain, 0.02 mg/kg, a dose which does not produce toxic side effects, was administered in a bolus intravenously and recordings were obtained continuously for the subsequent 30 min. In six dogs heart rate was controlled during the experiment with atrial stimulation.

All eight dogs were also studied on a separate day after general anesthesia had been induced with Na pentobarbital, 30 mg/kg. In these experiments respiration was controlled with a Harvard pump to prevent anesthesia induced hypoxia or acid base imbalance. Arterial blood gas and pH measurements in this situation are not significantly different from values obtained in the conscious state. In seven of these experiments heart rate was returned to control levels by means of atrial stimulation for 1 min periods each at 5, 10, 15, and 30 min following ouabain. Six of the eight dogs were also studied in the conscious state after the administration of a large dose of propranolol, 3.0 mg/kg. Beta adrenergic blockade can be achieved with much smaller doses and such a large dose, in addition to producing complete blockade, exerts a direct depressant effect on myocardial function. Three dogs were also studied after cholinergetic blockade with atropine 0.2 mg/kg, a dose which blocked the changes in heart rate and arterial pressure observed with acetylcholine 4 µg/kg. Experiments in the same animal were conducted at intervals of 3–7 days to insure complete disposition of the glycoside administered in the course of the previous experiment. Three dogs were studied in the conscious state for the first time, three dogs were studied first while anesthetized, and two dogs were studied after propranolol first.

The left ventricular pressure gauges (27), were calibrated in vivo against a calibrated Statham P23 Db strain gauge manometer. At autopsy the position of the miniature pressure transducer within the ventricular lumen was confirmed. An electronic pacemaker was used for atrial stim-

uloration. An improved ultrasonic transit time dimension gauge was used to measure left ventricular diameter; the principle of operation is similar to other ultrasonic gauges described previously (28–30). In brief, the instrument measures the transit time of acoustic impulses travelling at the sonic velocity of approximately 1.5 × 10^6 mm/sec between the 5 MHz piezoelectric crystals sutured to the left ventricular epicardium at opposing sites. The transit time was calibrated by substituting signals of known time duration from a pulse generator which was referenced to a quartz crystal controlled oscillator frequency. A voltage proportional to transit time is recorded and calibrated in terms of crystal separation. In this manner a measure of the external diameter of the left ventricle is continuously recorded. At a constant temperature the drift of the instrument is less than 0.15 mm/hr, and its frequency response is 0 to 100 Hz.

The signals were directly coupled to a multichannel tape recorder and played back on a direct writing oscillograph at a paper speed of 100 mm/sec. A cardiotachometer triggered by the signal from the pressure pulse provided instantaneous and continuous records of heart rate. Continuous records of dP/dt and dD/dt were derived from the left ventricular pressure and diameter signals using Philbrick operational amplifiers connected as differentiators. A triangular wave signal with known slope (rate-of-change) was substituted for pressure and a computer to calibrate directly the dP/dt and dD/dt channels.

The actions of ouabain on myocardial force-velocity relations were assessed by determining its effects on the velocity of shortening and intraventricular pressure (P) at an identical ventricular diameter (D) by the technique described in detail previously (31). When, at any given instantaneous myocardial diameter or length, (isolength point), the velocity of shortening (V_{isolength}, i.e., V_{iso}) increases while intraventricular pressure (P_{isolength}, i.e., P_{iso}) rises or remains constant, a shift in myocardial force-velocity relations reflecting a positive inotropic effect is considered to have occurred. All isolength points were obtained during the first one-third of ejection. In addition, the effects of peak dP/dt and the relations of dP/dt to developed pressure, i.e., (dP/dt)/P) were examined (32, 33). The latter was calculated as the quotient of dP/dt to left ventricular pressure minus end diastolic pressure; the same level of pressure which occurred during the isovolumetric contraction period, before and after ouabain and in the control, anesthetized, and propranolol-treated animals was used for this calculation and dP/dt was always measured at that level of pressure. This technique for evaluating the myocardial contractile state has been described in detail previously (32, 33).

RESULTS

**Control (conscious) dogs.** In all eight dogs studied in the conscious state left ventricular pressure increased from 118 ± 5 (SEM) mm Hg to 130 ± 6 mm Hg at 3-5 min following the administration of the drug, and gradually fell to 124 ± 5 mm Hg at 30 min. (Table 1). Left ventricular end diastolic pressure did not change significantly, from an average value of 7 ± 1 mm Hg, V_{iso} gradually increased, to reach a maximum of 9 ± 2%

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2 Konigsberg Pn, Konigsberg Instruments, Inc., Pasadena, Calif.
3 Construction details available from authors.
5 Medtronic, Inc., Minneapolis, Minn.
6 Statham Instruments, Inc., Los Angeles, Calif.

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above a control of 68 ± 4 mm/sec at 15–30 min following injection, while peak dP/dt rose to a maximum of 20 ± 2% above a control of 3440 ± 170 mm Hg per sec at the same time (Figs. 1, 2); (dP/dt)/P rose from a level of 51 ± 5 sec⁻¹ to reach a peak value of 21 ± 2% above control at 30 min. The timing of the increase in

### Table I

**Effects of Ouabain in Conscious**

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Heart rate</th>
<th>Pressure (systolic/endo diastolic)</th>
<th>Peak dP/dt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control/ Ouabain*</td>
<td>Control/ Ouabain*</td>
<td>Control/ Ouabain*</td>
</tr>
<tr>
<td></td>
<td>beats/min</td>
<td>mm Hg</td>
<td></td>
</tr>
<tr>
<td>Dog 1</td>
<td>Conscious</td>
<td>72/66</td>
<td>144/7</td>
</tr>
<tr>
<td></td>
<td>Anesthetized</td>
<td>115/81</td>
<td>137/7</td>
</tr>
<tr>
<td></td>
<td>Anesthetized paced</td>
<td>115</td>
<td>152/4</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>68/62</td>
<td>147/9</td>
</tr>
<tr>
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<td>Conscious</td>
<td>62/62</td>
<td>121/7</td>
</tr>
<tr>
<td></td>
<td>Anesthetized</td>
<td>114/86</td>
<td>117/8</td>
</tr>
<tr>
<td></td>
<td>Anesthetized paced</td>
<td>114</td>
<td>124/5</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>62/56</td>
<td>109/9</td>
</tr>
<tr>
<td>Dog 3</td>
<td>Conscious</td>
<td>66/65</td>
<td>126/5</td>
</tr>
<tr>
<td></td>
<td>Anesthetized</td>
<td>114/76</td>
<td>127/5</td>
</tr>
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<td>114</td>
<td>148/4</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>66/58</td>
<td>122/8</td>
</tr>
<tr>
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<td>87/80</td>
<td>108/5</td>
</tr>
<tr>
<td></td>
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<td>122/104</td>
<td>102/6</td>
</tr>
<tr>
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<td>110/4</td>
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<td>104/9</td>
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<td>100/9</td>
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<tr>
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<td>Anesthetized paced</td>
<td>120</td>
<td>106/6</td>
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<tr>
<td></td>
<td>Propranolol</td>
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<td>100/11</td>
</tr>
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<td>105/8</td>
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<td>Anesthetized paced</td>
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<tr>
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<td>136/10</td>
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<td>128/7</td>
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<tr>
<td>Dog 8</td>
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<td>102/7</td>
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<tr>
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<td>Anesthetized</td>
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<td>98/6</td>
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<tr>
<td>Average</td>
<td>Conscious</td>
<td>75 ± 4</td>
<td>73 ± 4</td>
</tr>
<tr>
<td></td>
<td>Anesthetized</td>
<td>117 ± 9</td>
<td>92 ± 4</td>
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<tr>
<td></td>
<td>Anesthetized paced</td>
<td>119</td>
<td>126 ± 7/5</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>75 ± 4</td>
<td>68 ± 4</td>
</tr>
</tbody>
</table>

*Results at 30 min.
† Isolength.

S. F. Vatner, C. B. Higgins, T. Patrick, D. Franklin, and E. Braunwald
(dP/dt)/P following ouabain closely paralleled the increase in V_{10} (Fig. 3). Heart rate decreased from an average of 75 ± 4 beats/min, to a minimum level 13 ± 2% below control during the first 5 min and gradually returned to within 2% of control at 30 min. Left ventricular end diastolic diameter showed no significant

### Anesthetized, and Propranolol-Treated Dogs

<table>
<thead>
<tr>
<th>dP/dt (sec⁻¹)</th>
<th>Diameter (end diastolic/end systolic)</th>
<th>Velocity†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control Ouabain*</td>
<td>Control Ouabain*</td>
</tr>
<tr>
<td></td>
<td>mm mm/sec</td>
<td>mm/sec</td>
</tr>
<tr>
<td>37</td>
<td>43 63.2/56.2 63.4/55.4</td>
<td>56 60</td>
</tr>
<tr>
<td>20</td>
<td>29 61.5/56.4 62.6/55.5</td>
<td>36 51</td>
</tr>
<tr>
<td>33</td>
<td>49 63.8/57.0 63.7/56.2</td>
<td>49 60</td>
</tr>
<tr>
<td>43</td>
<td>57 70.8/60.6 70.8/60.4</td>
<td>81 88</td>
</tr>
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<td>47 68.3/61.4 68.7/59.9</td>
<td>65 88</td>
</tr>
<tr>
<td>48</td>
<td>48 67.7/59.9</td>
<td>86</td>
</tr>
<tr>
<td>35</td>
<td>55 72.0/62.8 71.8/60.8</td>
<td>62 104</td>
</tr>
<tr>
<td>41</td>
<td>50 68.1/61.4 68.0/60.6</td>
<td>66 72</td>
</tr>
<tr>
<td>22</td>
<td>36 65.9/61.8 66.7/61.1</td>
<td>42 60</td>
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<td>33</td>
<td>48 68.6/62.1 68.6/61.3</td>
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<td>62 64.6/59.6 65.0/58.1</td>
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<td>51 72</td>
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<tr>
<td>46</td>
<td>63 71.0/66.8 71.0/66.2</td>
<td>64 74</td>
</tr>
</tbody>
</table>

| 51 ± 5        | 62 ± 5 67.4 ± 1.9/60.2 ± 1.0 67.4 ± 1.4/59.5 ± 0.8 | 68 ± 4 74 ± 4     |
| 33 ± 3        | 48 ± 4 65.8 ± 1.7/60.7 ± 1.5 66.1 ± 0.9/59.5 ± 1.2 | 48 ± 4 63 ± 4     |
| 49 ± 5        | 49 ± 5 64.2 ± 1.6/58.6 ± 1.3                          | 61 ± 5     |
| 41 ± 4        | 62 ± 6 66.6 ± 1.3/59.8 ± 0.9 66.3 ± 0.7/58.5 ± 1.6 | 52 ± 2 75 ± 7     |

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change and end systolic diameter decreased gradually and only slightly. Intermittently returning heart rate to control values by means of atrial stimulation did not significantly alter any results. When four of the dogs were restudied in the conscious state in a separate occasion, the effects of ouabain were not significantly different from their individual initial responses.

Propranolol. Propranolol, 3.0 mg/kg, slightly increased end diastolic and systolic diameters and end diastolic pressure, decreased $V_{100}$ ($P < 0.01$), peak $dP/dt$ ($P < 0.01$), and $(dP/dt)/P$ ($P < 0.01$) and did not significantly change left ventricular systolic pressure or heart rate. In the six conscious dogs studied after the administration of propranolol, ouabain caused similar early increases in left ventricular systolic pressure and decreases in heart rate as in the control dogs. End diastolic diameter decreased by an average of 0.3 ±0.1 mm at 30 min from a control value of 66.6 ±1.3 mm, and end diastolic pressure declined from 9 ±1 to 7 ±1 mm/Hg. End systolic diameter decreased by 1.3 ±0.2 mm from a control of 59.8 ±0.9 mm. Ouabain increased $V_{100}$ by 47 ±6%, above a control value of 52 ±2 mm/sec, to a value of 75 ±7 mm/sec, which was almost identical with that attained by the conscious dogs after ouabain (Fig. 4). A similar large increase was noted in left ventricular $(dP/dt)/P$ (50 ±3%) (Fig. 5) while peak $dP/dt$ increased by 46 ±4% above a control of 2750 ±190 mm Hg/sec at 30 min. The increases in $V_{100}$, peak $dP/dt$, and $(dP/dt)/P$ produced by ouabain were two to three times as great as those observed in the same dogs when they had not received propranolol; these increases were significantly greater ($P < 0.01$) when expressed either in terms of per cent change from control or in absolute values.

Cholinergic blockade. In three conscious dogs given atropine, 0.2 mg/kg, in which heart rate was controlled with atrial stimulation the effects exerted by ouabain were similar to those observed in the control dogs. Left ventricular pressure increased from 127/4 to 137/4 at 30 min; $V_{100}$ increased by 8% and $(dP/dt)/P$ increased by 17%.

Anesthesia. Pentobarbital, 30 mg/kg, reduced $dP/dt$, ($P < 0.01$), $(dP/dt)/P$ ($P < 0.01$) and $V_{100}$ ($P < 0.01$). Pentobarbital increased heart rate but did not significantly affect pressure; end diastolic diameter decreased slightly and end systolic diameter increased slightly. Initially the heart rate after anesthesia was higher, but fell to 117 ±9 beats/min when ventilation was improved by the respirator. However, the average resting heart rate value in the conscious state, 75 ±4 beats/min, was significantly lower than that obtained in the anesthetized state, 117 ±9 beats/min ($P < 0.01$). In the eight dogs studied in the anesthetized state, ouabain increased left ventricular $P_{iso}$ to a similar extent as in the control state. Heart rate decreased to a greater extent ($P < 0.01$), falling by 29 ±3% below 117 ±9 beats/min at 3–5 min, representing a maximal reduc-

![Figure 2](image-url) The average (±SEM) changes in a variety of circulatory measurements. Changes 30 min after ouabain are compared in eight conscious dogs (left panel); in eight anesthetized dogs, both when heart rate was allowed to vary and after atrial stimulation (middle panel), and in the six dogs after propranolol (right panel).

![Figure 3](image-url) The average (±SEM) responses to ouabain at 1, 3, 5, 10, 15, and 30 min in eight conscious dogs. The changes in left ventricular diameter are shown in mm, while the changes in left ventricular pressure, velocity, $dP/dt$, and heart rate are shown as per cent changes from control. Average control values for the conscious dogs are shown before ouabain administration.
tion of 32 ± 5 beats/min and remaining depressed by 19 ± 4% at 30 min. As was the case for propranololtreated dogs, in the pentobarbital-anesthetized animals, ouabain increased $V_{a+}$ and peak $(dP/dt)/P$ to a much greater extent than in the conscious, control state. The increases were significantly greater ($P < 0.01$) when expressed either in terms of per cent change from control or in absolute values. $V_{a+}$ rose to a maximum at 30 min of 32 ± 3% above a control of 52 ± 2 mm/sec and peak $dP/dt$ increased to a maximum of 46 ± 8% above a control of 2230 ± 140 mm Hg/sec 30 min after the glycoside, while $(dP/dt)/P$ rose 48 ± 3% from a control value of 33 ± 3 sec$^{-1}$.

End diastolic diameter increased slightly (Figs. 1, 2) while end systolic diameter decreased to a greater extent than in the conscious, control state, by 1.2 ± 0.2 mm at 30 min. Heart rate declined by 26 beats/min below control at 30 min. Returning heart rate precisely to control with atrial stimulation at 30 min, a maneuver which did not affect left ventricular end diastolic or end systolic diameters or end diastolic pressure in the conscious dogs, caused end diastolic diameter to decrease by 0.9 ± 0.2 mm below control and end diastolic pressure to decrease from 7 ± 1 to 5 ± 1 mm Hg in the anesthetized dogs but did not affect the reduction in systolic diameter. The changes in systolic pressure, $V_{a+}$ and $(dP/dt)/P$ were not significantly affected by controlling heart rate (Fig. 2).

**DISCUSSION**

In the nonfailing heart of the conscious dog in the control state a relatively large dose of ouabain produced only a slight positive inotropic response; left ventricular velocity and pressure, at isovelocity points, both rose minimally, by averages of only 9 and 5% respectively. Ventricular end diastolic diameter was unaltered 30 min after ouabain, and thus increases in the rate of pressure development and rate of myocardial shortening reflect an improvement in the contractile state of the myocardium. However, these improvements in the myocardial contractile state are substantially less than those observed in earlier studies (1, 12–20).

A number of associated effects of ouabain might have attenuated a direct inotropic effect. For example, digitalis glycosides increase vagal activity and to a great extent, it is this mechanism which is responsible for the slowing of heart rate produced by this drug (34–36). Both vagal activation (37) and bradycardia tend to reduce myocardial contractility (38–40) and therefore significant bradycardia and negative inotropic effects mediated by the vagi might have interfered with the positive inotropic effects of the glycoside. In the present study, however, heart rate returned to within 2% of control 30 min following ouabain and it was not deemed likely that such a small change in rate seriously interfered with the positive inotropic effect. Furthermore, in six dogs, heart rates were returned precisely to control levels by means of atrial stimulation, and the observed positive inotropic effects were no greater. In order to
study the possible influence of increased vagal activity on contractility, the effects of ouabain were restudied in three dogs after cholinergic blockade with atropine. This intervention also had little effect on the response of the conscious dog to the glycoside. Thus, it does not appear that increased vagal activity masked the inotropic action of ouabain.

Daggett and Weisfeldt have suggested that a reflex withdrawal of sympathetic stimulation of the myocardium is caused by the elevation of arterial pressure that occurs after digitalis administration and that this reflex reduction in contractility opposed the direct positive inotropic action of the drug (41). It is unlikely that this mechanism was operative in the present study since the maximal effects of ouabain on contractility were observed 15-30 min after the drug, at a time when pressure had returned almost to control levels. The reflex withdrawal of sympathetic tone, as proposed by Daggett and Weisfeldt, should have occurred also in the anesthetized state, since pressure increased in these experiments as well. However, despite the rise in pressure, ouabain elicited a much more profound inotropic effect in the anesthetized state.

The temporal difference between the peak systemic arterial pressor effect of cardiac glycosides and their maximal inotropic action has been noted previously in anesthetized humans (17). The maximal increases in total systemic resistance and resistances in the regional circulations occur early after ouabain administration in both conscious and anesthetized dogs as well (42, 43). Since in the present experiments the peak inotropic action occurred later, at a time when pressure had returned almost to control, changes in peripheral resistance should not have significantly influenced measurements of velocity of contraction or dP/dt. This reasoning is substantiated by the fact that dP/dt and (dP/dt)/P, which is relatively independent of changes in afterload, reached similar levels when the peak inotropic effects of ouabain occurred. (Fig. 3).

An effort was made to reconcile the differences between the present findings of only a small inotropic effect and the much greater inotropic effects elicited by digitalis, reported previously in studies conducted in anesthetized preparations, (1, 12-17, 20). Accordingly, the effects of ouabain were compared in the same dogs studied in the conscious and anesthetized state. Despite a much greater reduction in heart rate, and a slightly greater increase in left ventricular systolic pressure than that occurring in conscious dogs, ouabain increased the velocity of myocardial fiber shortening by 32% in the anesthetized state, an increase more than three times that observed in the same dogs studied while in the conscious state. Correspondingly greater increases in dP/dt and (dP/dt)/P were also observed (Fig. 5). Similar increases in velocity and dP/dt were maintained in the anesthetized dogs when electrical stimulation returned heart rate to control (Fig. 2). Cardiac glycosides have been reported to reduce end diastolic ventricular size in the nonfailing heart of anesthetized animals (8, 44), and in studies in conscious man, utilizing radiographic techniques to assess cardiac size (45, 46). However, when cardiac size was measured directly and continuously in the conscious dog in the present investigation and in the study by Horwitz and Bishop (47) ouabain did not have this effect and end diastolic diameter remained at control.

The greater augmentation of the contractile state produced by digitalis in the anesthetized compared to the conscious state may be related to the pentobarbital-anesthesia-induced depression of myocardial contractility. This did occur, as reflected in the significantly lower base line values of V.<sub>100</sub>, peak dP/dt, (dP/dt)/P Fig. 5), and a depression of the force-velocity relationship (Fig. 4), before the administration of the glycoside. This is not surprising since barbiturates (21-24) and other anesthetics, such as halothane (21, 24, 48) have been reported to cause myocardial depression, and digitalis has been shown to be protective in anesthetic-induced myocardial depression by these agents (49, 50).

The fundamental mechanism responsible for the more profound stimulation of myocardial contractility by ouabain after anesthesia is not clear. However, there is evidence to suggest that barbiturates inhibit calcium uptake by the sarcoplasmic reticulum (51), and at the same time increase the binding of calcium to phospholipid of the sarcoplasmic reticulum (52), which would act to decrease calcium stores and interfere with the excitation-contraction coupling mechanism (53). It has been reported that ouabain reverses the inhibition of calcium uptake by the sarcoplasmic reticulum (51) and can also reverse the affinity of sarcoplasmic reticulum phospholipid for barbiturate (52). Thus, it is possible that the depression of contractility induced by anesthesia is specifically reversible by the cardiac glycoside.

It is also possible that the extent of stimulation of contractility by cardiac glycosides is conditioned by the level of contractility present before the administration of the drug; a lower initial level permitting a greater effect, and vice versa. To test this possibility the effects of ouabain were reexamined in the same dogs in the conscious state after the myocardial contractile state had been depressed by a different agent, propranolol. In the large dose employed (3 mg/kg) this drug reduced the heart's contractile state both by blocking sympathetic stimulation of the myocardium, as well as by a nonspecific, direct effect (26). The elevation of contractile
state induced by ouabain in the propranolol-depressed heart of the conscious dog was found to be similar to that observed in the anesthetized dog. This supports the major finding of this investigation, i.e., that digitalis augments myocardial contractility significantly in the depressed heart but exerts only a slight effect on the nonfailing heart of normal, healthy conscious dogs.

It has previously been suggested that the inotropic effects of digitalis are dependent on catecholamines and that these effects can be attenuated by prior treatment with reserpine or beta adrenergic receptor blocking agents (54-57). If this were the case then little increase in contractility would have been observed with ouabain after beta receptor blockade, when in fact the increases were actually far greater than in the conscious dogs without propranolol. This finding in the intact conscious dog supports the conclusion derived from other studies (20, 58-62) that cardiac glycosides act independently of cardiac catecholamine stores.

Thus, cardiac glycosides exert a relatively minor inotropic effect on the nonfailing heart of the normal, healthy conscious animal but substantially augment myocardial contractility in the anesthetized animal. We have previously shown that the circulatory response to carotid sinus nerve stimulation is radically altered by general anesthesia (63) and the results of this study demonstrate again the profound effect of general anesthesia on the circulatory response to a variety of interventions. It may be that the results of studies in anesthetized preparations, on which so many current concepts of cardiovascular physiology and pharmacology are based, are biased by the prior administration of an anesthetic agent which alters the central nervous system's regulation of circulatory responses and which also depresses the contractile state of the myocardium.

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REFERENCES

the heart: review Anesth. Analg. 39: 487.
1964. Left ventricular dynamics in dogs during anes-
thesia with alpha-chloralose and sodium pentobarbital.
Amer. J. Cardiol. 13: 349.
The mechanics of left ventricular contraction in acute
and its role in the response to anesthesia and surgery.
Anesthesiology. 30: 519.
Cohen, and C. D. Schoenfeld. 1964. The effect of digi-
talis on ventricular ejection in normal human subjects.
Circulation. 29: 721.
consumption in acute experimental cardiac depress-
ion. Circ. Res. 21: 123.
of blood pressure from free ranging animals via an
Left ventricular dimensions recorded by sonocardi-
29. Franklin, D. L., R. L. Van Citters, and R. F. Rush-
mer. 1962. Left ventricular function described in physi-
30. Stegall, H. F., M. B. Kardon, H. L. Stone, and V. S.
Appl. Physiol. 23: 289.
Myocardial force-velocity relations studied in intact un-
Covell, J. Ross, Jr., and H. S. Marcus. Assessment of
cardiac contractility: the relation between the rate of
pressure rise and ventricular pressure during isovolumic
systole. Circulation. 44: 47.
33. Wolk, M. J., J. F. Keefe, O. H. L. Bing, L. J. Finkel-
stein, and H. J. Levine. 1971. Estimation of Vmax in
auxotonic systoles from the rate of relative increase in
isovolumic pressure: (dP/dt)/Kp. J. Clin. Invest. 50:
1276.
Sur le mecanisme reflexe de la bradycardie provoquee
44: 31.
Wang. 1967. Mechanisms of bradycardia induced by
tropic effects of cardiac glycosides in cats, dogs,
man. 1965. Depression of ventricular contractility by
stimulation of the vagus nerves. Circ. Res. 17: 222.
1963. Intrinsic effects of heart rate on left ventricular
39. Boerth, R. C., J. W. Covell, P. E. Pool, and J. Ross,
Jr. 1969. Increased myocardial oxygen consumption and
contractile state associated with increased heart rate in
40. Covell, J. W., J. Ross, Jr., R. Taylor, E. H. Sonnen-
blick, and E. Braunwald. 1967. Effects of increasing fre-
quency of contraction on the force-velocity relation of
the sympathetic nervous system on the response of the
normal heart to digitalis. Amer. J. Cardiol. 16: 394.
42. Vatner, S. F., C. B. Higgins, D. Franklin, and E.
Braunwald. 1971. Effects of digitalis glycoside on coro-
nary and systemic dynamics in conscious dogs. Circ.
Res. 28: 470.
43. Higgins, C. B., S. F. Vatner, D. Franklin, and E.
Braunwald. 1971. Effects of digitalis on regional vas-
cular resistances in conscious dogs with and without ex-
str.)
44. Cusmny, A. R. 1925. Digitalis and its allies. Longmans,
Green and Co., Ltd., London. 112.
45. Stewart, H. J., and A. E. Cohn. 1932. Studies on the
effect of the action of digitalis on the output of blood
from the heart. III. J. Clin. Invest. 11: 917.
46. Eddleman, E. E., Jr., K. Willis, M. J. Greve, and H. E.
Heyer. 1951. The effect of digitoxin on the apparent
stroke volume, postero-anterior cardiac diameter, and
the cardiac cycle in normal subjects as studied by the
47. Horwitz, L. D., and V. S. Bishop. 1970. Effects of oua-
bain on left ventricular performance in conscious dogs.
48. Shimosato, S., T. H. Li, and B. Etsten. 1963. Ventricu-
lar function during halothane anesthesia in closed chest
1961. The effect of digitoxin pretreatment on heart con-
tractile force during thiopentol infusion in dogs. Anes-
esthesiology. 22: 974.
digitalized heart during halothane anesthesia. Anesthesi-
ology. 24: 41.
lum uptake by cardiac vesicles: inhibition by amytol
and reversal by ouabain. Biochem. Z. 345: 122.
influence of amobarbital and ouabain on calcium bind-
ing to phospholipids isolated from cardiac sarcoplasmic retic-
The mechanism of the effects of sodium pentobarbital
and norepinephrine on isolated cardiac muscle. Arch.
Int. Pharmacodynam Ther. 138: 276.
54. Tans, R. D. 1964. The action of ouabain on cardiac
muscle treated with reserpine and dichloroisoproterenol.
55. Tans, R. D., and S. M. Marcus. 1966. Influence of en-
dogenous cardiac catecholamine depletion on the force
and rate of isolated heart preparations and their re-
56. Levy, J. V., and V. Richards. 1965. The influence of
reserpine pretreatment on the contractile and metabolic
effects produced by ouabain on isolated rabbit left atria.
57. Tans, R. D., W. M. Coram, C. Brining, and T. Cava-
lie. 1968. The inotropic action of ouabain in relation

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