Depressant Effects of Quinidine Gluconate on Left Ventricular Function in Conscious Dogs with and Without Volume Overload

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with the technical assistance of Linda Van Nyhuis

SUMMARY To assess the effects of quinidine gluconate on left ventricular (LV) performance, sonomicrometer length gauges and micromanometer catheters were implanted in 17 conscious dogs. Studies were carried out before and after the development of volume overload LV hypertrophy induced by an aortocaval fistula. Quinidine gluconate was given intravenously in two successive doses of 6 mg/kg, yielding serum levels in the usual therapeutic range. In eight normal dogs, the heart rate increased (p < 0.01), LV end-diastolic pressure (EDP) fell (p < 0.01), and peak LV systolic pressure (SP) was unchanged 15 minutes after the second dose. Mean normalized shortening rate (MNSR) decreased (p < 0.05) and dP/dt at 40 mm Hg of developed pressure (dP/dt 40) was unchanged. When the heart rate was held constant by atrial pacing during β-adrenergic blockade induced by propranolol 0.5 mg/kg, quinidine resulted in a fall of LVSP from 123.7 ± 6.1 to 106.7 ± 2.2 mm Hg (p < 0.05) and LVEDP was unchanged. MNSR decreased from 0.85 ± 0.10 to 0.62 ± 0.10 lengths at onset of ejection (LOE)/sec (p < 0.01), and dP/dt 40 decreased from 2140 ± 99 to 1725 ± 102 mm Hg/sec (p < 0.01). In 11 dogs with volume overload hypertrophy, LV performance was unchanged or increased after quinidine. However, when the heart rate was held constant by atrial pacing during β-adrenergic blockade, quinidine produced a fall in LVSP from 121.4 ± 3.5 to 106.2 ± 2.3 mm Hg (p < 0.01), no change in LVEDP, a decrease in MNSR from 1.52 ± 0.22 to 1.35 ± 0.19 LOE/sec (p < 0.01) and a decrease in dP/dt 40 from 2331 ± 94 to 1989 ± 143 mm Hg/sec (p < 0.01) 15 minutes after the second dose. We conclude that quinidine causes depression of LV performance in normal dogs and in dogs with LV hypertrophy due to volume overload. Augmented sympathetic tone during quinidine administration may mask these depressant effects. This study may serve as a pharmacologic model to study the effects of drugs on LV performance.

QUINIDINE IS WIDELY USED to treat cardiac arrhythmias in patients with coexistent myocardial disease,1-4 but its effects on myocardial performance are poorly defined. Studies in isolated heart muscle have shown a dose-dependent depression of contractility.5-8 The results of studies in the intact heart have been conflicting, some having shown no change in indices of left ventricular (LV) performance9 and others depression of LV function.10-15 Further, changes in loading conditions, which may alter indices of myocardial performance independently of changes in inotropic state, have usually not been well characterized in previous investigations, or anesthetic agents that may alter both autonomic tone and myocardial performance have been used.16 Because quinidine is an arteriolar vasodilator13,17 and a venodilator,18 both due to its direct action on vascular smooth muscle and to its α-adrenergic blocking properties,17,19 changes in loading conditions and autonomic tone are to be expected after administration of the drug and must be considered in evaluating its effect on LV performance.20-21 Therefore, we reexamined the effects of quinidine on LV performance using conscious, chronically instrumented dogs. Normal dogs and dogs with LV hypertrophy experimentally produced by a chronic volume overload served as experimental models.

Methods

Seventeen fasting mongrel dogs that weighed 21-35 kg were anesthetized with sodium pentobarbital, and a thoracotomy was performed through the fifth left intercostal space. The heart was supported in a pericardial cradle and instrumented as follows. A polyethylene tube and a high-fidelity micromanometer (model P-20, Konigsberg Instruments, Inc., Pasadena, California) were inserted through stab wounds at the apex of the left ventricle and secured with pursestring sutures. Two piezoelectric sonomicrometer gauges, each consisting of a crystal pair, were then implanted at the midpoint of and perpendicular to the ventricular long axis, one pair in the midwall of the anterior left ventricle measuring a myocardial segment approximately 1.5 cm long and the other pair on the endocardium of the anterior and posterior walls measuring a LV chord.22-24 Pacing electrodes were then sutured to the left atrial appendage. All electrical cables and the left ventricular catheter were tunneled subcutaneously to a pocket in the posterior neck. The thoracotomy was closed and the dogs were allowed to recover for at least 7 days.

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After they were trained to lie quietly on the laboratory floor, eight dogs (group 1 pre-fistula) were studied. First, basal recordings of LV pressure and dimensions and a lead II ECG were made. LV pressure was determined from the micromanometer, which we calibrated by matching it to the pressure from the fluid-filled LV catheter. The latter was connected to a Statham P23db pressure transducer (Statham Instruments Division, Gould Inc., Oxnard, California) and calibrated with a mercury manometer; the zero reference point was the level of the vertebral column. The first derivative of pressure from the high-fidelity micromanometer was obtained by electronic differentiation (Model 350-16, Hewlett-Packard Co, Palo Alto, California) with a high-frequency response linear to 150 Hz calibrated with a triangular wave form of known slope. Techniques for measuring LV dimensions using the sonomicrometer gauges have been described in detail.21-23 Data were recorded on an eight-channel, forced-ink recorder (Model 7868A, Hewlett-Packard, Waltham, Massachusetts) and on an FM tape recorder (Model 7600, Honeywell Corp, Minneapolis, Minnesota) for later computer processing.

Quinidine gluconate, 6 mg/kg diluted in 37 ml of 0.9% NaCl (dose A), was then infused over 5 minutes using a Harvard infusion pump.9 Recordings were repeated 5 and 15 minutes after the infusion. After the last recording, a second dose of quinidine gluconate 6 mg/kg (dose B) was infused. Recordings were again made 5 and 15 minutes after the infusion. Blood samples were withdrawn from the LV polyethylene tube 5 and 15 minutes after each infusion for determination of serum quinidine levels. At least 48 hours after the first study, a second quinidine infusion study was performed during autonomic blockade with intravenous atropine 1.0 mg and propranolol 0.5 mg/kg. Recordings were made when the dogs were in sinus rhythm and in the autonomic blockade study during a short period of atrial pacing at a rate of 130 beats/min. Adequacy of beta-adrenergic blockade was assured by the absence of a heart rate response to a 4-μg intravenous bolus of isoproterenol.

A separate group of nine dogs was instrumented as described above. In these nine dogs and in two dogs from group 1, a laparotomy was performed and a side-to-side infrarenal anastomosis of the descending aorta to the inferior vena cava approximately 1 cm long was constructed. Quinidine infusion studies were repeated 2-4 weeks after establishment of the volume overload state (group 2) in the 11 dogs. The protocol was identical to that before aortocaval fistula surgery, except that the dose of quinidine was reduced to 5 mg/kg in the last eight studies because serum quinidine levels tended to be higher than in the pre-fistula studies. After completion of the quinidine infusion studies, the dogs were sacrificed and total heart weight, LV and right ventricular (RV) weight, and LV and RV wall thickness were measured to confirm the presence of ventricular hypertrophy. The volume overload state induced by an aortocaval fistula has been established as a reliable model of ventricular hypertrophy and dilatation.22, 23

Data Analysis

The FM magnetic tape was replayed and monitored on an oscilloscope for analog-to-digital conversion on an EAI 590 hybrid computer with a sampling frequency of 3 msec. After the data were in digital format, 10-20 beats (at least two respiratory cycles) were used to produce an average beat. The averaged beats were then processed on a Burroughs 6700 digital computer for calculation of percent shortening and mean velocity of shortening for the LV diameter and segment, and calculation of the time constant (T) for LV isovolumic pressure fall.26, 27 T was derived from an exponential fit of the relation of the micromanometric LV pressure vs time plotted from the time of peak negative dP/dt to a pressure 15 mm Hg greater than the LV end-diastolic pressure (EDP). In actual practice, a plot of the natural logarithm of LV pressure vs time was produced. The inverse negative slope of this line is equal to T. The r value for exponential fit was greater than 0.98 in all cases.

For all segment and diameter calculations, length at onset of ejection (LOE) was defined at the time of peak positive dP/dt. End-systolic length (ESL) was defined as the shortest length within 50 msec of peak negative dP/dt and ejection time (LVET) was the time between peak positive dP/dt and ESL. Mean normalized shortening rate (MNSR) was calculated from the formula ((LOE-ESL)/(LVET × LOE)). LVEDP was defined at 1% of the peak positive dP/dt and checked visually. The value of dP/dt at 40 mm Hg developed pressure (EDP + 40 mm Hg [dP/dt 40]) was derived from digitized data using linear interpolation between 3-msec intervals.

Statistical significance was tested by analysis of variance separately for group 1 and group 2. Variables included heart rate, peak LV pressure, peak positive LV dP/dt, dP/dt 40, percent segment and diameter shortening, MNSR, LOE, T, and serum quinidine level. Tukey's modification was used for calculating differences.28 Because shortening results for the LV diameter and segment showed no statistically significant differences, only the segment data are presented. Serum quinidine levels were determined by the method of Gelfman and Seligson.29

Results

Group I

Mean quinidine blood levels were within the usually accepted therapeutic range (3.0-9.0 mg/l) for all studies (table 1).

Without Autonomic Blockade

LVEDP, LOE and indices of LV performance decreased after dose B (table 1; figs. 1 and 2). Fifteen minutes after dose B, the decrease in dP/dt 40 was 11% and the decrease in MNSR was 15%.
TABLE 1. Serum Quinidine Levels

<table>
<thead>
<tr>
<th></th>
<th>Dose A (5 min)</th>
<th>Dose A (15 min)</th>
<th>Dose B (5 min)</th>
<th>Dose B (15 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>4.9 ± 0.9</td>
<td>5.1 ± 1.0</td>
<td>6.4 ± 0.8</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>Autonomic blockade</td>
<td>6.2 ± 1.7</td>
<td>7.0 ± 1.7</td>
<td>6.7 ± 1.4</td>
<td>6.8 ± 1.4</td>
</tr>
<tr>
<td>Blockade/paced</td>
<td>6.9 ± 0.8</td>
<td>7.4 ± 1.3</td>
<td>8.1 ± 1.0</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>7.9 ± 0.6</td>
<td>7.5 ± 0.6</td>
<td>9.4 ± 0.7</td>
<td>9.0 ± 0.7</td>
</tr>
<tr>
<td>Autonomic blockade</td>
<td>9.0 ± 0.8</td>
<td>8.3 ± 0.9</td>
<td>10.4 ± 1.0</td>
<td>9.9 ± 1.2</td>
</tr>
<tr>
<td>Blockade/paced</td>
<td>8.4 ± 0.6</td>
<td>7.7 ± 0.8</td>
<td>9.5 ± 0.9</td>
<td>8.8 ± 0.8</td>
</tr>
</tbody>
</table>

All values ng/l (mean ± SEM).

With Autonomic Blockade

In the presence of β-adrenergic blockade, indices of LV performance decreased after dose A (p < 0.01) and decreased further after dose B (p < 0.01) (table 2; figs. 1 and 2). Fifteen minutes after dose B, dP/dt 40 decreased by 25% and MNSR by 27%. The heart rate did not change. LV systolic pressure (LVSP) and LVEDP fell significantly.

With Autonomic Blockade and Atrial Pacing

Under these conditions, the only change in loading conditions was a fall in LVSP 15 minutes after dose B.

Indices of LV performance decreased after dose A and dose B (table 2; figs. 1 and 2). Fifteen minutes after dose B, MNSR fell by 19% and dP/dt 40 fell by 27%.

Group 2

Serum quinidine levels tended to be higher in the post-shunt dogs, and some values were above the usual therapeutic range (table 1). LV weight (148.4 ± 42.7 g) and wall thickness (1.59 ± 0.12 cm) confirmed the presence of LV hypertrophy in all dogs.21, 22

With Autonomic Blockade

The heart rate increased and LVEDP decreased, while LVSP did not change. Indices of LV performance remained unchanged or increased after dose A and dose B. T decreased after dose B (table 3; figs. 3 and 4).

With Autonomic Blockade

Under these conditions, the heart rate and LVSP decreased, but LVEDP did not change. Indices of LV performance decreased after dose A and decreased further after dose B (table 3; figs. 3 and 4). Dp/dt 40 fell by 20% and MNSR by 18% 15 minutes after dose B. T increased, except 15 minutes after dose A.

With Autonomic Blockade and Atrial Pacing

LVSP fell after dose A and dose B, but LVEDP did not change. Isovolumic indices of LV performance tended to decrease after dose A. Both isovolumic and ejection phase indices decreased after dose B (table 3; figs. 3 and 4). Fifteen minutes after dose B, dP/dt 40 fell by 15% and MNSR by 11%.

Figure 1. Hemodynamic data and heart rate from group 1 dogs. LVSP = left ventricular peak systolic pressure; EDP = left ventricular end-diastolic pressure; HR = heart rate.

Figure 2. Indices of ventricular performance from group 1 dogs. MNSR = mean normalized shortening rate; dP/dt 40 = value of dP/dt at a developed pressure of 40 mm Hg.
Table 2. Group 1: Hemodynamic and Dimension Data

<table>
<thead>
<tr>
<th></th>
<th>Control (5 min)</th>
<th>Dose A (15 min)</th>
<th>Dose B (15 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without autonomic blockade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>11.1 ± 1.6</td>
<td>8.7 ± 1.7*</td>
<td>8.7 ± 1.5*</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>119.5 ± 3.4</td>
<td>117.6 ± 4.3</td>
<td>112.6 ± 5.1</td>
</tr>
<tr>
<td>dP/dt 40 (mm Hg/sec)</td>
<td>2285 ± 99</td>
<td>2166 ± 133</td>
<td>2124 ± 107</td>
</tr>
<tr>
<td>LOE (mm)</td>
<td>13.1 ± 0.7</td>
<td>12.8 ± 0.6*</td>
<td>12.9 ± 0.7</td>
</tr>
<tr>
<td>MNSR (LOE/sec)</td>
<td>0.96 ± 0.06</td>
<td>0.86 ± 0.06</td>
<td>0.88 ± 0.07</td>
</tr>
<tr>
<td>T (msec)</td>
<td>25.0 ± 1.5</td>
<td>23.7 ± 1.8</td>
<td>24.9 ± 0.8</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89.4 ± 7.8</td>
<td>103.7 ± 6.5</td>
<td>101.2 ± 7.7</td>
</tr>
</tbody>
</table>

| **With autonomic blockade** |       |       |       |
| EDP (mm Hg)              | 8.3 ± 2.6      | 8.6 ± 1.2      | 6.9 ± 1.4      |
| LVSP (mm Hg)             | 124.3 ± 5.3    | 114.1 ± 3.5    | 114.8 ± 2.9    |
| dP/dt 40 (mm Hg/sec)     | 2195 ± 118     | 1809 ± 133†    | 1938 ± 122*    |
| LOE (mm)                 | 23.1 ± 4.8     | 23.4 ± 4.9     | 23.3 ± 4.8     |
| MNSR (LOE/sec)           | 0.88 ± 0.09†   | 0.71 ± 0.09†   | 0.77 ± 0.08*   |
| T (msec)                 | 21.7 ± 3.0     | 23.4 ± 1.5     | 21.6 ± 2.0     |
| HR (beats/min)           | 110.3 ± 5.2    | 113.6 ± 5.3    | 102.6 ± 4.5    |
| EDP (mm Hg)              | 5.6 ± 2.1      | 6.0 ± 1.4      | 4.4 ± 1.4      |
| LVSP (mm Hg)             | 123.7 ± 6.1    | 115.4 ± 2.6    | 117.0 ± 3.0    |
| dP/dt 40 (mm Hg/sec)     | 2140 ± 99      | 1790 ± 122*    | 1955 ± 110     |
| LOE (mm)                 | 22.4 ± 4.6     | 23.0 ± 4.8     | 22.6 ± 4.7     |
| MNSR (LOE/sec)           | 0.85 ± 0.10†   | 0.65 ± 0.08†   | 0.66 ± 0.10†   |
| T (msec)                 | 20.2 ± 2.6     | 21.4 ± 2.0     | 20.0 ± 1.9     |
| HR (beats/min)           | 132.6 ± 6.4    | 132.7 ± 6.0    | 131.4 ± 6.4    |

All values are mean ± SEM. All lengths refer to segment data.

*p < 0.05 vs control.
†p < 0.01 vs control.
‡p < 0.05 vs dose A.
§p < 0.01 vs dose A.

Abbreviations: EDP = left ventricular end-diastolic pressure; LVSP = left ventricular peak systolic pressure; dP/dt 40 = dP/dt at a developed pressure of 40 mm Hg; LOE = length at onset of ejection; MNSR = mean normalized shortening rate; T = time constant for left ventricular isovolumic pressure fall; HR = heart rate.

Discussion

Quinidine is known to alter myocardial loading conditions and heart rate, both by venodilatation and arteriolar dilatation. The latter appears to result from a direct effect on vascular smooth muscle as well as α-adrenergic blockade, while the former is thought to be a consequence of α-adrenergic blockade alone. Thus, venodilatation after quinidine may decrease venous return, resulting in diminished ventricular preload and in reflex increases in heart rate. Arteriolar dilatation may decrease systolic pressure, resulting in baroreceptor-induced changes in sympathetic tone that increase the heart rate and the inotropic state. Quinidine also has a direct negative chronotropic effect, as well as vagolytic effects on the sinus node.

Considerations Regarding LV Function

Changes in loading conditions and the heart rate may independently alter LV performance, and must be considered in evaluating the effects of any pharmacologic agent on LV function.Isovolumic indices (peak positive dP/dt and dP/dt 40) are relatively unaffected by changes in afterload and only slightly influenced by alterations in preload. The level of dP/dt 40 in particular is unaffected by afterload, and changes only slightly with large alterations in preload, but is very sensitive to changes in contractility in the conscious dog. The advantage of dP/dt 40 over peak positive dP/dt is that the latter may be artifactually decreased by low aortic diastolic pressure and “early” aortic valve opening. However, dP/dt 40 is also dependent on heart rate, increasing at higher rates. In contrast, ejection phase indices of LV performance (percent shortening and MNSR) are unresponsive to changes in preload but quite sensitive to alterations in aortic pressure and heart rate. The sensitivity of these indices of performance to loading conditions is unaffected by β-adrenergic blockade. Both isovolumic and ejection phase indices of LV performance are affected by heart rate. Augmented
sympathetic tone due to either reflex alterations in sympathetic nerve traffic to the myocardium or changes in circulating catecholamines can markedly improve indices of ventricular performance. Reflex changes in parasympathetic tone may also alter heart rate and thus affect indices of ventricular performance. For these reasons we also performed studies after β-adrenergic blockade with propranolol and at constant heart rates in order to detect whether any direct myocardial depressant effects of quinidine could be unmasked by β-adrenergic blockade. The dose of propranolol selected (0.5 mg/kg) is known to produce pharmacologic levels of β-adrenergic blockade without resulting in myocardial depression independent of adrenergic blocking effects.40

**Group 1 Studies**

Group 1 dogs without β-adrenergic blockade had a small but significant decrease in LV performance after quinidine. However, the decrease in preload (decreased LVEDP) could have independently decreased isovolumic indices. Counterbalancing this effect are the increase in heart rate and changes in sympathetic tone (resulting from the decrease in systolic pressure or vagolytic effects), which would tend to increase both isovolumic and ejection indices.

During autonomic blockade, the heart rate was no longer significantly increased after quinidine, and because loading conditions and indices of LV performance changed in a parallel fashion for the spontaneous heart rate and atrial paced studies, they may be considered together. The decrease in indices of LV performance suggest a direct depressant effect of quinidine. This conclusion is further supported by the marked decrease in ejection phase indices that occurred despite a decrease in LVSP, which by itself would tend to increase these indices. Further, comparison of the unblocked and blocked studies suggested the mechanisms involved. LVEDP fell in the unblocked but not in the blocked-paced dogs after quinidine, suggesting that most of the preload decrease in the unblocked studies was secondary to the increase in heart rate, although it is possible that
preload could have been maintained by increased venous return due to venoconstriction after \( \beta \)-adrenergic blockade.

LVSP fell significantly only during autonomic blockade. However, \( \beta \)-adrenergic blockade should not alter the direct effect of quinidine on the peripheral circulation.\(^{17}\) Thus, these data suggest that augmented sympathetic tone and increased heart rate tended to maintain normal or near-normal LV performance and that \( \beta \) blockade unmasked the direct myocardial depressant effect of quinidine. It is also possible that propranolol and quinidine act synergistically through a direct mechanism to produce myocardial depression. Although we cannot exclude a synergistic effect, it is likely, if present, to be minor, because quinidine produced myocardial depression in the absence of \( \beta \) blockade, although our hemodynamic data support the presence of reflex increase in sympathetic tone that was blocked by propranolol.

**Group 2 Studies**

Ventricular hypertrophy and circulatory congestion altered the effects of quinidine in group 2 dogs. Serum quinidine levels were higher than for group 1, and some mean values were above the usual therapeutic range after dose B (table 1) despite the reduced dosage of 5 mg/kg in most dogs. Although total blood volume is markedly increased in dogs with aortocaval fistulas, this difference may result from a decreased effective volume of distribution, as reported in patients with congestive heart failure.\(^2\) In dogs without \( \beta \)-adrenergic blockade, quinidine did not depress LV performance. The decrease in preload (LVEDP) in these studies would by itself be expected to decrease isovolumic indices, and the increase in heart rate would be expected to have the opposite effect.

As in group 1 dogs, the effects of quinidine after autonomic blockade suggest an augmentation of sympathetic tone and/or withdrawal of parasympathetic tone in response to quinidine in unblocked animals, while decreases in isovolumic and ejection phase indices after quinidine infusion and autonomic blockade reflect direct myocardial depression by quinidine. The decrease in indices of performance with heart rate maintained constant by atrial pacing cannot be explained by altered loading or heart rate and must therefore reflect a direct depressant effect of quinidine on the hypertrophied left ventricle.

The sinus slowing after quinidine in group 2 dogs with adrenergic blockade probably resulted from direct effects of quinidine on the sinoatrial node.\(^{35, 34}\) This effect was not observed in group 1 dogs, perhaps because serum quinidine levels were lower. The membrane effects of propranolol, while small at this dose, could also have contributed. Another difference between the two groups is apparent in the unblocked studies. After quinidine, indices of ventricular performance tended to decrease in group 1 and increase in group 2, perhaps as a result of greater myocardial functional reserve in response to catecholamine stimulation in these hypertrophied hearts. Studies have shown normal or possibly enhanced myocardial performance in this model,\(^{22, 23, 41}\) but whether functional reserve is altered is unknown. Alternatively, it is possible that quinidine resulted in quantitatively different effects on the peripheral circulation and loading conditions in the volume overload state.

**LV Relaxation**

The time constant of LV isovolumic pressure fall (T) is relatively insensitive to changes in preload, but
in the intact ventricle is dependent on heart rate, inotropic state and systolic pressure.\textsuperscript{26, 27} Thus, positive inotropic changes increase the rate of relaxation (a decrease in T) and increases in aortic pressure increase T. During autonomic blockade, quinidine increased T significantly at several points despite a reduction in systolic pressure. Thus, this depression of relaxation by quinidine is also consistent with depression of systolic function.

Other Studies

Other studies on anesthetized animals have generally shown a decrease in LV performance after quinidine.\textsuperscript{11-14} However, in some of these studies,\textsuperscript{11, 13-15} pentobarbital, a major direct myocardial depressant,\textsuperscript{16} was used for anesthesia. Markiewicz and co-workers\textsuperscript{8} demonstrated a decrease in peak positive LV dP/dt in β-blocked, anesthetized, open-chest dogs that was not significant after aortic pressure was returned to control levels by aortic clamping. In the latter study, it was assumed that returning aortic pressure to control levels by aortic clamping could compensate for changes in LV dP/dt due to the prior decreases in aortic pressure. However, this may not be the case, because acute elevations in aortic pressure produced by aortic clamping in dogs causes a marked independent increase in peak positive dP/dt at the same preload and in the presence of autonomic blockade.\textsuperscript{42} These authors did not comment on alterations in preload that could also have independently changed peak positive dP/dt.\textsuperscript{37}

In five cardiac transplant recipients, intravenous quinidine produced a decrease in aortic and central venous pressure but no change in the mean rate of circumferential fiber shortening or ejection fraction.\textsuperscript{10} There are two possible explanations for the discrepancy between these results in man and our results in conscious dogs. First, reinervation of the autotransplanted dog heart is functionally significant at 9–12 months.\textsuperscript{43} Thus, it is possible that patients with heterotransplants may have partial reinervation. Second, it is also possible, if not likely, that such patients have alterations in circulating catecholamine levels. Third, depression of myocardial contractility by quinidine could have been masked by augmented sympathetic tone in a fashion analogous to our results without autonomic blockade.

Conclusions

Our results indicate that quinidine is a direct depressant of myocardial systolic performance and isovolumic relaxation both in the normal and volume-overloaded left ventricle. Alterations in autonomic tone compensate at least partially for this depression. This study demonstrates the need for careful consideration of changes in loading conditions, heart rate and autonomic tone in the evaluation of LV performance after drug administration, and may serve as a pharmacologic model for testing the effects of drugs on LV performance. Although clinical extrapolation of our results must be made with caution, significant depression of myocardial function by quinidine could occur in patients receiving β-adrenergic blocking agents or in patients with limited inotropic reserve. One recent study in patients failed to show any depression of ventricular performance after quinidine, but adrenergic blockade was not used.\textsuperscript{44} Further studies in man using β-adrenergic blockade and in which loading conditions are controlled or carefully taken into account are warranted.

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