Normal Myocardial Contractile State in the Presence of Quinidine

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SUMMARY Since quinidine is one of the few agents available to treat and prevent ventricular arrhythmias in ambulatory patients, its hemodynamic effects have been re-evaluated. When given in therapeutic doses to anesthetized mongrel dogs, quinidine significantly reduced heart rate, aortic pressure and flow, but it did not significantly change the first derivative of the left ventricular pressure curve (left ventricular dp/dt) in nine dogs. A subsequent group of dogs was studied after vagotomy and practolol administration to block cardiac reflexes. This group showed significant reductions in heart rate, aortic pressure and left ventricular dp/dt, with the latter returning to predrug control values when preload, afterload and heart rate were maintained constant. These studies suggest that quinidine does not directly affect myocardial contractility when given in therapeutic doses. Furthermore, the reduction in heart rate in these animals provides support for a direct depressant effect of quinidine on the sinus node. The adverse effects of quinidine on cardiac function previously reported may be due to the use of toxic doses or are secondary to quinidine peripheral circulatory effects, rather than due to a direct reduction in cardiac contractile state.

QUINIDINE is widely used to treat and prevent cardiac arrhythmias, and its hemodynamic effects have been studied extensively. However, the effects of this agent on myocardial contractility remain controversial. Experiments in isolated heart preparations show that quinidine can reduce cardiac contractile force.1-4 Studies in anesthetized animals usually demonstrate a reduction of indices reflecting myocardial contractility.5-7 However, most reported experiments have used quinidine doses far above the therapeutic range. Marked changes in blood pressure and heart rate also occurred which could by themselves affect the indices of contractility measured without necessarily implying direct myocardial effect of quinidine. Other authors have found no change, or an increase in cardiac contractile force following quinidine administration.8-9 The aim of this study is to assess the effect of therapeutic doses of quinidine on myocardial contractility in an open-chest, anesthetized dog preparation when the influence of other circulatory parameters and of the autonomic nervous system are controlled.

Methods

Eighteen fasting mongrel dogs weighing 16.6–25.9 kg were anesthetized with intravenous chloralose, 85 mg/kg, and urethane, 625 mg/kg. The animals were intubated with a cuffed endotracheal tube and ventilated using a Harvard pump administering humidified room air. Blood gases were analyzed frequently using a Corning Model 165 gas analyzer. Depth and rate of respiration were adjusted to maintain an arterial pO2 over 80 mm Hg, and pCO2 between 7.35 and 7.45. Temperature was maintained with a heating pad. A large-bore catheter was inserted via the right carotid artery to the central aorta, and drug infusion and sampling catheters were placed in the jugular and femoral veins. The chest was opened via a mid-line sternotomy. A Micron MP-10 implantable pressure transducer was placed via a stab wound into the apex of the left ventricle. A PE-240 polyethylene catheter was positioned in the left atrium via a stab wound in the left atrial appendage and connected to a saline-filled glass manometer for the measurement of the mean left atrial pressure. A small incision was made in the left chest wall, and an adjustable screw clamp positioned around the descending aorta distal to the origin of the left subclavian artery so that arterial pressure could be increased when required. Aortic flow was measured by means of an externally calibrated electromagnetic flow probe* positioned around the proximal ascending aorta. Pacing wires were attached to the right atrial appendage and connected to a Grass Model S4 stimulator. Recordings were made on a Honeywell Model 1508 visiorder oscillograph.

The zero for all pressure measurements was taken at mid-chest level. Aortic pressure was recorded using a Statham P23Db transducer, with mean aortic pressure derived electronically. The first derivative of the left ventricular pressure curve (left ventricular dp/dt) was obtained by an electronic differentiator circuit with a linear amplitude response to more than 500 Hz. Lead II of an external electrocardiogram was also recorded. During instrumentation, dextrose 5% in distilled water (D5W), 5 cc/kg, was infused slowly intravenously to compensate for blood volume losses. Left atrial pressure was regularly monitored, and an infusion of normal saline begun whenever left atrial pressure fell more than 3 cm H2O below the control level. Small amounts of the anesthetic mixture (10% of the initial dose) were given when required. Two sets of experiments were performed:

Group 1 (9 dogs)

Hemodynamic parameters were recorded every five minutes until three successive measurements showed that the preparation was stable. The mean value for these three measurements was taken as the control value. Hemodynamic parameters were also recorded during right atrial pacing at approximately 30 beats/min above the spontaneous heart rate, in order to provide a set of controls which could be used if quinidine were to cause an increase in

* Biotronex Model 410 Electromagnetic blood flowmeter.
heart rate (control with pacing). A commercially available solution of quinidine gluconate* containing 800 mg of the salt of the alkaloid in 10 ml of sterile water was diluted to 50 cc, using D5W as the diluent. Eight dogs received 6 mg/kg, and one dog received 4 mg/kg of quinidine base infused intravenously over five minutes, using a Harvard pump (dose A). Hemodynamic parameters were recorded 30 and 60 seconds, and 3, 5, 10 and 20 minutes after the start of the infusion. Heart rate and mean arterial pressure were then returned to pre-drug levels by right atrial pacing at either control or control with pacing heart rate, and by slowly constricting the aorta (constrictor on and pacing). After recording all the parameters, pacing was stopped, and the aortic constrictor was slowly released. Blood pressure was allowed to stabilize and another recording made (constrictor off, no pacing). Venous blood was withdrawn in eight dogs for drug level determination before drug infusion, 5, 10 and 20 minutes after the start of the infusion, with the aortic screw clamp on, and after its release. Another dose of quinidine gluconate (dose B), similar in amount to dose A, was injected into each dog over a five minute period, and all measurements and blood for drug levels taken as described for dose A.

Group 2 (9 dogs)

Following instrumentation, both cervical vagi were isolated and cut, and practolol,* 2.5 mg/kg, was injected slowly intravenously. Hemodynamic parameters were recorded every five minutes until three successive measurements showed stabilization of the preparation. The mean value of these three measurements was taken as the control value. Hemodynamic parameters were also recorded during right atrial pacing at a rate of approximately 30/min above control heart rate. Each dog received a single dose of 8 mg/kg quinidine base, prepared as described above, and injected intravenously over a five minute period. Recordings were taken as for group 1 dogs. Blood samples were taken just before release of the aortic constrictor (constrictor on and pacing). A bolus of isoproterenol (4γ) was injected intravenously prior to the infusion of quinidine and at the conclusion of the experiment to document the adequacy of the beta-adrenergic blockade induced by practolol. Plasma quinidine levels were determined by measuring the fluorescence of trichloroacetic acid filtrate10 employing a modification of the Gelfman and Seligson technique.11

STATISTICAL ANALYSIS

Paired t-tests were performed to compare control values with hemodynamic parameters obtained at various intervals after quinidine infusion. Regression lines correlating percent changes in hemodynamic parameters and quinidine plasma levels were obtained using the least squares technique and correlation coefficients were calculated.

Results

Group 1

Group 1 results are presented in figure 1 and table 1.

In dogs with anatomically intact autonomic nervous

*Eli Lilly and Co., Indianapolis.
and while a relation was noticed between the fall in mean aortic pressure and the quinidine plasma levels, the correlation was poor \( r = -0.49 \).

**Group 2**

Group 2 results are presented in figure 2 and table 2.

In the study group with autonomic block, there was a small \((-9\%)\) but highly significant \((P < 0.01)\) decrease in heart rate following quinidine infusion. Mean aortic pressure fell markedly until the end of the infusion, then increased slowly but was still significantly reduced \((-30\%, \ P < 0.01)\) at the end of the experiment. Left ventricular \(dp/dt\) was significantly reduced between 3 and 20 minutes after infusion, rose thereafter, and was only slightly reduced at the end of the experiment \((-11\%, \ NS)\). Aortic flow and left atrial pressure did not change significantly throughout the study.

When mean aortic pressure and heart rate were brought to near control levels using the aortic constrictor and right atrial pacing, left ventricular \(dp/dt\) was slightly increased above control values \(+9\%, \ NS\) after quinidine administration (fig. 2, table 2).

**BLOOD LEVELS**

Mean quinidine plasma levels were 5.78 \(\pm\) 0.97 mg/L at the time the aortic screw clamp was released. There was no significant relation between changes in blood pressure and quinidine blood levels.

**Discussion**

The effects of quinidine on the cardiovascular system have previously been studied extensively \textit{in vitro}, in the animal and in man. However, there is still no general agreement as to whether therapeutic doses of quinidine affect myocardial contractile state.

\textit{In vitro} studies demonstrate that large doses of quinidine produce marked negative inotropic effects on the myocardium; however, when tissue bath concentration is within the usual therapeutic range, there is much less reduction in contractile force. Other studies using isolated rabbit atria demonstrate that quinidine produces a positive or negative inotropic effect, depending on the frequency of stimulation, the concentration of quinidine, and the time of measurement after administration of quinidine. The negative inotropic effect of the drug is observed primarily at more rapid stimulation rates and with higher concentration of quinidine, and has been related to a quinidine-induced change in excitation rather than to a direct effect of quinidine on contractile process. Various metabolic actions have been attributed to quinidine, including inhibition of the (Na\textsuperscript{+}, K\textsuperscript{-}) -- ATPase complex, similar to the effect produced by cardiac glycosides. Changes in Ca\textsuperscript{2+} metabolism occurring.

### TABLE 1. Hemodynamic Measurements in Group 1 Dogs

<table>
<thead>
<tr>
<th>Dose A</th>
<th>Plasma quinidine levels (mg/L)</th>
<th>Heart rate (beats/min)</th>
<th>BP mean (mm Hg)</th>
<th>LV dp/dt (mm Hg/sec)</th>
<th>Aortic flow (cc/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>200.9 (\pm) 7.2</td>
<td>101.8 (\pm) 5.8</td>
<td>4634.3 (\pm) 580.0</td>
<td>1905.0 (\pm) 300.8</td>
<td></td>
</tr>
<tr>
<td>1'</td>
<td>200.7 (\pm) 11.5</td>
<td>69.1 (\pm) 6.4**</td>
<td>4663.7 (\pm) 745.7</td>
<td>1940.7 (\pm) 311.3</td>
<td></td>
</tr>
<tr>
<td>5'</td>
<td>4.70 (\pm) 0.71</td>
<td>192.8 (\pm) 8.2</td>
<td>4196.7 (\pm) 426.9</td>
<td>1924.5 (\pm) 345.9</td>
<td></td>
</tr>
<tr>
<td>10'</td>
<td>3.90 (\pm) 0.66</td>
<td>183.9 (\pm) 7.5*</td>
<td>4187.2 (\pm) 426.5</td>
<td>1579.7 (\pm) 352.1**</td>
<td></td>
</tr>
<tr>
<td>20'</td>
<td>3.61 (\pm) 0.73</td>
<td>182.2 (\pm) 6.8*</td>
<td>4174.4 (\pm) 425.2</td>
<td>1611.3 (\pm) 270.2**</td>
<td></td>
</tr>
<tr>
<td>32' (Constr. on and pacing)</td>
<td>3.54 (\pm) 0.64</td>
<td>198.3 (\pm) 6.2</td>
<td>4913.9 (\pm) 451.2</td>
<td>1475.8 (\pm) 227.3*</td>
<td></td>
</tr>
<tr>
<td>39' (Constr. off, no pacing)</td>
<td>3.19 (\pm) 0.63</td>
<td>180.8 (\pm) 7.5*</td>
<td>4428.9 (\pm) 452.2</td>
<td>1610.1 (\pm) 225.0*</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BP = blood pressure; LV dp/dt = first derivative of left ventricular pressure curve; Constr. = aortic constrictor.

**Constr. on and pacing** indicates that mean aortic pressure and heart rate have been brought to approximately control levels using the aortic constrictor and right atrial pacing.

**Constr. off, no pacing** indicates that the aortic constrictor has been slowly released and right atrial pacing stopped.

Dose A and dose B are similar: 6 mg/kg quinidine base (8 dogs), 4 mg/kg (1 dog).

Mean values \(\pm\) standard error of the mean are shown \((N = 9)\).

Statistical significance: * = \(P < 0.05\).

** = \(P < 0.01\).
after quinidine administration have been interpreted as consistent with a positive\(^6\) or negative inotropic effect.\(^7\)
Angelakos showed that large doses of quinidine produce a decrease in myocardial catecholamines.\(^8\) While not depressing the intrinsic contractile state of the myocardium, reduced stores of catecholamines may interfere with the ability of the adrenergic nervous system to support the function of the failing myocardium.\(^9\) In evaluating these in vitro results, it should be emphasized that in the intact animal, quinidine is highly bound to serum albumin,\(^8\) so that the concentration of the drug available for pharmacological action at the cellular level might be quite different in each type of preparation. Thus, these studies performed in vitro do not allow firm conclusions as to the effect of therapeutic doses of quinidine on myocardial contractility.

Most studies performed in anesthetized animals demonstrate a marked reduction of the indices reflecting myocardial contractility.\(^5\)\(^-\)\(^7\) However, Darby et al. found an increase in heart force occurring in both anesthetized and fully conscious dogs after quinidine administration.\(^8\) These effects of quinidine on myocardial force were abolished after sympathetic blockade and were attributed to reflex responses to acute hypotension. Similar findings have been reported by Pruett and Woods.\(^9\) Other studies have indicated that quinidine causes an increase in adrenergic activity by action mediated through sympathetic pathways.\(^10\) Such reflex changes in sympathetic tone may alter myocardial contractility independently from any direct effect of quinidine on the heart.\(^11\) Conn\(^12\) also suggested that quinidine may have a beta-adrenergic blocking action, but this effect is not believed to account for the negative inotropic effect observed following large doses of quinidine.\(^13\)

In evaluating these results, the effect of barbiturate anesthesia, used by most investigators, must also be taken into consideration: barbiturates have a depressant effect on the cardiovascular system\(^14\) which could mask inotropic effects produced by quinidine. In addition, quinidine possesses a well-known vagolytic action,\(^15\) which might also lead to changes in myocardial contractile state.\(^16\) Rapid infusion of quinidine in the anesthetized animal causes hypotension and usually bradycardia. Such changes in heart rate and aortic pressure can greatly influence left ventricular performances.\(^17\) Thus anesthesia, sympathetic reflexes, preload, afterload and heart rate must be considered if the effects of quinidine on myocardial contractility are to be assessed.

To circumvent these problems, we used a mixture of chloralose and urethane to anesthetize our animals since these drugs produce less depressant effects on the cardiovascular system than barbiturates.\(^18\)\(^,\)\(^19\) Left ventricular dp/dt was used to assess variations in inotropic state secondary to drug administration. When such determinants of myocardial contractility as heart rate, mean left atrial pressure (preload), mean aortic pressure (afterload), and sympathetic tone are maintained constant, left ventricular dp/dt is a reliable index of acute changes in cardiac contractile state.\(^20\)\(^,\)\(^21\)\(^,\)\(^22\)

In the first set of experiments (group 1), we studied the effect of quinidine in animals with anatomically intact nervous systems. Left ventricular dp/dt was not significantly depressed despite a decrease in blood pressure and heart rate. When mean aortic pressure and heart rate were returned to pre-drug control levels, left ventricular dp/dt rose above, but was not significantly different from, control values. Thus, no change in myocardial contractile state was detected in these animals. However, failure to demonstrate a negative inotropic effect after quinidine administration could have been related to sympathetic stimulation secondary to hypotension mediated by baroreceptor reflexes.

In order to clarify further the action of the drug, a second set of experiments was performed (group 2). Both cervical vagi were cut, and a dose of practolol sufficient to produce a near total beta-adrenergic blockade\(^23\) was given prior to quinidine administration, so that autonomic nervous system influence on myocardial contractility would be minimized. A marked drop in blood pressure associated with bradycardia was again noted, and this time left ventricular dp/dt was significantly reduced. However, when mean aortic pressure and heart rate were brought back to near control levels, left ventricular dp/dt rose to 9\% above control levels. This change was not statistically significant. Thus, quinidine did not cause any significant change in myocardial contractility in our animal model at a time when quinidine blood levels were in the therapeutic range. The significant reduction in left ventricular dp/dt seen after quinidine infusion in the second subset of dogs was most likely secondary to the reduction in heart rate and blood pressure. Moreover, this study demonstrates that hypotension was due to the peripheral vascular effects of quinidine, and not to any direct depressant effect on the heart.

Various degrees of hypotension have been observed after rapid intravenous administration of quinidine in the anesthetized animal. Recent studies have shown that quinidine interferes selectively with alpha-adrenergic vasoc constriction and possesses a direct vasodilator effect as well.\(^24\) The magnitude of vasodilator response depended on the integrity of adrenergic vasoconstrictor tone. Quinidine
also appears to affect pulmonary and coronary vessels. Studies in perfused canine saphenous vein demonstrated that quinidine significantly reduced constrictor responses to adrenergic stimuli. Such action on capacitance vessels, in addition to the action on resistance vessels, might contribute to hypotension after administration of quinidine. The near-maximal fall in blood pressure after only one minute of infusion in our study suggests that quinidine’s vasodilator activity may occur at doses considered subtherapeutic for treating arrhythmias.

The effect of quinidine on heart rate is variable, depending on the type of model used. Experiments which directly perfuse the sinus node through its artery demonstrate three actions of quinidine: a direct negative chronotropic effect which is insignificant at concentrations below 10 mg/L, an anticholinergic, and an antiadrenergic action. A reflex sympathetic action has been invoked to explain the usual acceleration of heart rate observed in intact awake dogs given quinidine orally. Our study demonstrated that in the vagotomized dog with a nearly total beta-adrenergic blockade, quinidine caused a modest but significant reduction in heart rate, presumably due to a direct depressant effect on the sinus node. This effect occurred at serum concentration within the usual therapeutic range.

We also noted a wide range in blood levels following administration of quinidine. Such variation was present as early as five minutes following intravenous infusion, and probably reflects wide variations in distribution volume. Similar observations have been made in man and in animals.

While quinidine has been used as an antiarrhythmic agent for over 50 years, few data are available to document its hemodynamic effects in man. Many authors attribute the hypotension commonly seen after quinidine administration to both a central and peripheral effect of the drug, but this dual action has never been adequately demonstrated. In one study, the major hemodynamic effect of a single oral dose of 0.8 gm of quinidine sulfate in subjects with a normal circulation was a fall in aortic blood pressure which occurred in 50% of the subjects, while in patients with congestive heart failure, a fall in arterial blood pressure was usually combined with a drop in a previously elevated right ventricular systolic pressure and an increase in a previously low cardiac output. Changes in heart rate were variable. Most other hemodynamic studies in man were performed before and after conversion of atrial fibrillation to sinus rhythm by quinidine. Improvement in cardiac function was usually seen, and was attributed to both restoration of sinus rhythm and to the peripheral action of quinidine on the blood vessels. Whether quinidine has a potentially beneficial afterload-reducing effect in addition to its well-known antiarhythmic effect has not yet been investigated.

Our study in open-chest, anesthetized dogs demonstrated normal myocardial contractility in the presence of therapeutic blood levels of quinidine. However, caution is advised in extrapolating these results to man. While quinidine binding to plasma proteins and plasma half-life values are not very different in man and dog, similar plasma concentration may not necessarily mean similar effect on myocardial inotropic or chronotropic. Finally, the effects of quinidine in heart disease may be dissimilar to those observed in this set of experiments. Further investigation is required to clarify the effects of quinidine in the human with heart disease, but our animal studies suggest that when given in therapeutic doses, this drug may produce fewer adverse hemodynamic side effects than previously assumed.

References

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Complication Rate of Coronary Arteriography

A Review of 5250 Cases Studied by a Percutaneous Femoral Technique

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SUMMARY Distressing rates of embolic complications from coronary arteriography performed by the percutaneous femoral approach have been reported since 1972. From 1970–1974, 5250 patients underwent coronary arteriography in our laboratory by the same percutaneous femoral technique with preformed polyethylene catheters and no systemic heparinization. Data were recorded during and for 24 hours postcatheterization. The annual mortality rate averaged 0.23% and remained relatively stable. Our incidence of embolic complications was very low. In patients with normal coronary arteries, no fatal or serious nonfatal complications occurred. Left main coronary artery disease was present in all cases of mortality and ≥ 60% stenosis was shown in nine of 12 instances. Thus major risk was proportional to the severity of disease in the left coronary system. The use of more aggressive supportive measures in these high-risk cases appears essential to reduce the total complication rate from coronary arteriography significantly.

RECENTLY, A DISTRESSING INCIDENCE of thromboembolic complications from coronary arteriography performed by the percutaneous femoral technique has been reported in many institutions.1–10 This has raised the important question: What is an acceptable rate of mortality and serious complications from the procedure? In 1972, the ad hoc Committee on Coronary Artery Surgery of the Inter-Society Commission for Heart Disease Resources11 recommended that deaths associated with coronary arteriography should not exceed 0.3% and that mortality rates above this level should be considered unacceptable. More recently, Judkins and Gander12 have suggested that laboratories with a death rate of over 0.1% should give serious thought and study to methods of reducing their total serious complication rate. The present review was undertaken with this objective in mind and demonstrates that even in institutions that experience few technical problems, this projection is presently unrealistic. Whereas mortality and a high rate of serious nonfatal complications are unacceptable in subjects with normal coronary arteries, more adequate preventive measures applied prior to coronary arteriography must be instituted before the mortality rate of patients with severe coronary artery disease can be reduced significantly below 0.3%.

Material

Between January 1, 1970, and December 31, 1974, 5250 patients underwent at least one percutaneous transfemoral coronary arteriogram at the Montreal Heart Institute. This material forms the basis of the present review. A small number of cases with a Leriche syndrome who were investigated through a percutaneous axillary approach (also using preformed polyethylene catheters) were excluded. In most instances, coronary artery disease was strongly suspected or was documented clinically and the patients were studied primarily to determine their appropriate therapeutic management. The severity, extent, and localization of coronary artery disease and quality of the distal vascular bed were evaluated at coronary arteriography and left ventricular function was estimated from cineventriculography. Clinical diagnoses included stable, usually severe angina, crescendo angina, acute coronary insufficiency, and previous myocardial infarction. Patients with recent or acute myo-
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