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STUDIES ON THE EFFECT OF QUINIDINE ON CARDIOVASCULAR HEMODYNAMICS AND ON MYOCARDIAL MINERAL AND CARBOHYDRATE METABOLISM

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of the Ohio State University

By

Pura Norma Suarez Roldan, B.S., M.D.

****

The Ohio State University
1962

Approved by

[Signature]
Adviser
Department of Physiology
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To Dr. Leo Sapirstein, I express my appreciation for his sound advice and for making available his valuable research equipment when most needed.

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I. INTRODUCTION

Quinidine, one of the main natural alkaloids present in the cinchona (Jesuit's, Cardinal's) tree bark was first described in 1848 by Van Heyningen and was prepared in 1853 by Pasteur, who gave the compound its present name. Chemically, it has the same structural formula as quinine yet the steric configuration of its secondary alcohol group renders it the dextro-rotary isomer (1). Although its active alkaloids (quinine, quinidine, cinchonine and cinchonidine) had been isolated from the cinchona bark as early as 1820 by Pelletier and Caventou (2), it was not until over a century later that Woodward and Doering (3) synthesized quinine and quinidine by the conversion of a petroleum (or coal) derivative, hydroxyiso-quinoline into quinotoxine, from which both drugs were in turn synthetically produced. However, this procedure proved to be too complex and expensive to provide a practical source of the chemicals which are at present still commonly obtained from natural sources.

The use of cinchona for medicinal purposes as an anti-malarial agent dates back to the early seventeenth century (4, 5) when the Spaniards learned the secret of the Peruvian bark from the native indians, as recorded by Barba de Sevilla in 1642 (6). The effect of this crude powder preparation on the heart was not reported until
much later, when in 1749, Jean - Baptiste de Seńac employed the drug successfully for what he called "rebellious palpitation" (7). Serious attention was not paid to this use of the cinchona alkaloids up to 1914, when Wenckebach wrote of the beneficial effects of quinine in certain cases of auricular fibrillation (8). Impressed by this report, Frey, in 1918, studied and demonstrated the superiority of quinidine (over quinine and cinchonine) in the treatment of atrial fibrillation (9). His observations were quickly confirmed by others (10, 11) and since then the drug has been used in a variety of cardiac arrhythmias including paroxysmal auricular tachycardia, auricular flutter, ventricular tachycardia, and auricular and ventricular fibrillation (12, 13).

The basic actions of quinidine (on the heart) which render it a suitable therapeutic agent in the treatment of these arrhythmias have been studied by numerous investigators (14 - 23) during these past four decades and can be summarized as follows:

1. Quinidine increases the refractoriness of the various cardiac structures as shown by:
   a) Prolongation of the refractory time of the heart muscle (14, 15, 16, 21)
   b) Ultimate retardation effect on the rate of impulse discharged from the
pacemaker, whether it be situated at either the sino-auricular or atrio-ventricular node (17)

c) Slowing of conduction in cardiac muscle at both auricular and ventricular levels as evidenced in studies of the isolated atrium (18, 21, 23, 24) and in electro-cardiographic tracings by increased QRS time, various types of block, and slowing of electrical systole associated with a prolonged Q-T interval (25)

d) Depression of myocardial (both atrial and ventricular) excitability (15, 16, 21).

2. Quinidine is a cardiac muscle depressant as shown by:

a) Reduction of the contractile force of the heart (21, 26, 27)

b) A decrease in the cardiac efficiency index (29)

c) Its inhibition of the cardiac effects of such well known cardiac stimulants as epinephrine and ouabain (29, 30, 31)

3. Quinidine exhibits a marked and specific vago-paralytic
effect at the heart level (15, 32). This peripheral site of action has been substantiated by the studies of Briscoe and Burn (33) showing an apparent competitive inhibition between the alkaloid and endogenous myocardial acetyl choline for conducting tissue receptor sites.

The importance of the increase in refractory period in its relationship to successful anti-arrhythmic therapy with quinidine has been recently stressed by West and Amory (23) in their studies on atrial transmembrane action potentials as affected by the drug. The reverse effects of vagal stimulation or acetyl choline (34) on these action potentials has led to the speculation that the vago-paralytic effect of quinidine is effected by a decrease in membrane conductance.

Although the mechanism responsible for the effect of quinidine on cardiac refractoriness has not been yet clearly explained at the cellular level, it is worthwhile to notice that the studies performed by Sokolow et al. (35) in humans and Hiatt et al. (32) in dogs indicate that the plasma levels of the drug required for successful conversion of auricular fibrillation in humans, are those which will bring about no hypotensive effects in dogs while achieving a complete vagal block.
The widespread use of quinidine in cardiac arrhythmias is limited by the etiological factors of the condition (35); by the common presence of congestive heart failure in this type of patient (which renders the use of this drug a dangerous risk due to its easy accumulation in the blood of such cases) (36, 37, 38, 39); and by the development of toxic effects ranging from cinchonism and allergic skin reactions to the severer thrombocytopenic purpura (40, 41, 42, 43), and cardiovascular collapse (44).

In more recent years, however, the introduction of the drug as a useful agent in the field of anesthesiology has revived interest concerning its effect upon different physiological mechanisms including mineral and metabolic pathways. At relatively large doses, quinidine has been shown to inhibit the sensitization of cardiac muscle by epinephrine in cyclopropane anesthesia (45) and has proven a remarkable inhibitor of ventricular fibrillation development in hypothermia (46, 47). It is believed that this newly encountered usefulness for quinidine may be related to its effects on the electrolyte and metabolic pathways in the heart associated with a depressant type of action on the myocardium (27).

The purpose of this dissertation is to present and discuss the results obtained from studies dealing with the effects of quinidine on cardiovascular hemo-dynamics and on certain aspects of the mineral and carbohydrate metabolism of the heart.
II. STUDIES ON THE HEMODYNAMIC EFFECTS

OF QUINIDINE

On the basis of the above mentioned studies concerning the
effect of quinidine on cardiac excitability and contractility, it is
generally accepted that the alkaloid acts mainly as a myocardial
depressant. It is interesting, indeed, to notice that in spite of this
widely accepted concept, the great majority of the relatively few
studies which have been conducted on the working heart, fail to show
adequate investigation of the parameters essential to the determina-
tion of the inotropic effect exerted by the drug (48).

The first reported search into this problem is that of Bodo in
1927 (26), who demonstrated cardiac dilatation with no increase in
cardiac output in the electrically driven heart of a Starling heart-
lung preparation under the influence of small doses of quinidine.
Reynolds et al. (49) and Halsey et al. (50) followed with reports on
increased cardiac output in dogs after intravenous administration of
the drug. Their results are also in disagreement with the well
established hypotensive effects of intravenous quinidine (14, 29, 51,
52). In 1937, Starr and his associates (53) studying quinidine among
many other drugs, found that it effected a small but consistent fall
in cardiac output associated with decreases in stroke volume and
stroke work. Yet, on the basis of their empirical calculations of
cardiac volume they concluded that it was a cardiac stimulant.
From an impressive study on humans utilizing right side cardiac catheterization, Ferrer et al. (54), concluded that quinidine, although a hypotensive agent in approximately 70 - 80% of the cases studied, exerted no depressant effect on the cardiac output in man. Her results have been confirmed by the works of Kory (55) and Rowe (28). It is worthwhile mentioning though, that in Ferrer's study, a single oral dose of quinidine sulfate was used assuming a peak plasma and tissue value of the alkaloid one to two hours after ingestion.

This assumption can be reasonably debated on the basis of the following evidence:

1. Hiatt's (56) and Sokolow's (35) reports on the individual variability of quinidine plasma values after a single oral dose.

2. The lack of correlation between plasma and cardiac tissue drug levels after using a similar procedure in Wegria's experiments with humans (57).

3. The existing time difference for attainment of maximum plasma versus myocardial quinidine concentrations after single oral treatment, as reported by Weisman (58, 59).
Furthermore, a close analysis of their obtained values shows that when the determinations were performed at the time in which individual electrocardiograms (and/or systemic or right ventricular pressure) gave evidence of maximum quinidine effect, the cardiac output was diminished by approximately 22 - 30%. The later confirmatory studies of Rowe present results of procedures carried out at a time interval in which over 95% of the intravenously injected dose has been shown to have already disappeared from the plasma (31).

The recent work of Carney, Ross and Cooper (27) shows (by means of the use of a myocardial strain gauge arch) a marked diminution in canine myocardial contractility associated with a decrease in stroke volume and stroke work following large doses of intravenously administered quinidine gluconate. Although this work has measured some parameters which tend to indicate a negative inotropic effect of the agent under study, similar results have not been reported at small therapeutic dosages.

Definite evidence of the inotropic action of a substance requires that this substance alter the relationship between work performed and end diastolic volumes. In general, this requires simultaneous measurements of work and of diastolic volume, or some other index of diastolic volume such as left atrial pressure.
Therefore, we may conclude that unequivocal evidence of the inotropic action of quinidine has yet to be established.

The main purpose of our study has been to investigate the effect of various quinidine salts on the dog's heart working capacity. Our experiments have been designed to study this action, following the principles derived from Starling's law of the heart (60) in both intact animals and in modified Starling heart-lung preparations.

Methods and Procedures

Two experimental series were carried out in mongrel dogs as follows.

Heart-Lung Preparations

A series of six Nembutalized (30 mg./kg I.V.) fasting healthy dogs ranging in weight from 11.2 - 13.0 kilograms were utilized in modified Starling heart-lung preparations from which left atrial pressure, arterial pressure, standard lead II electrocardiographic tracings and cardiac outflow measurements were recorded on a direct writing multiple channel Grass polygraph Model No. 580. All pressure recordings were obtained by the use of Statham gauges attached respectively to a 3 mm. (internal diameter) metal atrial cannula and to a straight No. 17 hypodermic needle inserted into the arterial tubing system of the preparation.
Outflow measurements were directly fed into the polygraph from a Wilson flowmeter inserted between the peripheral resistance and the blood reservoir. Constant blood temperature was thermostatically maintained at 37°C; and a slow (5 drops/minute) glucose-insulin-saline drip (as described by Bayliss, Müller and Starling (61) was administered for the duration of the experiment.

After a period of time (20 - 30 minutes) allowed for stabilization of the preparation at a high cardiac output and stable mean arterial pressure, a series of control measurements were made. At the same time samples of blood were taken before and after the injection of Evans Blue (T-1824; 1% solution; 2 ml. injection) for blood volume determinations following Stewart's principle with the indicator-dilution technique (62). In most preparations, quinidine gluconate was added to the reservoir in an isotonic saline drip at a rate of 2 - 3 ml/minute. On one occasion (experiment No. 4), 20 mg. of quinidine gluconate were injected into the aortic outflow tubing leading to the rotameter chamber. The initial cardiac effect of quinidine was monitored by electrocardiographic changes in heart rate and the drip was stopped immediately after any variations in T-wave were observed, but recordings were quantitatively analyzed at the time of maximum effect on the parameters under study (in which the Q-T interval was used as the electrocardiographic criterion for maximal effect).
Outflow blood sampling for plasma K analysis was carried out in several experiments prior to, during and after quinidine administration (these results are presented in the following section).

**Intact Dogs**

A second series of six experiments was performed in fasting dogs ranging in weight from 12.2 - 15.3 Kgs. and under a relatively light anesthetic dose of 20 mg./kg. of intravenous sodium pentobarbital. The femoral vein and contralateral femoral artery were cannulated with No. 15 and No. 18 gauge Cournand needles respectively. These were used for simultaneous venous injection and arterial sampling in cardiac output determinations. A peripheral branch of the femoral artery was catheterized by means of a No. 160 polyethylene tube (i.d. 0.045 in.) introduced into the iliac artery and peripherally attached to an arterial Statham gauge transducer for pressure recording. A standard cardiac catheter (i.d. - 2 mm.) was placed within the left ventricular cavity via the left carotid artery and the left intraventricular pressure recorded by Statham gauge transducer. In some experiments, a rigid metal catheter (i.d. - 2 mm.) was inserted into the right jugular vein and lodged in the atrium for right atrial pressure recordings. All pressures plus electrocardiogram (standard lead II) were recorded in a multiple channel Grass polygraph model no. 580.
Pressure calibration records were obtained prior to onset and after completion of each experiment. Extreme care was taken in establishing the zero line for all pressure recordings and checking at various intervals during the experiment to detect any possible drift in the zero values. After completion of cannulation, the animals were heparinized with an initial dose of 2.2 mg./kg. and a maintenance dose of 0.2 mg./kg. every half hour. Cardiac outputs and blood volumes were determined by means of the Stewart-Hamilton indicator-dilution technique (62, 63, 64) (using Evans Blue T-1824) before and after the administration of intravenous quinidine. The drug was injected approximately 25 minutes after the first Evans Blue injection in doses ranging from 1.5 to 6.5 mg./kg. and its effect monitored by both electrocardiographic and arterial pressure changes. Immediately after the drug's effect was obvious (usually within the first 1 - 2 minutes) a second injection of Evans Blue was given for cardiac output determination. Calculations of heart rate, mean arterial blood pressure, stroke volume and stroke work were derived from those values in recordings simultaneous to the sampling for cardiac output.
Results

Heart-Lung Preparations

Effect of quinidine on the electrocardiogram: The heart rate was diminished in all experiments except the one in which quinidine sulfate was administered. This change was immediately followed by T-wave changes consisting of either inversion or increase in voltage plus prolonged duration. Notching of the T-wave was sometimes observed. The P-R interval was prolonged in five experiments, and the QRS time and Q-T interval were invariably prolonged. These changes can be observed in Figure 1, which shows the sequence of quinidine effects on the parameters under study.

Effect on cardiac output, left atrial and arterial pressures: As shown by Table 1, the cardiac output was diminished in all cases by a fraction roughly proportional to the total quinidine dosage. In spite of the slower heart rate, the decrease in output was of such magnitude as to result in a lowered stroke volume. The decrease in mean arterial blood pressure was probably due to the physical properties of the equipment. The left atrial pressure increased markedly, this increase being slower in onset, but more permanent and stable than all other changes recorded.

Effect on stroke volume and stroke work: Table 1 shows the consistent decreases in stroke volume, and the significant decrease
in stroke work on all experiments after quinidine administration.

**Intact Dogs**

**Effect on electrocardiogram:** There was an increase in heart rate over control levels in 50% of the experiments. This change went pari-passu with T-wave changes identical to those in the heart-lung preparation. It preceded, by a few beats (3-12), the effect observed on blood pressure. The P-R interval was not significantly prolonged, but QRS time and Q-T interval were increased:

**Effect on cardiac output and stroke volume:** As shown in Table 2, cardiac output was significantly decreased in four of the six experiments. In one experiment with quinidine SO, there was an increase of over 40% the control value. Stroke volume followed the changes observed in cardiac output.

**Arterial pressure:** Mean pressure was decreased in all cases, showing that during the optimum concentration of the drug in the blood associated with its cardiac effects, even small concentrations of quinidine will bring about this peripheral effect independent of cardiac output as shown by experiments 4 and 5. This arterial pressure drop was effected by a small diminution of systolic and a more marked decrease in diastolic blood pressure.

**Stroke work** was significantly diminished in all cases except one (experiment 5).
FIGURE 1

RECORDS SHOWING SEQUENCE OF QUINIDINE EFFECTS
ON LEFT ATRIAL PRESSURE, CARDIAC OUTPUT,
ECG, AND MEAN ARTERIAL PRESSURE IN
A HEART-LUNG PREPARATION
EXP 4:

CONTROL VALUES

LEFT ATRIAL PRESSURE (mean)
3.5 mm. Hg.

1 min. after Quin. (20 mg.)
0.5 mm. Hg.

MAXIMAL EFFECT
9.5 mm. Hg.

CARDIAC OUTPUT

1030 cc/min.

900 cc/min.

640 cc/min.

E.C.G.

H.R. 105/min.

100/min.

96/min.

A.B.P. (mean)

107 mm. Hg.

100 mm. Hg.

94 mm. Hg.
Left ventricular end diastolic pressure: Although these changes were not as marked as those of left atrial pressure in the previous series, they are consistent and significantly increased in three of the six experiments.

Peripheral resistance values as calculated by pressure/flow ratio show a decrease of 14 to 60% in all cases except one. These changes are not relatable to heart rate variations (see Table 3).

Discussion

In the first series of experiments the results present unequivocal evidence of the negative inotropic effect of quinidine upon the working heart of a heart-lung preparation. In these preparations, where changes in heart rate are more or less predictable and mean arterial pressure can be uniformly maintained, the relationship of stroke work to left atrial pressure (Table 1) is a clear indication of the reduced working capacity of the heart under quinidine treatment. Therefore, the direct depressant action of the alkaloid upon the heart's capacity to circulate blood is obvious in this study and is confirmed more rigidly when related to the findings of Bodo (26), Di Palma (21), and Carney (27). The decreased S-A nodal rhythm and the depressed conduction at both auricular and ventricular levels found in our preparations has already been clearly established for the past forty years, and deserves little discussion except for the
FIGURE 2

LEFT VENTRICULAR PRESSURE, ELECTROCARDIOGRAM
AND MEAN ARTERIAL PRESSURE BEFORE
AND AFTER QUINIDINE TREATMENT
IN AN INTACT DOG
L.V.E.D.P. (mm. Hg.)

control

after Quin.

RIGHT ATRIAL PRESSURE

(mean) 4.5 mm. Hg. 3.5 mm. Hg.

E.C.G.

H.R. 180/min. 200/min.

A.B.P. (mean) 104 mm. Hg. 54 mm. Hg.
TABLE I

EFFECT OF QUINIDINE ON CARDIAC WORK IN THE
CANINE HEART-LUNG PREPARATION

(The experimental values are those obtained at the
time of maximal drug effect on the recorded par-
ameters)
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>CARDIAC OUTPUT</th>
<th>HEART RATE</th>
<th>STROKE VOLUME</th>
<th>MEAN ARTERIAL PRESSURE</th>
<th>STROKE WORK</th>
<th>LEFT ATRIAL PRESSURE</th>
<th>STROKE WORK/LEFT ATRIAL PRESSURE</th>
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<tr>
<td></td>
<td>(cm³/min)</td>
<td>(per min)</td>
<td>(cm³)</td>
<td>x 10³ (mm Hg) (dynes/cm²)</td>
<td>x 10³ (dyne*cm)</td>
<td>x 10³ (mm Hg) (dynes/cm²)</td>
<td>(cm³)</td>
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<td>1</td>
<td>CONTROL</td>
<td>1120</td>
<td>120</td>
<td>9.1</td>
<td>84</td>
<td>111</td>
<td>1038</td>
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<td></td>
<td>QUIN, GLUC,</td>
<td>840</td>
<td>92</td>
<td>8.9</td>
<td>79</td>
<td>105</td>
<td>963</td>
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<td>(13, 0 mg/L)</td>
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<td>QUIN, SO₄</td>
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<td>(20 mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.0</td>
</tr>
</tbody>
</table>
### TABLE 2

**ACUTE EFFECTS OF QUINIDINE ON CARDIAC OUTPUT AND CARDIAC WORK IN INTACT DOGS**
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>CARDIAC OUTPUT (cm³/min)</th>
<th>HEART RATE (per min)</th>
<th>STROKE VOLUME (cm³)</th>
<th>MEAN ARTERIAL PRESSURE x 10³ (mm Hg) (dynes/cm²)</th>
<th>STROKE WORK x 10² (dynes cm)</th>
<th>LEFT VENTRICULAR END DIASTOLIC PRESSURE x 10² (mm Hg) (dynes/cm²)</th>
<th>STROKE WORK/LVEDP (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CONTROL 1991</td>
<td>160</td>
<td>12</td>
<td>94</td>
<td>125</td>
<td>1511</td>
<td>1,0</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 30 mg.</td>
<td>937</td>
<td>6</td>
<td>38</td>
<td>51</td>
<td>279</td>
<td>5,0</td>
</tr>
<tr>
<td>2</td>
<td>CONTROL 2348</td>
<td>140</td>
<td>17</td>
<td>160</td>
<td>213</td>
<td>3574</td>
<td>4,5</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 20 mg.</td>
<td>1772</td>
<td>13</td>
<td>100</td>
<td>133</td>
<td>1748</td>
<td>3,3</td>
</tr>
<tr>
<td>3</td>
<td>CONTROL 3102</td>
<td>180</td>
<td>17</td>
<td>104</td>
<td>139</td>
<td>2387</td>
<td>4,2</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 60 mg.</td>
<td>2207</td>
<td>11</td>
<td>52</td>
<td>69</td>
<td>764</td>
<td>3,6</td>
</tr>
<tr>
<td>4</td>
<td>CONTROL 2492</td>
<td>168</td>
<td>15</td>
<td>176</td>
<td>234</td>
<td>3477</td>
<td>4,7</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 40 mg.</td>
<td>2979</td>
<td>20</td>
<td>84</td>
<td>112</td>
<td>2222</td>
<td>2,8</td>
</tr>
<tr>
<td>5</td>
<td>CONTROL 2902</td>
<td>160</td>
<td>18</td>
<td>152</td>
<td>202</td>
<td>3672</td>
<td>4,5</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 40 mg.</td>
<td>4126</td>
<td>22</td>
<td>125</td>
<td>167</td>
<td>3616</td>
<td>8,0</td>
</tr>
<tr>
<td>6</td>
<td>CONTROL 2979</td>
<td>200</td>
<td>15</td>
<td>160</td>
<td>213</td>
<td>3174</td>
<td>5,0</td>
</tr>
<tr>
<td></td>
<td>QUIN, GLUC, 80 mg.</td>
<td>2185</td>
<td>10</td>
<td>125</td>
<td>167</td>
<td>1692</td>
<td>9,0</td>
</tr>
</tbody>
</table>
TABLE 3

EFFECT OF QUINIDINE ON THE PERIPHERAL RESISTANCE AND HEART RATE OF INTACT DOGS

(Showing lack of quantitative or qualitative relationship between peripheral resistance and heart rate changes)
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>PERIPHERAL RESISTANCE (dynes sec./cm$^5$)</th>
<th>PERCENT CHANGE (P.R.)</th>
<th>HEART RATE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Before Quinidine</strong></td>
<td><strong>After Quinidine</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3773</td>
<td>3241</td>
<td>- 14</td>
</tr>
<tr>
<td>2</td>
<td>5446</td>
<td>4510</td>
<td>- 17</td>
</tr>
<tr>
<td>3</td>
<td>2679</td>
<td>1883</td>
<td>- 30</td>
</tr>
<tr>
<td>4</td>
<td>5644</td>
<td>2254</td>
<td>- 60</td>
</tr>
<tr>
<td>5</td>
<td>4186</td>
<td>2421</td>
<td>- 42</td>
</tr>
<tr>
<td>6</td>
<td>4292</td>
<td>4572</td>
<td>- 6</td>
</tr>
</tbody>
</table>
basic responsible mechanism which will be presented in the following section.

The experiments on intact dogs support the conclusions gathered in the heart-lung preparations concerning the negative inotropic effect of quinidine. In this type of study (using intact animals under pentobarbital anesthesia) quinidine brings about unpredictable variations in heart rate over which we have no means of control. That very uncertainty may lead to the assumption of a positive inotropic effect in less precise experiments. Yet, when the end diastolic pressure values are compared with the work performed by the heart in the stroke following (stroke work/LVEDP), before and after quinidine effect, evidence of the drug's negative inotropic influence appears as unequivocal as in the heart-lung preparations. The direct or reflex mediated effects of quinidine on heart rate may exaggerate its depressant action on the myocardium or may compensate for it wholly or in part.

The advantages offered by continuous recordings in this study have allowed us to test for the required parameters at an apparently optimum time in absence of analytical determinations of plasma and tissue quinidine levels. Observations on the recovery of these animals from the studied effects agree with Weiss and Hatcher (31) and Weisman (37) in that the effective plasma concentration of the drug diminishes rapidly after single dosage.
It should be mentioned that the whole of this research has been carried out with an attempt to use minimal intravenous quinidine doses as compared to those used by other investigators in research and clinical practice (ranging from 15 - 125 mg/kg) (28, 36). Our doses have been determined on the basis of minimal cardiac effects and the reversibility of the changes observed.

The prompt and reversible hypotensive effect of intravenous quinidine in these animals is against Wasserman's theory that acidosis and acid-base disequilibrium is mainly responsible for the cardiac and peripheral effects of quinidine (65). Although studies on blood pH were not carried out, the small dosages used here which caused a marked hypotensive effect and the promptness of reversal without any alkali therapy do not seem to indicate that this is a primary mechanism of action of quinidine.
STUDY ON THE EFFECT OF QUINIDINE ON MYOCARDIAL BLOOD FLOW

According to most of the scarce experimental evidence available on this specific subject, quinidine does not seem to affect coronary flow significantly in any given direction. Bodo (1927) (26) reported on a decrease in flow only after the use of very large doses in the heart-lung preparation. Kountz (1932) (66), using a dilute quinidine sulfate solution, observed no effects on either isolated coronary arterial rings or on the revived human (children's) heart perfused by the Langendorff method. Similar results were reported by Elek and Katz (67) using the perfused dog heart. More recently the works of Rowe et al. (28) and of Szekeres (68), show significant changes in the coronary flow of canine heart using pharmacological doses of the alkaloid. In intact animals and by means of the nitrous oxide method, Rowe and co-workers have observed large increases in coronary flow fifteen minutes after intravenous quinidine administration. Szekeres, using a Langendorff preparation has shown a paradoxical effect of quinidine on myocardial blood flow by perfusing the fibrillating heart at varying temperatures. His results consist of a prolonged decrease in flow at normal temperatures and a marked increase in coronary perfusion at a low (26°C) temperature.
In our laboratory, efforts to quantitate the myocardial uptake of glucose and potassium led us to the measurement of coronary flows in canine heart-lung preparations.

Methods

Seven mongrel dogs, ranging in weight from 9.3 to 12.8 kilograms were anesthetized and treated similarly to those described in the previous Starling heart-lung experiments. Cardiac output, mean arterial pressure and lead II electrocardiographic tracings were continuously recorded in the direct-writing Grass polygraph, but no measurements of left or right atrial pressures were attempted. The coronary sinus was cannulated by means of a straight Morawitz metal cannula (i.d. 4.5 mm.) introduced via a small right auricular incision with adequate precautions taken to avoid complications of air embolism. Sinus blood drained into the lucite chamber of a calibrated Andrews outflow recorder (69) which in turn was connected to either a piston recorder or to a Grass volumetric pressure transducer (PT-5-A) feeding into the polygraph pre-amplifier. Special care was taken to adjust the level of the outflow tubing connected to the Morawitz cannula to avoid obstructing the coronary sinus outflow. Continuous flow tracings were successfully obtained in five of the seven experiments; direct timed measurements of coronary sinus blood draining into
a calibrated flask were done in the other two preparations at frequent intervals (every 15 - 30 seconds) prior to and after quinidine administration. Coronary sinus outflow blood was returned to the venous reservoir by means of a pump.

Since previous reports (70, 71) have demonstrated temporal variations of coronary flow in heart-lung preparations, two initial control experiments were performed to determine, if possible, the characteristics of any flow behavior pattern apparent in these denervated hearts. In the experimental animals ample time (20 - 30 minutes) was allowed for stabilization of the preparation. Mean arterial pressure was maintained at a constant value throughout each experiment. Blood volume determinations by the indicator-dilution method using T-1824 were done for the purpose of quantitating quinidine dosage. After a steady coronary flow was ascertained, treatment with quinidine (30 - 40 mg/liter of blood) was instituted either as a single injection into the aortic outflow tubing or as a continuous drip (0.25% in saline solution; 40 gtts/minute) into the reservoir blood until electrocardiographic evidence of early quinidine effects was noticed. Although the dosage of quinidine used in these experiments is higher than that given in the previous series it is considerably lower than that reported by others in similar studies and the intravenous dose used in clinical treatment.
Results

The control experiments show that in our heart-lung preparations, which in this study lasted from 40 to 140 minutes, coronary sinus flow remains unaltered as long as the mean arterial pressure is kept constant. Pre-treatment coronary sinus flow values for all experiments range from 36.0 ml/minute to 68 ml/minute at mean arterial pressure of 75 to 112 mm Hg respectively.

Treatment with quinidine invariably brought about an initial and almost immediate increase in coronary sinus outflow lasting approximately 45 to 75 seconds, followed by a slower but permanent significant decrease in flow of approximately 39 - 49 percent of the control values. Figure 3 shows the recordings of one control and two typical experimental studies. Table 4 presents a summary of coronary sinus flows observed before and after quinidine administration at similar time intervals.

A chi square test performed under the null hypothesis that all changes observed were due to chance or sampling variation led to its rejection at a 0.001 level of confidence. The initial increase and the later sustained decrease (2 minutes and 15 minute plus intervals) in coronary sinus flow, when tested under the same hypothesis, were found to be significant at the 0.02 and 0.001 level of confidence respectively.
These changes in coronary sinus flow are apparently independent of mean arterial pressure and always preceded any change in cardiac output.

Discussion

Our observations on the coronary sinus flow of heart-lung preparations thermostatically maintained at a constant 37°C temperature are in agreement with Szekeres' studies in fibrillating rabbit hearts (68). It is difficult to try to explain the transient initial increases in coronary flow on the basis of the hemodynamic effects discussed in the preceding section. The evidence suggests a temporary diminution of the intrinsic coronary smooth muscle resistance possibly mediated by chemical and metabolic factors. Studies on the effect of quinidine on myocardial metabolism have shown that this drug will inhibit oxygen uptake (72) and glucose utilization by the heart (73), impair oxidative phosphorylation (74) and will block intermediate metabolic processes (to be discussed further in the following sections) at the cardiac cellular level. It is also known that the myocardium will specifically react to quinidine treatment by increasing its active potassium cellular influx at a very early stage apparently simultaneous with the initial ECG effects (see section on potassium studies). On the basis of this evidence, it could be logically assumed that the initial increase in coronary
FIGURE 3
CORONARY SINUS BLOOD OUTFLOW RECORDINGS

A. Control Experiment

B. and C. Quinidine Experiments
A

B

C
TABLE 4

EFFECT OF QUINIDINE ON THE CORONARY SINUS FLOW OF HEART-LUNG PREPARATIONS
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>MEAN ARTERIAL PRESSURE (mm Hg)</th>
<th>CORONARY SINUS FLOW (ml/min)</th>
<th>MAXIMUM PERCENT CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before 0 time</td>
<td>After 45-70sec</td>
</tr>
<tr>
<td>1</td>
<td>CONTROL</td>
<td>105</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>CONTROL</td>
<td>112</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>CONTROL</td>
<td>75</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>QUIN. GLUC. (30 mg/L)</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>QUIN. GLUC. (30 mg/L)</td>
<td>103</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>QUIN. SO₄ (25 mg/L)</td>
<td>110</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>QUIN. SO₄ (30 mg/L)</td>
<td>85</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>QUIN. GLUC. (40 mg/L)</td>
<td>75</td>
<td>36</td>
</tr>
</tbody>
</table>
flow is associated with a lowered coronary resistance resulting from a negative energy supply - energy demand balance. In this case the energy demand being enhanced (at least in part) by the active K fluxes and the energy supply lowered by shifts in metabolic patterns. It is interesting to notice the similarity of this phenomenon to the "spontaneous" change in coronary flow described by Katz and his collaborators (75) consisting of an increase in coronary flow concomitant with a decrease in cardiac oxygen consumption, when the limit of normal physiological adjustment of cardiac oxygen consumption to oxygen availability is surpassed.

The possibility of a specific yet reversible effect of quinidine on coronary smooth muscle cannot be discarded at this point, and merits further investigation.

The more prolonged decrease in coronary flow which follows the observed decrease in cardiac output and cardiac work is more indicative of the drug's direct action upon the coronary system. Although no clear-cut evidence is available showing an increase in intracellular potassium at the coronary smooth muscle cell level, work done by Katz and Linden (76) on perfused dog hearts and by Emanuel (77) utilizing the dog's forelimb, suggests that an increase in intracellular smooth muscle potassium beyond a certain level will produce an increase in arteriolar resistance leading to a
marked decrease in regional blood flow. A similar effect brought
about by quinidine added to its established negative inotropic in-
fluence would constitute a plausible explanation for the coronary
blood flow changes reported in this study.
IV. QUINIDINE AND POTASSIUM METABOLISM

The physiological importance of potassium has been the subject of extensive reviews in the literature (78, 79, 80) and its critical role in muscular excitability and conductivity is of long standing certainty (81). The vast amount of literature prompted by the importance of potassium in Familial Periodic Paralysis and in metabolic and endocrine disorders has been also reviewed by Danowski and Elkinton (82), and the extra-renal factors involved in potassium homeostasis have been carefully reported on by Reinecke and co-workers (83, 84). During the past decade studies on ionic fluxes and cellular electrophysiology have brought forth evidence stressing the importance of this cation in the basic mechanisms underlying: 1) pathological disorders of the heart such as auricular fibrillation (85, 86) and possibly non-metabolic congestive heart failure (87); 2) incidence of ventricular fibrillation in hypothermia (46, 47) and under certain anesthetic agents such as cyclopropane (45); 3) effect of epinephrine on the heart (88); 4) changes in peripheral (skeletal muscle) (77) and regional blood flow and vascular resistance changes at cardiac and skeletal muscle levels (76, 77); and 5) the beneficial (or toxic) effects of cardiac drugs such as quinidine, procaine amide, and acetyl strophanthidin (87, 89, 90).
The potassium transfer kinetics have been studied in the isolated heart most consistently by Holland et al. (91), Wood and Conn (92) and Wilde (93). Holland has described the patterns of active and passive potassium fluxes in rabbit atria and has induced permanent fibrillation in his preparations upon net loss of potassium in excess of a determined critical value (86, 94), suggesting that one of the main causes in the etiology of auricular fibrillation is an increase in membrane permeability to potassium ions. Conn has reported on the linear correlation between ventricular contraction frequency and the rate of cellular potassium exchange; the latter being dependent on external K concentrations. This correlation was absent in cases of ventricular fibrillation and was explained as possibly due to the incomplete cell membrane depolarization associated with this disorder. Efflurometric studies with potassium (93) using turtle hearts have enabled Wilde to show that K release from the heart during systole is pulsatile in nature, starting at the plateau of the action potential. More complete studies on this subject have been reported by Cranefield and Hoffman (95). Ulrich (96) has recently reported on the active transport of potassium by heart mitochondria, a mechanism believed to be adversely affected in congestive heart failure.
Interest in these ionic dynamics and their relationship to quinidine therapy was revived in 1951 following the observations of Huggins and Chapman (97) on decreases in plasma potassium as caused by intravenous quinidine lactate. Comparing the effects of digitoxin and quinidine on rabbit hearts, Gertler et al. (98) found a significant increase in intracellular ventricular K with the alkaloid which was associated with a decrease in intracellular sodium. This work on K was confirmed by Armitage (99) who further roughly correlated the decreased contractility of isolated rabbit atria and the slowing in heart rate effected by quinidine to its action on K exchange. His theory explained the decreases in K efflux as due to a cell membrane rendered less permeable by the alkaloid drug. Similar experiments in isolated but fibrillating rabbit atrial preparations were conducted by Holland (100, 101) obtaining exactly the same results as Armitage. At this point, we became interested in exploring the cardiac effects of quinidine in animals partially depleted of K by extracorporeal vivo dialysis. Preliminary studies in intact dogs receiving intramuscular quinidine sulfate (30 mg/kg) every hour for a total period of four hours, showed that the femoral arterial and venous plasma K levels fell by approximately 50% of the initial control values (Figure 4). No changes in plasma
sodium or urinary potassium (or sodium) values were observed. Analysis of the arterio-venous K difference shown in Figure 5 failed to demonstrate any significant change with quinidine treatment suggesting that the K disappearing from the blood was not retained at the skeletal muscle cellular level (102). The following table presents the statistical significance of these findings.

TABLE 5

ANALYSIS OF VARIANCE

Effect of quinidine on arterial and venous plasma potassium in intact animals

<table>
<thead>
<tr>
<th>SOURCE OF VARIATION</th>
<th>d.f.</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>F Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMPLES (arterial and venous)</td>
<td>1</td>
<td>0.90</td>
<td>0.90</td>
<td>0.17</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>EXPERIMENTS (control and experimental)</td>
<td>3</td>
<td>370.84</td>
<td>123.61</td>
<td>23.50</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>INTERACTION</td>
<td>3</td>
<td>0.39</td>
<td>0.13</td>
<td>0.02</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>ERROR</td>
<td>70</td>
<td>368.43</td>
<td>5.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>77</td>
<td>740.56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This work agreed in part with the findings of Orabona and Manganelli (103) consisting of no alteration in red blood cell K content and a decrease in skeletal muscle K after oral quinidine administration to rats. The reversibility of the plasma K changes upon quinidine withdrawal in the above described experiments prompted us to speculate as to a possible specific site responsible for K retention (and later release) in these intact animals. Since the specificity of cardiac muscle response to this drug is its most outstanding effect, we decided to investigate the K exchange by the heart in a preparation isolated from any nervous or endocrine influences which may be brought about by other (previously described) effects of quinidine.

**Materials and Methods**

Two separate groups of mongrel dogs were treated and studied similarly to the heart-lung preparations described in Section II, except for minor modifications as specified in this description. The six animals of the first group comprised a pilot study (one control and five quinidine treated preparations) designed to investigate: a) K disappearance (if any) from blood circulating in an isolated, controlled type of preparation under the effect of an attempted single variable, quinidine sulfate administration; and b) whether this effect on K was of such
FIGURE 4

MEAN VENOUS PLASMA POTASSIUM CHANGES

IN INTACT DOGS UNDER THE EFFECT OF

INTRAMUSCULAR QUINIDINE SULFATE

(Courtesy of Dr. R. M. Reinecke's laboratory,
University of Puerto Rico School of Medicine,
Department of Physiology, San Juan, Puerto Rico)
MEAN VALUES OF PLASMA K

○ CONTROL
△ EXPERIMENTAL
FIGURE 5

ARTERIO-VENOUS PLASMA POTASSIUM DIFFERENCES
IN INTACT DOGS TREATED WITH INTRA-MUSCULAR QUINIDINE SULFATE

(Courtesy of Dr. R. M. Reinecke's laboratory, University of Puerto Rico School of Medicine, Department of Physiology, San Juan, Puerto Rico)
PLASMA K ARTERIO-VENOUS DIFFERENCES

- ○ CONTROL
- △ EXPERIMENTAL
magnitude as to quantitatively account for the K changes observed in intact animals. The alkaloid was introduced into the stabilized preparation as a 0.25% saline solution at a drip rate of 25 - 60 gtts/minute until a definite effect was observed in the electrocardiogram (lead II). The estimated total quinidine dose ranged from 14 - 90 mgs. per liter of blood. Sampling from the aortic outflow tubing was done at 5 - 10 minute intervals before treatment, serially during quinidine drip and every 2 - 5 minutes after ECG alterations. The blood was immediately centrifuged and plasma potassium measured with the Model 52A Perkin and Elmer flame photometer employing the lithium internal standard principle (104). Cardiac outputs were determined by measuring 6 second outflows into a calibrated cylinder, arterial pressures were read from a mercury manometer connected to the aortic outflow tubing, and the ECG recorded in the Physiograph (1956 Model of the E&M Instruments Co., Houston, Texas). A glucose-insulin-saline drip (5 - 9 gtts/minute) was infused in three of the five experiments in an attempt to compare its well known effect on K flux with that of a later quinidine sulfate dose.

The second series of experiments underwent the following modifications:

1. Coronary sinus cannulation and sinus outflow measurements (or recordings).
2. Simultaneous coronary sinus and arterial blood sampling for plasma K determinations.

3. Continuous recording of cardiac output, mean arterial pressure, coronary sinus flow and ECG in the Grass polygraph.

4. Blood volume determinations by the indicator-dilution technique using Evans Blue as indicator.

5. Simultaneous removal of the heart and lungs in several experiments immediately after collection of final blood samples. Upon removal of all visible fat from the heart, the organs were separately weighed and oven dried to constant weight. Tissue analysis for K was done following Lowry's and Hastings' technique (105) with the Perkin and Elmer flame photometer.

6. Except for one experiment, infusion of glucose-insulin-saline solution was not given.

The techniques, materials and recording's procedures involved in the above modifications have been described in the preceding two sections. To determine myocardial K uptake, total
arterial coronary flow was estimated as 5/3 coronary sinus flow. In the seven experiments (one control, six treated) of this second group, the quinidine salt (sulfate or gluconate) was added after blood volume determination, either as a) a drip infusion or single injection into the venous reservoir with precautions taken for adequate mixing, or b) as a single injection into the aortic outflow tubing. The total dose ranged from 17 - 40 mgs. per liter of blood.

In two cases (Experiments 4 and 5) a single 1 cc. dose of epinephrine (1:50,000 solution) was added to the venous reservoir blood at the time of maximal quinidine effect (monitored by cardiac output and left atrial pressure recordings - as in Section I). Post-epinephrine blood samples for K were taken at 30 second (initially) to 5 minute intervals from the time of injection until full reversal of quinidine effects.

Quantitation of the K changes observed at the circulating plasma and myocardial tissue levels was done as follows:

1. Total Plasma K Removal in mEq =
   \[ \int \frac{\text{Plasma Volume}}{\text{Plasma K} \cdot dt} \]

2. Myocardial K Uptake in mEq =
   \[ \int \left( A_K - V_K \right) dt \int (\text{Total Coronary Flow}) t dt \]
Results

Group 1: The effect of quinidine sulfate on blood K was studied with respect to dosage and time in these experiments. It was also attempted to compare the drug’s effect to that of an insulin-glucose-saline drip which use has become a standard procedure in heart-lung preparation studies (61). The results obtained in this pilot group are summarized in Table 6. Figure 6 shows the time sequence changes in plasma K values of experiments with and without insulin but with quinidine treatment, giving the observer a clearer idea of the magnitude of each effect. It also includes the control values of the preparation receiving insulin plus glucose but no quinidine. The experimental observations can be stated as follows:

1. Plasma K values in these heart-lung preparations (Figure 6) are above the normal range found in intact animals (Figure 4) and tend to remain so even after stabilization or after insulin-glucose treatment.

2. Quinidine exerts a definite effect at the heart-lung level characterized, in part at least, as removal of significant amounts of K from the circulating blood by either or both organs. A chi square test of the removal values presented in Table 6 rejected the
null hypothesis at a level of confidence of less than 0.01.

The rate of K removal in these heart-lung preparations is from 10 - 50 x higher than in the intact dogs experiments initially described (102), suggesting a highly specific site responsible for the disappearance of K from the blood upon quinidine administration.

3. The plasma K variations following quinidine seem to be roughly proportional to the dosage used when correlated with the time duration of the myocardial effect (measured up to the time of electrocardiographic variations reversal). This fact is graphically illustrated by the calculated curvilinear regression curve shown in Figure 7.

The duration of the myocardial effect, though, is apparently independent of dosages (especially those in the lower range). This finding was to be anticipated if we consider the large number of variations in individual responses to similar quinidine doses in the group studies which have been reported with the clinical use of the drug (35, 36).

4. It is interesting to notice that with increasing increments in blood quinidine levels (as shown in
experiment 4) by rapid multiple dose treatment, there is a decrease in the duration of myocardial response. This effect has been previously described by Wegria (57) in cases of auricular fibrillation. The possibility of a toxic phenomenon has to be considered, although the quinidine dose utilized here is still below the maximum intravenous dose reportedly used by Ashly (106).

5. Figure 6 also gives a clear indication of the insulin-glucose effect on K as compared to that of quinidine, the latter being of a significant larger magnitude.

Group 2: Table 7 presents a summary of the most significant findings in six successful experiments. These confirm more extensively the results obtained in the pilot group concerning enhanced removal of K from the circulating blood in heart-lung preparations treated with quinidine. They also show further the significant specificity of the myocardium for K uptake when under the influence of this alkaloid. The initial increase in rate of myocardial uptake, which is maximum in most cases, can be explained on the basis of increases in both coronary flow and arterial venous potassium extractions. After the initial increase in coronary flow has subsided and even fallen
TABLE 6

EFFECT OF QUINIDINE SULFATE ON PLASMA POTASSIUM OF HEART-LUNG PREPARATIONS

(Plasma K disappearance is expressed as removal of total mEq K from the calculated plasma volume circulating in the preparation)
<table>
<thead>
<tr>
<th>EXPERIMENT</th>
<th>INSULIN AND GLUCOSE (DRIP)</th>
<th>QUINIDINE DOSE (mg/l)</th>
<th>DURATION QUINIDINE EFFECT (Minutes)</th>
<th>PLASMA K REMOVAL mEq (Total)</th>
<th>K REMOVAL mEq(l) min, (Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>Yes</td>
<td>___</td>
<td>___</td>
<td>0.200</td>
<td>0.004</td>
</tr>
<tr>
<td>1</td>
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<td>63.0</td>
<td>74</td>
<td>1.144</td>
<td>0.018</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>25.0</td>
<td>14</td>
<td>0.378</td>
<td>0.027</td>
</tr>
<tr>
<td>4 a)</td>
<td>Yes</td>
<td>30.0</td>
<td>12</td>
<td>1.890</td>
<td>0.158</td>
</tr>
<tr>
<td>b)</td>
<td>No</td>
<td>9.0</td>
<td>9</td>
<td>0.168</td>
<td>0.019</td>
</tr>
<tr>
<td>c)</td>
<td>No</td>
<td>15.0</td>
<td>7</td>
<td>0.336</td>
<td>0.048</td>
</tr>
<tr>
<td>d)</td>
<td>No</td>
<td>45.0</td>
<td>3</td>
<td>0.378</td>
<td>0.126</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>14.0</td>
<td>53</td>
<td>1.092</td>
<td>0.021</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>17.5</td>
<td>51</td>
<td>0.875</td>
<td>0.017</td>
</tr>
</tbody>
</table>

* Complicating pulmonary edema early in experiment
FIGURE 6

PLASMA POTASSIUM IN HEART-LUNG PREPARATIONS:

QUINIDINE VS. INSULIN-GLUCOSE EFFECT
FIGURE 7

CURVILINEAR REGRESSION CURVE SHOWING CORRELATION BETWEEN QUINIDINE DOSAGE, PLASMA K VARIATIONS AND DURATION OF MYOCARDIAL EFFECT
Y = 0.03073 + 0.00819X1 + 0.0000414X2

(Where: X2 = duration of effect in minutes)
below the control values, enhanced $A_{K-V_K}$ extraction is responsible for maintaining a decrease in arterial $K$ of the circulating blood as shown by a representative experiment in Figure 8. Statistical analysis of the $K$ removal and myocardial uptake values shown in Table 7 by the chi square test under the null hypothesis that all variations were due to chance led to its rejection at a $< 0.001$ level of confidence. Further analysis of variance for the plasma $K$ removal and myocardial $K$ uptake changes demonstrated a positive correlation between these $K$ fluxes ($P = < 1.0\%$).

It must be mentioned that in those experiments where a quinidine drip was used, and serial simultaneous sampling of arterial and coronary blood obtained, it was possible to correlate the changes in ECG with those of plasma potassium. In these preparations, the ionic change was simultaneous (or preceded by a few beats) to the heart rate and T-wave first observed variations. In one case, where left atrial pressure was being measured, the maximum $K$ change occurred at the same time as the pressure increase was detectable.

Total myocardial potassium content, as determined by dry tissue analysis, was increased by $5 - 10\%$ over control values in the quinidine treated preparations. Similarly
analyzed pulmonary tissue potassium was apparently not altered by the drug.

In the two experiments where epinephrine was added at the time of established quinidine effect, a reversal in $K^+$ flux was observed preceding the reversal of coronary flow and inotropic effects of the alkaloid by epinephrine. At the time of maximum coronary flow associated with the latter drug's effect, $K^+$ efflux was approximately 400% above the pre-quinidine control flux values (Figure 9).

Summary and Discussion

In both groups of experiments, it has been observed that, under the influence of quinidine, blood $K$ is significantly decreased in heart-lung preparations. This effect is brought about by an enhanced rate of $K$ removal by the myocardium when under the influence of the drug (as evidenced by the time relationship of the initial ECG and ionic changes which are simultaneous in occurrence). By serial and simultaneous sampling of arterial and venous blood it is possible to detect the normal variations in $K^+$ flux which occur in the stabilized preparations with an apparently constant coronary flow. As may be observed in Figures 8 and 9, influxes and effluxes of the ion are not difficult
TABLE 7

SUMMARY OF MYOCARDIAL POTASSIUM DYNAMICS AS AFFECTED BY QUINIDINE IN HEART-LUNG PREPARATIONS
<table>
<thead>
<tr>
<th>Experiment</th>
<th>Blood K Removal</th>
<th>Myocardial K Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (mEq/min)</td>
<td>Total (mEq)</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>QUIN. GLUC. (20 mg/L)</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>QUIN. GLUC. (17.5 mg/L)</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>QUIN. GLUC. (23 mg/L)</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>QUIN. GLUC. (36 mg/L)</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>QUIN. SO₄ (35 mg/L)</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>QUIN. SO₄ (42 mg/L)</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>QUIN. GLUC. (30 mg/L)</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>CONTROL (Insulin &amp; Glucose)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
FIGURE 8

VARIATIONS IN ARTERIO-VENOUS PLASMA POTASSIUM

(CONTROL AND QUINIDINE EXPERIMENTS)
PLASMA K (mEq/L)

---

**CONTROL**

**QUIN**

**EXPERIMENTAL**

**ARTERIAL**

**VENOUS**

---

TIME (Minutes)
FIGURE 9

REVERSAL OF QUINIDINE'S EFFECT BY EPINEPHRINE

AS OBSERVED BY PLASMA K CHANGES
to observe during the control period. Yet, when quinidine is administered, there is evidence to show a sustained influx of K and a progressive decrease in venous values. These observations suggest an enhancement of active K transport across the myocardial cell membrane exceeding the inhibition of passive efflux, if present; and agrees with Holland's initial observations in rabbit atrial preparations (100). From results of studies performed in this laboratory (Roldan, Ogden, Sapirstein, unpublished work) concerning the effect of quinidine on Rb\textsuperscript{86} uptake by the myocardium, it appears that 1) the intracellular myocardial K compartment is an increasingly available one until a large steady reservoir is attained at equilibrium and 2) under the effect of quinidine, this compartment increases at a much higher initial rate (therefore, showing a faster Rb\textsuperscript{86} uptake) and apparently becomes stabilized at a larger total value. Although there is no evidence at present to support a well defined reason for this increased K compartment under the influence of quinidine, Ulrich's (96) report on the active transport of K\textsuperscript{+} by myocardial cell mitochondria, and Furman's (107) observations on the "protein anabolic effect" of quinidine; added to the drug's known metabolic effects, pose a very interesting basis for speculation concerning the mechanism of action of quinidined.
The reversal of quinidine's cardiac conduction and mineral metabolic effects by epinephrine associated with the increased coronary flow, although suggestive, does not constitute irrevocable evidence of quinidine-epinephrine antagonism. Nelson's (30) long standing evidence of this antagonism at the peripheral vascular level and Hiatt's (52) work on the sympatholytic effects of quinidine (corroborated by Folle (108), where he proposes an inhibitory mechanism at the nerve-muscle endings, do not seem to apply as specifically to this denervated heart preparation. Our observations could be explained on the basis of the strong inotropic action of epinephrine, which with this relatively large injected dose, may have overcome whatever inhibitory action quinidine might have had on the heart's endogenous nor-epinephrine.
V. QUINIDINE AND MYOCARDIAL GLUCOSE UPTAKE

During the course of the initial K studies in intact animals mentioned in the preceding section, it was observed that in some cases where blood glucose was determined, the latter underwent unexpected variations under the effect of quinidine considering the direction of the K change. In Table 8 it can be observed that the increases in blood glucose were of such magnitude as to warrant further investigation.

TABLE 8

BLOOD GLUCOSE LEVELS BEFORE AND AFTER INTRAMUSCULAR QUINIDINE SULFATE ADMINISTRATION IN INTACT DOGS

(Percent Increase in Venous Plasma Glucose of Simultaneous Control and Quinidine Experiments)

<table>
<thead>
<tr>
<th>TIME</th>
<th>CONTROL</th>
<th>EXPERIMENTAL</th>
<th>CONTROL</th>
<th>EXPERIMENTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs.</td>
<td>43.27</td>
<td>120.91</td>
<td>80.95</td>
<td>191.24</td>
</tr>
<tr>
<td>4 hrs.</td>
<td>23.67</td>
<td>102.15</td>
<td>62.43</td>
<td>210.95</td>
</tr>
</tbody>
</table>

(Courtesy of Dr. Roger M. Reinecke's laboratory, Department of Physiology, U.P.R. School of Medicine, San Juan, Puerto Rico)
It is known that quinidine will inhibit glucose utilization in incubated rat heart slices (109); impair glucose utilization in humans, who tend to show an abnormal glucose-tolerance test when ingesting the drug (107); and will inhibit both glucose and fructose uptake in the rat diaphragm abolishing also the stimulation of glycolysis by these two sugars (110). Yet, the marked increase in blood glucose of fasting (30 hrs.) animals, significantly above the control changes (probably due to experimental stress) and maintained for a relatively long period of time, suggested that some mechanism for glucose release may be triggered by quinidine. The most obvious site for investigation would be a liver isolated of extra-hepatic endocrine influences, and studies on this subject have been initiated. Yet, the availability of heart-lung preparations plus the reports on glucose metabolism in congestive heart failure (111) and in cardiac glycoside therapy (112) prompted us to pursue the study of quinidine's effect on myocardial glucose uptake.

Methods and Materials

Six experiments (one control, five experimental) were conducted in mongrel dogs which underwent similar preparation and treatment as described in Section III. Four of these dogs were utilized for simultaneous studies of coronary flow and
glucose uptake. In two experiments a glucose-insulin drip (1.2% glucose in saline solution containing 15 units of insulin) was used in order to investigate further into the possibility of the so-called quinidine-insulin antagonism (107). In the remaining four experiments, d-glucose was added to the reservoir blood prior to onset of the experiments so as to attain a concentration ranging from 80 - 150 mg/100 ml of blood. Coronary sinus cannulation and flow measurements, blood volume, cardiac output, arterial pressure and ECG (lead II) recordings were done as previously described. Blood glucose was determined by the glucostat colorimetric technique (113, 114) as described by Saifer (115).

After a period of time allowed for stabilization of the preparation (average = 40 minutes), control samples and recordings were obtained, followed by injection of quinidine gluconate (20 - 30 mg/liter of blood) either into the venous reservoir or into the aortic outflow tubing. Serial sampling and continuous recordings after treatment were taken as in previous experiments.

Calculations for total coronary flow, glucose disappearance from the circulating blood, myocardial rate of uptake and total myocardial glucose uptake were performed during control and post-treatment periods, following the same quantitation
Techniques as for the K data analysis described in Section IV.

Results

Table 9 presents a summary of the effects of quinidine on the blood glucose of these preparations. As expected, in the insulin experiments the rate of glucose removal and uptake are of such magnitude as to maintain values well below normal in the stable preparation. Upon addition of quinidine, there is a definite inhibition of myocardial glucose uptake with no apparent release from the heart. In those animals where no insulin was used, the myocardial uptake inhibition was more marked, with glucose release (or efflux) at the time of maximum quinidine effect (Figure 10). This quinidine induced variation is small in magnitude and transitory in nature. It is also reversed by epinephrine.

Summary and Discussion

An attempt was made to study the effect of quinidine on the glucose uptake of hearts working at near maximum capacity in heart-lung preparations. From the results obtained it can be stated:

1. Relatively small doses of quinidine will effect a decrease in:

   a) the total amount of glucose removed from the circulating blood, and
TABLE 9

BLOOD GLUCOSE REMOVAL AND MYOCARDIAL
GLUCOSE UPTAKE IN
CANINE HEART-LUNG PREPARATIONS

(QUINIDINE VS. INSULIN EFFECTS)
<table>
<thead>
<tr>
<th>Experiment</th>
<th>Blood Glucose Removal Rate (mg/min)</th>
<th>Total (mg)</th>
<th>Myocardial Glucose Uptake Rate (mg/min)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>18.0</td>
<td>956</td>
<td>9.9</td>
<td>442</td>
</tr>
<tr>
<td>(Insulin and Glucose) plus Quin. Gluc. 17.5 mg/L</td>
<td>17.6</td>
<td>12.7</td>
<td>300</td>
<td>204</td>
</tr>
<tr>
<td>3</td>
<td>8.0</td>
<td>2.2</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>(Quin. Gluc. 23 mg/L)</td>
<td>8.4</td>
<td>8.3</td>
<td>225</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>16.2</td>
<td>1.7</td>
<td>225</td>
<td>39</td>
</tr>
<tr>
<td>(Quin. Gluc. 42 mg/L)</td>
<td>8.9</td>
<td>8.9</td>
<td>62</td>
<td>15</td>
</tr>
</tbody>
</table>
FIGURE 10

INHIBITORY EFFECT OF QUINIDINE ON THE MYOCARDIAL GLUCOSE UPTAKE OF CANINE HEART-LUNG PREPARATIONS
b) in the rate of this removal.

2. The total glucose and rate of its myocardial uptake are also significantly decreased. In some cases a negative glucose balance was observed as shown in Figure 10.

3. These effects are also brought about by the drug in preparations receiving an insulin infusion.

4. The observed inhibition on glucose uptake is initiated in the early phase of the quinidine electrocardiographic effect and at a time where the coronary flow has been shown to be enhanced.

From the above mentioned results we may conclude that quinidine has a definite inhibitory effect on myocardial glucose uptake, the nature of which is not affected by insulin. Quantitation of this inhibition does not account for the marked hyperglycemia observed in intact quinidine treated animals, as has been shown to happen with respect to the K effect (Section IV).

These results are in partial agreement with those reported by Webb and his associates (72) in isolated rat heart incubation studies showing inhibition of glycolysis with quinidine. Yet,
our observations show an apparent time relationship between the metabolic, electrical and the initial hemodynamic effects of the drug, of which, the first two were not found to be related in Webb's work. Inhibition of glycolysis by this alkaloid (as a result of quinidine's inhibitory action on transphosphorylating enzymes (73, 74, 107) supports the idea that the energy forming reactions involved in the normal metabolic patterns of a working heart are in deficit with respect to the increased energy demands resulting from its effect on active transport. Should this mechanism, wholly or in part, be responsible for the oxygen uptake variations observed with the drug (28) it could also help in explaining the initial coronary flow changes reported in our study. The reversed glucose fluxes observed in some experiments constitute a finding which deserves further investigation, although a shift in extracellular free glucose equilibrium may be the result of a decreased glucose utilization.
VI. FINAL SUMMARY AND DISCUSSION

The well known cardiac anti-fibrillatory drug, quinidine, has been studied with respect to its effects on certain aspects of cardiovascular hemodynamics and on the mineral (K) and carbohydrate (glucose) metabolism of the working canine heart. An attempt has been made to observe the drug's actions under strictly controlled conditions and utilizing the smallest effective dosage possible so as not to incur on observations of its toxic effects. Continuous monitoring of the parameters under study has enabled us to determine initial and maximal effects of the agent. It has also been possible to determine quantitative, qualitative, and time occurrence correlation of these effects; which have been missing in the literature due to the varied methods, techniques and dosages used by a large number of independent investigators.

In general, we can summarize our observations as follows:

I. A definite and significant negative inotropic effect can be attributed to quinidine as studied in the working heart of heart-lung preparations and intact dogs. The non-specific variations in heart rate and in cardiac outputs observed in intact animals (which
may have led other investigators to different conclusions) when studied in relation to the other parameters necessary for the establishment of the inotropic effect of the drug, show that the former give no clear indication of quinidine's depressant action on myocardial work. Therefore, they are not desirable measures of a drug's inotropic effect when studied per se.

2. Quinidine brings about an initial increase in myocardial blood flow which we have attempted to explain on the basis of its effects on ionic (K) transport and on myocardial carbohydrate metabolism. It should be mentioned that the drug's maximum effect on coronary flow is on the opposite direction (decreased) at a time when the maximal negative inotropic effect is also observed. The constancy of the maximum decrease in flow effected by varying doses of quinidine constitutes an interesting finding which may merit further investigation.

3. Quinidine exerts a definite and specific effect on the inward active transport of K at the myocardial level. This effect is closely related to the drug's
well known action on the tissue excitation recovery process as has been described by many investigators for the past six decades. In our studies we were able to detect the very initial ECG heart rate and T-wave changes and correlate these with the ionic variations.

4. Myocardial uptake of glucose is significantly inhibited by quinidine action at a time when both coronary flow and K active transport are enhanced by the drug.

The above changes are found to be reversible at the termination of quinidine electrocardiographic effects and are also reversed (wholly or in part) by the addition of epinephrine to our preparations.

From these observations it can be reasonably assumed that the mechanism involved in quinidine's effect upon the myocardium is initially one of enhancement of active K⁺ flux into the cell associated with the very early T-wave changes seen in the electrocardiogram. This enhanced K⁺ transport may be associated with changes in membrane permeability effecting a net and sustained increase in intracellular K⁺. The energy demands imposed by such a mechanism apparently surpass the energy supply impaired
by the drug due to its action at enzymatic levels, with such an imbalance resulting in a slowing of the myocardial tissue recovery process as evidenced by the Q-T changes seen when the effect of the drug is fully established. The changes observed in coronary flow and myocardial glucose uptake, added to evidence presented by other investigators (previously mentioned) lend support to this working hypothesis.

The negative inotropic effect of quinidine can also be explained as a consequence of these ionic and metabolic derangements. Although it is probable that the myocardium has shifted its metabolic pattern under quinidine in a fashion similar to that described by Laurent and Katz (75), a deficit in energy supply would still remain making it impossible for the heart to maintain its working load.

Recently, an attempt has been made to explain the mechanism of quinidine action on the basis of its inhibition of Na+ transport (24, 116), initially proposed by Weidmann in 1955 (117). It is our belief that the evidence for this explanation, based on depolarization rate changes under the effect of quinidine and utilizing different stimulation frequencies for isolated cardiac tissue, has been clearly debated as erroneous by West and Amory (23, 118). Our findings do not totally disagree with the Weidmann group.
idea, since it is very possible that Na\(^+\) influx is inhibited at the time of maximal quinidine effect. It is our impression though, that this Na effect is a consequence of quinidine's primary action on potassium. The reversibility of this K effect by epinephrine, coupled with reversal of other quinidine effects lends itself to speculation of a possible inhibition of the myocardial contained endogenous sympathetic hormone by the studied alkaloid as has been postulated by Hiatt (52) at the peripheral vascular level.

Therefore, we may conclude that the studies presented in this work show results that can be correlated to give a clearer idea of the mechanism of action of quinidine on the working heart, which appears to be primarily based on the alkaloids' effect upon K dynamics.


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a) Researches on the circulation time in organs and on the influences which affect it. I. Preliminary paper. II. The time of the lesser circulation. III. The circulation time in the thyroid gland, and the effect of section and
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118. West, T. C. and D. W. Amory: Role of stimulation rate on the quinidine effect on depolarization and repolarization in rabbit atrium. Pharmacologist. 1;76, 1959.
I, Pura Norma Suárez Roldán, was born in Caguas, Puerto Rico, August 16, 1931. I received my secondary school education in the public schools of my home town. At the University of Rochester, New York, I trained as an undergraduate student from 1947 to 1949. The University of Puerto Rico granted me the Bachelor of Science degree in 1951. From the School of Medicine of the University of Puerto Rico, I received my degree of Doctor in Medicine in 1956. I fulfilled my one year internship requirements at the Presbyterian Hospital, San Juan, and at the Fajardo District Hospital, Fajardo, Puerto Rico, in 1957. In July, 1958, I was appointed Research Associate in the Physiology Department of the University of Puerto Rico Medical School. In August, 1959, I was appointed Associate in Physiology at the same school. I held this position until March, 1960, when I was granted a post-doctoral fellowship by the National Institutes of Health to continue graduate studies in the Department of Physiology at the Ohio State University. During the tenure of this three year fellowship, I completed the requirements for the Doctor of Philosophy degree.

I have tentatively accepted a position as Assistant Professor in Physiology at the School of Medicine of the University of Puerto Rico.