Increased Survival with Prophylactic Quinidaine After Experimental Myocardial Infarction

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SUMMARY

Experimental myocardial infarction was produced in 60 farm pigs by gradual coronary occlusion with an Ameroid constrictor placed around the left anterior descending coronary artery. Twenty animals were treated with 10 mg/kg/6 hr of quinidine, 10 with 5 mg/kg/6 hr, and 10 with 2.5 mg/kg/6 hr for a total period of 72 hours. Twenty animals served as controls. Serum quinidine levels were measured at 6-hour intervals. Significantly increased survival, when compared to controls, were observed in those animals treated with 5 and 10 mg/kg/6 hr of quinidine, but not in those receiving 2.5 mg/kg/6 hr. Under the described experimental conditions, designed to cause a reproducible, consistent infarction, quinidine treatment in nontoxic and well-tolerated doses significantly increased survival. Furthermore, there is a dose level below which this effect is lost. Whether the results of this study are applicable to man in preventing sudden death is unknown.

Additional Indexing Words:
Ameroid constrictor Gradual coronary occlusion

Sudden Death is a well-known phenomenon in coronary artery disease, especially in the clinical setting of acute myocardial infarction or severe angina pectoris. Previous studies have established that the acute localized myocardial ischemia or injury associated with these two conditions is often a prelude to a terminal cardiac arrhythmia. Furthermore, it has been shown that a myocardial depressant such as procainamide or quinidine can control or abort such arrhythmias in individual clinical cases or under experimental conditions. Quinidine is one of the most frequently used anti-arrhythmic agents because a given dosage schedule of the drug can be closely correlated with therapeutic and toxic effects; it can also be readily and accurately measured in the serum.

Despite the recognized ability of quinidine to revert ventricular arrhythmias, no evidence is available to advocate its routine use as a prophylactic measure after acute myocardial infarction or during myocardial ischemia. The results of clinical studies are conflicting because of small patient populations, the lack of adequate controls, and the failure to correlate treatment with dosage or serum con-
centration of the drug. Previous animal studies are difficult to interpret because of the variables necessarily introduced by acute coronary ligation in an open-chested animal under anesthesia. Thus, the value of routine treatment with quinidine in myocardial ischemia and infarction remains an unresolved issue.

This study was undertaken to evaluate quinidine as a protective measure during experimentally produced myocardial ischemia and infarction in the farm pig. The technique was designed to provide gradual coronary occlusion in an anesthetized ambulatory animal. The pig was chosen because the coronary arterial distribution, unlike that of the dog, is both consistent and similar to that of man.

**Methods**

Sixty locally raised farm pigs, weighing between 25 and 35 pounds, were randomly selected without regard to sex. Each animal was premedicated with atropine (0.4 mg intramuscularly), anesthetized with Fluothane, and intubated. Respirations were controlled by a Harvard pump respirator with the animals breathing a mixture of Fluothane and oxygen. A thoracotomy was performed with sterile technique, and the pericardium was exposed and widely excised. The left atrium was retracted with a bulldog clamp and the left anterior descending coronary artery was carefully dissected to free a 6 to 10-mm segment just distal to its origin from the main left coronary artery. An Ameroid constrictor with a 1.5-mm lumen was placed around the exposed segment (fig. 1). Such a constrictor will not initially interrupt flow, but the hygroscopic Ameroid material absorbs water from the body fluids and gradually swells to occlude the vessel within 24 to 48 hours. Following placement of the constrictor, the thoracotomy was closed and the chest was drained of air by means of a chest tube. A 12 F Bardic polyvinyl catheter was inserted into the external jugular vein for chronic blood sampling and administration of medication. The animals recovered in individual cages and ate and drank ad libitum during the study period.

The 60 animals were then divided into a control group (20 animals), a group treated with quinidine, 10 mg/kg/6 hr (20 animals), a group treated with 5 mg/kg/6 hr (10 animals), and a group treated with 2.5 mg/kg/6 hr (10 animals). The total doses of quinidine gluconate (calculated as pure anhydrous quinidine), diluted in 20 to 40 ml of 0.9% saline, that were administered per 24 hours were 40, 20, and 10 mg/kg, respectively. The drug was infused slowly through the intravenous neck catheter over a 5-minute period. The control animals received equal volumes of saline. Treatment was continued for 72 hours at which time the study was terminated. A sample of blood was drawn from every animal just prior to each injection, and the serum quinidine was determined on all samples from the treated groups by the method of Brodie and Udenfriend.

In addition to the study animals described, seven pigs underwent a sham procedure identical to the one described except that a constrictor was not placed on the left anterior descending coronary artery although the artery was dissected free. Three of these pigs were treated with 10 mg/kg/6 hr of quinidine, three with 15 mg/kg/6 hr, and one received only saline.

Electrocardiographic telemetry was accomplished by a frequency modulated transmitter with a stabilizing FM to FM subcarrier unit, a frequency response of 0.1 to 200 or 300 cps, and an input impedance of approximately 5,000 ohms. The transmitted signal was received by a Sherwood FM stereo tuner filtered with a demodulator. This signal was then passed through a Tektronics cathode ray oscilloscope for continuous visual monitoring and preamplification for recording on 1/4-inch magnetic tape at a speed of 1 inches/sec via an eight-channel Mnemotron recorder. ECG records stored in this way were easily available for replay on an Electronics-for-Medicine photographic recorder.

Postmortem coronary arteriography was performed within 6 hours of death or the hearts were immediately frozen until the study was accomplished. The procedure was carried out by cannulation of each coronary artery (right coronary, left anterior descending, and left circumflex) with polyethylene catheters, through which was flushed 500 ml of physiological saline followed by finely pulverized liquid barium sulfate under a constant pressure of 100 mm Hg for

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*Fluothane, brand of halothane, furnished through the courtesy of Ayerst Laboratories, New York, New York.
†Harvard Apparatus Co., Dover, Massachusetts.
‡Three Points Products, Montreal, Canada.

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§Injectable Quinaglucone, 0.08 g of quinidine gluconate per ml, 62.3% anhydrous quinidine, generously supplied by the Vitamex Pharmaceuticals, Inc., Philadelphia, Pennsylvania.

**Monitor Instruments, Chapel Hill, North Carolina.
Ameroid constrictor is around the left anterior descending coronary artery of the heart of a pig just distal to the bifurcation of the left coronary artery. On the right is an end-view of the constrictor showing the outer steel ring and a 1-mm longitudinal slit allowing access to the 1.5-mm central lumen. Note the centimeter ruler at the base of the illustration.

20 minutes. The barium suspension was prepared by adding 240 ml of Micropaque powder* to 320 ml of warm distilled water with 30 g of gelatin and 1.5 g of sodium chloride. The contrast material was fine enough to penetrate to the capillary level but did not traverse the capillaries and fill the veins. After injection the hearts were fixed in 10% Formalin, and both anteroposterior and lateral stereoscopic roentgenograms were obtained for evaluation of constrictor closure and collateral vascularization. Following the roentgenographic study, multiple sections were obtained from both ventricles and the interventricular septum. Paraffin-embedded tissue was stained with hematoxylin and eosin. The histopathological findings were graded as follows:

Grade 0: No pathological findings
Grade I: Minimal spotty areas of necrosis in subendocardium only
Grade II: Scattered subendocardial infarction
Grade III: Uniform subendocardial infarction
Grade IV: Large transmural infarction

*Micropaque Powder, Damancy Company Limited,
The mean serum quinidine level measured at 6-hour intervals for each successive 24-hour period of treatment for the indicated dose schedules are plotted as bars. The numbers at the top of each bar indicate the number of determinations from which each mean value was derived.

The lungs were examined for significant pulmonary atelectasis, congestion, infection, or infarction. Animals surviving beyond the 72 hours of treatment were sacrificed at intervals from 1 to 6 weeks after operation.

Survival times in each of the three quinidine-treated groups were compared statistically with the control population by means of Kolmogorov-Smirnov nonparametric tests.

Results

Those pigs receiving 10 mg/kg/6 hr of quinidine survived longer than the control animals (P < 0.01). This increase in survival can be readily appreciated in figure 2, where the survival times of individual animals are shown as single bars composing the total of survival times for the treated and control groups. Three control animals (15%) and seven treated animals (35%) survived the 72 hours of treatment. Animals which survived 72 hours were termed “survivors” and generally lived until sacrificed 1 to 6 weeks later. All other animals died during the treatment period and hence were termed “non-survivors.” Although the percentage of survivors within the treated groups compared to those in the control group is not significant statistically, the increased numbers of survivors nonetheless agreed well with the increase of survival time demonstrated when all the animals of each group are compared.

The two smaller study groups receiving the smaller doses of quinidine are included for comparison in figure 2. Statistical analysis comparing all animals in each treated group reveals a significant difference still present at the 5.0 mg/kg/6 hr dose of quinidine, but absent at the 2.5 mg/kg/6 hr level. In figure 3 are compared only those animals of the four groups which died before the end of the treatment period, that is, the nonsurvivors. Again, those animals treated with 5.0 and 10 mg/kg/6 hr of quinidine show a significant increase in survival time, while those at the lowest dose do not.

Serum quinidine determinations were carried out on blood samples obtained from each treated animal just prior to the next quinidine injection, or 6 hours after the last dose. The mean serum levels for each successive 24 hours of the 72-hour treatment period can be seen in figure 4. As would be expected, the higher dose level resulted in a higher serum level. “Sham operated” animals receiving 10 mg/kg/6 hr of quinidine and animals with a constrictor in place given the same dose had similar mean serum quinidine levels. The three “sham operated” animals receiving 15 mg/kg/6 hr of quinidine achieved serum levels of 7 to 9 mg/L with no apparent ill effect.

Eight animals were telemetered continuously after operation; six were nonsurvivors and two were survivors. ECG changes became apparent between 12 and 24 hours (usually as T-wave inversion with ST-T segment depression) and showed evidence of progressive injury with deepening Q waves until the animal died or reached the end of the treatment period. Most striking was the appearance in the same animal of ventricular
irritability with single extrasystoles increasing in frequency to paroxysms of ventricular tachycardia which eventually did not resolve spontaneously but deteriorated to ventricular fibrillation and death (fig. 5). The animal was observed to die suddenly, with no apparent preliminary distress despite the ventricular irritability and electrocardiographic changes of severe ischemia or infarction, or both. All nonsurviving animals that were observed to die did so in a similar manner which was assumed to be secondary to the abrupt onset of irreversible ventricular fibrillation.

While vessel narrowing with compromise in myocardial blood supply occurred between 12 and 24 hours, postmortem coronary arteriography revealed that complete occlusion did not occur before 48 hours (fig. 6A and B). Any animal surviving 2 weeks or longer after surgery showed the development of collateral vascularization most noticeable in the area of infarction but often including a much larger area (fig. 6C and D). During postmortem arteriography of these hearts, contrast material could be seen flowing retrograde around the apex and into the left

\[\text{Figure 5}\]

(A to D) Representative electrocardiographic tracings from telemetered animals demonstrate the ST-T wave changes of ischemia, myocardial irritability, and the sudden onset of ventricular fibrillation terminating in death.
Figure 6
Postmortem coronary arteriograms. (A) Good filling of the left anterior descending coronary artery through the constrictor 36 hours after surgery (treated animal). (B) No filling of the left anterior descending coronary artery 54 hours after surgery (treated animal). (C) Collateral vascularization localized to the region of the infarct in a treated animal sacrificed 2 weeks after surgery. (D) Striking generalized collateral vascularization in a nontreated control animal sacrificed 2 weeks after surgery. LAD = left anterior descending coronary artery; LC = left circumflex artery; RC = right coronary artery.

anterior descending artery up to the distal end of the constrictor.

Gross and light microscopic examination of the hearts revealed that the earliest changes of myocardial necrosis occurred within a wide time interval, 10 to 68 hours. It can be seen in figure 7 that 85% of the animals dying within 36 hours had grade II or less myocardial changes, while 88% of those animals surviving at least 72 hours had a large grade III to IV anteroseptal infarction. These observations confirm the expected pattern of
longer survival resulting in a larger infarction, as the constrictor slowly narrowed then occluded the vessel. The pericardium, at autopsy, was thickened and adherent to the constrictor site, the pericarditis increasing in severity as the time of survival increased. The lungs grossly and microscopically showed prominent unilateral (usually right-sided) atelectasis in the immediate postoperative period, decreasing to insignificant focal patches within 24 hours. Mild vascular congestion was occasionally present and was not well related to survival time or extent of myocardial infarction. Infection was insignificant; no gross or microscopic pulmonary emboli were seen.

None of the seven “sham operated” animals died. They were sacrificed after 2 to 8 weeks. The animals tolerated the intravenous medication (0.9% saline for one animal, 10 mg and 15 mg/kg/6 hr of quinidine for three each of the remaining six) without any apparent distress. At autopsy the pericardium was again found to be thickened and adherent; the lungs were normal except for minor pleural adhesions at the operative site. There was no evidence of myocardial necrosis by histopathological techniques, nor did post-mortem coronary arteriography show evidence of vascular narrowing at the site of manipulation of the left anterior descending artery.

**Discussion**

As early as 1932, Levine suggested that ventricular fibrillation was an important cause of sudden death following myocardial infarction and that quinidine might be effective in preventing such arrhythmias. He demonstrated that quinidine produced an increase in the myocardial fibrillatory threshold in decerebrate cats. Since that time numerous reports have stressed the importance of suppressant therapy in patients with ventricular irritability and coronary artery disease.

The prophylactic value of quinidine therapy in patients with myocardial ischemia and infarction is difficult to evaluate from clinical studies because of the necessity of matching patients with regard to age, location and severity of the infarction, and incidence and type of cardiac arrhythmias which develop. Furthermore, it is often difficult to separate the effects of other drugs which might be operative in previous patient studies. Boone and Pappas in a retrospective survey of 190 patients with myocardial infarction noted a mortality rate of 16% in patients treated with quinidine and 35% in those who did not receive the drug. However, it is not clear which patients in this study received anticoagulants and whether quinidine was employed prophylactically or only after the appearance of ventricular irritability in some cases. On the other hand, Begg did not find a reduced mortality from quinidine therapy in 26 patients with myocardial infarction, who were also treated with anticoagulants. This investigator pointed out the difficulties in obtaining

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**Figure 7**

The survival time for both control and treated animals is correlated with the size of the myocardial infarction, grades I to IV (see text). In general, the longer the survival time the larger the size of the demonstrated infarct regardless of the treatment.
a large enough patient population from which to draw valid conclusions as to the efficacy of quinidine, and the problem of obtaining appropriate controls.

Hvidt and co-workers compared 109 patients who received quinidine, 200 mg three times daily beginning within 24 hours of infarction, with 103 patients who did not receive quinidine. Both groups were given anticoagulants. These investigators noted no significant difference between the two groups with regard to (1) the incidence of ventricular extrasystoles, (2) disturbances of sinus rate, or (3) mortality. The doses of quinidine employed in this study were small. Moreover, conspicuously absent in this and other patient studies are measurements of serum quinidine, which would allow further correlation between quinidine therapy and drug effects.

It is well known that experimental coronary occlusion in animals produces a high incidence of ventricular arrhythmias, often heralding sudden ventricular fibrillation and death. In addition, multiple studies have indicated that quinidine as well as procainamide can effectively reduce myocardial irritability resulting from localized ischemia or infarction. However, the previous experimental work has the drawback inherent in sudden closure of a major coronary vessel either by direct ligation in an open-chested anesthetized animal or by semi-selective and difficult to control embolization techniques. Sudden coronary occlusion by the above methods produces a high mortality rate which is not appreciably affected by therapy and bears little resemblance to coronary artery disease in man. The present experimental preparation utilizes Ameroid constrictors which gradually produce coronary occlusion over a 24 to 48-hour period at a time when the animal is awake and ambulatory, a model more analogous to the actual clinical situation.

In most previous studies the dog was used as the experimental animal. The myocardium of the dog is supplied by a predominant left coronary artery from which arises a large septal branch variable in point of origin and distribution. This anatomic peculiarity prevents standardization of the size and location of the infarcted area and adds unpredictable involvement of the conduction system as still another variable. The farm pig was chosen for the present experiment because the coronary artery pattern is both consistent and similar to that of man. Like man, the pig normally has few intercoronary artery anastomoses. The anterior descending coronary artery was used for the occlusion to avoid arrhythmias that might be introduced as a result of damage to the atrioventricular node, which in the pig as in most humans is supplied by the dominant right coronary artery. Gradual occlusion of the anterior descending coronary artery in the farm pig resulted in a reproducible myocardial lesion which varied in size primarily with time.

The present study demonstrates that treatment with quinidine in nontoxic, well tolerated doses during experimental myocardial ischemia and infarction in the farm pig significantly prolongs survival and reduces mortality. Furthermore, the measurements of serum quinidine obtained are comparable to levels in patients on therapeutic dosage schedules of the drug. The results also indicate that smaller doses of quinidine, producing less than accepted therapeutic blood levels, do not statistically alter survival. The presence of such a dose threshold further emphasizes the importance of measuring serum quinidine frequently in the clinical situation.

The present work emphasizes the need for extensive carefully controlled clinical investigation in an effort to establish the existence of beneficial effects of quinidine therapy in the prevention of fatal cardiac arrhythmias in patients with coronary artery disease. Despite well-equipped coronary care units in many medical centers and intensive efforts to detect and correct sudden cardiac arrhythmias with acute myocardial infarction, the mortality remains high. The sophisticated electronic detection and recording equipment which is now available would be of immense
assistance in a direct, objective, and quantitative evaluation of prophylactic quinidine therapy.

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