The Value of Quinidine in the Prevention of Atrial Fibrillation after Mitral Valvuloplasty

By Harrison Black, M.D., Bernard Lown, M.D., and Anthony F. Bartholomay, S.D.

Atrial fibrillation is the characteristic arrhythmia of the advanced stages of mitral stenosis, being present in 40 per cent of such cases. Paradoxically, mitral valve surgery, which relieves the obstruction and reduces the hemodynamic overload of the left atrium, frequently precipitates either transient or permanent atrial fibrillation. The reported incidence of this disorder after mitral operation ranges from 24 to 47 per cent.1-6 In the patient with normal sinus rhythm undergoing mitral valve surgery atrial fibrillation thus constitutes the most common operative complication.

Physiologic studies clearly indicate that atrial fibrillation compromises cardiac function. Restoration of normal sinus rhythm has been shown to increase the cardiac output at rest and especially after exercise.7-10 It has been observed that patients with atrial fibrillation have generally lower cardiac outputs, higher pulmonary vascular resistance, and higher left atrial and pulmonary arterial pressures than do patients with mitral stenosis in sinus rhythm.11,12 The ventricular rate in atrial fibrillation is unstable and prone to acceleration to more than 100 per minute. In some fully digitalized patients ventricular rates as high as 170 have been recorded following moderate exercise or administration of atropine.13 Occasionally in the presence of this arrhythmia congestive failure cannot be controlled, even though the heart rate is slow, until normal sinus rhythm has been restored. It has furthermore been shown that atrial systole plays a role in closure of the atrioventricular valves.14 Some degree of tricuspid insufficiency accompanies the development of atrial fibrillation in many patients.15 Of greater clinical importance is the fact that this arrhythmia bears an etiologic relationship to cerebral and peripheral arterial embolization. Thus, the prevention of atrial fibrillation and its prompt conversion to a normal mechanism are sound clinical practice.

The present study had as its primary purpose the assessment of the effectiveness of quinidine in the prevention of postoperative atrial fibrillation. In addition, observations were made on the safety of using quinidine prophylactically during and following a cardiac operation and on the background factors that might predispose to this arrhythmia.

Materials and Methods

The investigation consisted of two phases, a retrospective and a prospective study.

Retrospective Study

The retrospective study consisted of analysis of the records of 255 patients in normal sinus rhythm who underwent mitral valvuloplasty at the Peter Bent Brigham Hospital. These patients were drawn from a larger series of 1,000 who were operated on in the Boston area and reported previously.1* Of the 255 patients there were 226 who were classified as group III; in this category are included patients exhibiting severe progressive cardiac disability that has not yet reached the stage of the irreversible congestive failure or cardiac invalidism that characterizes group IV. The remaining 29 patients belonged in this latter category and are considered with a small group of similar patients in the prospective study. The major emphasis in the current investigation has centered on the group-III patients, since their larger number seemed more appropriate for statistical evaluation.

*We are indebted to Dr. Dwight E. Harkin for permission to use his patients in both the retrospective and prospective studies.

<table>
<thead>
<tr>
<th>(Retrospective Study)</th>
<th>No. in NSR*</th>
<th>No. with PO-AF†</th>
<th>% PO-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>38</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>Quinidine</td>
<td>188</td>
<td>41</td>
<td>22</td>
</tr>
</tbody>
</table>

*Normal sinus rhythm.  †Postoperative atrial fibrillation.

In the retrospective series quinidine prophylaxis had been applied empirically when it was observed that there was a very high incidence of postoperative atrial fibrillation following mitral valvuloplasty. Thirty-eight of the group-III patients, most of them from the first part of the series who were among the earliest operated on for mitral stenosis, received no quinidine and served as controls. The remaining 188 group-III patients received this medication, beginning within 6 hours of the end of operation in the majority and administered in doses of 0.8 to 1.2 Gm. per day. In group IV 22 of the 29 patients received quinidine.

Prospective Study

In order to determine the effectiveness of quinidine prophylaxis under more controlled conditions a prospective study was also undertaken. For a period of 18 months all patients in normal sinus rhythm admitted to the Peter Bent Brigham, Mount Auburn, and Malden Hospitals on the Thoracic Surgical Services for mitral valvuloplasty were included. The group-III and group-IV patients were segregated and within each group the patients were paired as they were accepted for operation. To avoid bias and insure uniformity of decision a coin was tossed to determine which person should be assigned to the quinidine-treated group and which to the control (no quinidine) group.

All patients were digitalized preoperatively if not already receiving this drug. In the therapy group, quinidine sulfate was given in 3 doses of 0.3 Gm. each, on the day prior to operation. On the day of operation and daily thereafter 0.3 Gm. was given every 6 hours, initially intramuscularly and thereafter by mouth.

Results

Retrospective Study

As shown in table 1, 50 per cent of the group-III patients in normal sinus rhythm preoperatively developed atrial fibrillation after operation. By contrast only 22.8 per cent of those receiving the drug manifested this arrhythmia. The difference is statistically highly significant with a p value of less than 0.001. Quinidine was equally effective whether the dose was 0.8 or 1.2 Gm. per day. There was indeed a lesser, though not significantly different, incidence of atrial fibrillation on the lower dose.

Prospective Study

In the prospective study sequential analysis was employed to test the significance of results in the 41 pairs of patients in group III. This method provides an effective and economical statistical design for clinical experiments. In this test independent evaluations of effectiveness of the two treatments (quinidine and control) were made. Guided by the results in the retrospective study the test was set up so that the treatment would be judged acceptable if it resulted in fewer than 20 per cent failures, whereas it would be rejected if it led to more than 40 per cent failures.
failures. In figure 1 the limits of 5 and 1 per cent error are shown. Separate curves for quinidine and control groups were drawn with the number of patients who fibrillated plotted against the total number of observations. The first time that either sequential curve crosses into the acceptance or rejection region, the appropriate decision is made.

In figure 1 it can be seen that the quinidine prophylaxis method was found acceptable at the lower 5 per cent level after only 14 cases and at the stricter 1 per cent level after 36 cases. On the other hand, the control method was found unsatisfactory after 20 cases at the 5 per cent level. Continuation of the test did not lead to rejection at the 1 per cent level by the forty-first case. Testing would have to be carried further to check the stronger criterion. These tests established that quinidine prophylaxis significantly decreased the incidence of postoperative atrial fibrillation.

As a further check on the validity of this conclusion these data were subjected to a runs analysis to test the randomness of each group individually. It was found that: 1. In the control group the series could represent a random series of trials. 2. In the quinidine-treated group with a level of confidence much greater than 99 per cent, it can be said that the sequence of values is not random, indicating the establishment of a definite trend. This finding may be taken as further evidence of the validity of the quinidine effect.

### Analysis of the Combined Series

Since in the retrospective and prospective studies the incidence of atrial fibrillation in the control and treated groups was virtually the same, the two series were combined in order to provide additional clinical information. There were 308 group-III patients in the combined series. Of this number 229 received quinidine and 50 or 22 per cent developed atrial fibrillation, while of 79 patients who did not receive this medication 33 or 42 per cent fibrillated. The Chi-square test indicated that the difference is statistically significant (p is less than 0.001). In 39 group-IV patients, however, the administration of quinidine prophylactically resulted in a reduction of postoperative atrial fibrillation.
Table 3
Prediction of Results with and without Quinidine Prophylaxis in Group-III Patients with Normal Sinus Rhythm Undergoing Mitral Valve Operation. (An Example)

<table>
<thead>
<tr>
<th></th>
<th>No quinidine</th>
<th>Quinidine treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Postoperative atrial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fibrillation</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Spontaneous reversion to normal sinus rhythm</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Conversion with quinidine</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Remaining in atrial fibrillation</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

from 62 per cent in controls to only 50 per cent in those treated. This difference is not statistically significant (p greater than 0.05).

In both the quinidine and the control series the median day of onset of atrial fibrillation was the third postoperative day. There appears to be a tendency for a greater number of those who received quinidine to develop the arrhythmia after the ninth day. There is no significant difference, however, in the mean days of onset between the two series (p equals 0.18).

In 27 patients of the prospective series a quinidine blood level was obtained on the first postoperative day 2 hours following one of the four doses. There is almost no difference between the levels observed for those who remain in normal sinus rhythm (mean 4.44 mg./L.) and those who fibrillated (mean 4.7 mg./L.). Although considerable scatter is present in both groups, those who developed atrial fibrillation had a mean quinidine blood level that was actually higher (mean 5.9 mg./L.; range 4.3 to 9.8) than the mean of the value obtained on the seventh postoperative day in those patients who remained in normal sinus rhythm (mean 4.04 mg./L.; range 1.9 to 8.0).

The influence of various clinical factors on the incidence of postoperative atrial fibrillation was also examined in this combined series. Table 2 presents the results of this analysis. In the control patients, receiving no quinidine, arthralgia as an indicator of rheumatic activity, the presence of mitral insufficiency and age beyond 35 years did not significantly alter the incidence of this arrhythmia. In these patients, however, the occurrence of prior atrial fibrillation, episodes of palpitation, and male sex resulted in approximately a two-fold increase in percentage of fibrillation. These differences, however, were just short of significance at the 5 per cent confidence level by Chi-square test.

These factors, namely, prior atrial arrhythmia, palpitation, and male sex were associated with an increased incidence of postoperative atrial fibrillation even when the patients were receiving prophylactic quinidine. Of the men who received quinidine, those above 35 years of age had a significantly greater incidence of this arrhythmia. It is noteworthy that the same factors (prior arrhythmia and male sex) caused a distinct increase in incidence of postoperative fibrillation in both control and treated groups. The failure to achieve the 5 per cent confidence level in the controls may be due to the small number of observations available for analysis.

Unlike atrial fibrillation occurring in the course of untreated mitral stenosis, the postoperative arrhythmia frequently reverted spontaneously without specific treatment other than rate control with increased doses of digitalis. Thus in group III, of 82 patients who fibrillated postoperatively, 27 or 33 per cent reverted spontaneously to normal sinus rhythm. In group IV 5 of 22 or 23 per cent reverted. There was no significant difference between the rates of spontaneous reversion whether or not quinidine prophylaxis had been employed.

In the majority of those patients who remained in atrial fibrillation even though the ventricular rate was controlled with digitalis, an attempt was made to revert the arrhythmia with quinidine on about the tenth postoperative day by the method of Sokolow.20 In group III this was successful in 89 per cent of trials and in group IV in 86 per cent.

Discussion

Atrial fibrillation is a common occurrence after pulmonary operations.21,22 The reported
incidence after pneumonectomy is 45 per cent when the resection is carried out within the pericardium and 21 per cent when the pericardium is not entered. This incidence can be reduced by the prophylactic administration of quinidine to 14 and 9 per cent respectively. Similar good results from prophylactic quinidine have been noted after mitral valvuloplasty. Kittle and Crockett found that the incidence of the arrhythmia was lowered from 32 to 15 per cent when quinidine and digitalis were employed together. Other observers, however, with extensive experience with patients undergoing mitral valvular surgery have reported no benefit from the use of quinidine. To date there has been no deliberate, objective study of the value of quinidine that has employed adequate controls and randomized treatment to minimize observer bias.

The present study conclusively demonstrates the value of quinidine in preventing atrial fibrillation after mitral valvuloplasty. From these results one would predict that in 100 patients of group III with normal sinus rhythm undergoing mitral valvuloplasty the use of quinidine will reduce the number who fibrillate postoperatively from 42 to 22. Eight of the 22 who thus fibrillate will revert spontaneously to normal sinus rhythm when their rate is controlled with additional doses of digitalis. Normal rhythm can be restored in 12 of the remaining 14 patients by the use of quinidine in increasing doses after the tenth postoperative day. Two patients of the original 100 will remain permanently in atrial fibrillation. When, however, prophylactic quinidine is not employed seven patients will remain in this disordered rhythm (table 3).

On the matter of dosage of quinidine to be used prophylactically, Kittle and Crockett advocate 0.4 Gm. every 4 hours or 2.4 Gm. per day. They note that their program requires daily monitoring of the electrocardiogram and serum quinidine levels. No convincing evidence is provided that this high dose is of any greater benefit than a lesser amount. Indeed our analysis of two dosage regimens (0.8 and 1.2 Gm. per day) indicates that the smaller amount gives equally good results.

In our series with total daily doses of 0.8 to 1.2 Gm. per day there were no deaths and no quinidine-induced arrhythmias. Quinidine had to be discontinued in only two patients of the 82 in the prospective study at 4 and 9 days postoperatively, respectively, because of gastrointestinal intolerance.

Conclusions

A study has been conducted to determine the effectiveness of quinidine prophylaxis in reducing the incidence of atrial fibrillation in patients with normal sinus rhythm undergoing operation for mitral stenosis. In both a retrospective study of 226 group-III patients and in a more rigidly controlled prospective study of 41 pairs of patients a statistically significant reduction in the incidence of this arrhythmia was observed (from 42 to 22 per cent). Moderate dosages (0.8 to 1.2 Gm. per day) were effective.

A history of palpitation or prior episodes of atrial fibrillation and male sex appeared to be related to the development of postoperative atrial fibrillation. Associated mitral insufficiency, Aschoff bodies in the atrial appendage, and recent history of arthralgia did not appear to increase significantly the incidence of this arrhythmia.

If prophylactic quinidine is employed and reversion is attempted after the tenth postoperative day in those patients who nonetheless developed atrial fibrillation, only 1.5 per cent of patients in normal sinus rhythm operated on for mitral stenosis will be discharged from the hospital with an irregular rhythm.

References

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