The grading system described appears to have served a useful purpose. It will be evident, especially to those who habitually study coronary artery and coronary bypass angiograms, that our system embodies a definitely subjective element. We have tried to offset this by applying the rules fairly, a constant spur to our objectivity being the cogent requirement for assigning realistic employment-oriented medical categories to military personnel. Our early experiments in grading coronary bypass grafts included a C grade and also attempted to quantitate, separately, impairment of antegrade and retrograde flow from graft to artery; these failed because the system became not only impossibly cumbersome but also dishonest in the pretense of measuring the immeasurable. We believe that the data on the rate of grafts graded A or B in early studies confirm both the validity and the prognostic value of our grade assignments.

If patent coronary bypass grafts improve blood flow to ischemic muscle (it has been suggested that such flow need not be a mechanism of benefit from operation), we have demonstrated excellent early and late graft patency rates which should augur well for the patients. Furthermore, by graft grading, we have shown that most patent grafts in this series were of excellent quality. Some of the factors associated with early and late graft failure have been noted. A most important determinant of good results appears to be surgical skill in fashioning bypass coronary anastomoses.

Acknowledgment

We are very grateful to Miss Barbara Wills, of Statistics Canada, for advice and assistance in handling statistical data.

References


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QT Interval Prolongation as Predictor of Sudden Death in Patients with Myocardial Infarction

P. J. Schwartz, M.D., and Stewart Wolf, M.D.

SUMMARY Fifty-five patients with recent myocardial infarction and 55 healthy controls, matched for age, sex, race, height, weight, education and job, had an electrocardiogram taken every two months for seven years. Twenty-eight patients and one control had a sudden cardiac death. The QTc (mean of all values recorded) was found prolonged in one control (2%), five of 27 surviving patients (18%) and in 16 of 28 patients who had sudden death (57%). The difference between surviving and sudden death patients is significant (P < 0.01). It is interesting that the only control with a long QT was the one who died suddenly of myocardial infarction. Among patients with previous myocardial infarction a prolonged QTc constitutes a 2.16 times greater risk for sudden death. We conclude that a constant prolongation of QTc in patients with myocardial infarction may help, with other risk factors, in defining a subgroup at higher risk for sudden death.

IN EARLIER STUDIES, an imbalance in cardiac sympathetic innervation which prolongs the QT interval was shown to increase the arrhythmias associated with coronary artery occlusion and to lower the ventricular fibrillation threshold. The present study focuses on whether or not a prolonged QT corrected for rate (QTc) (> 440 msec), irrespective of its causes, is associated with sudden death in patents with myocardial infarction.

Our attention to the possibility that QT interval prolongation might be associated with increased risk of sudden death was brought about by clinical and experimental data. Congenital prolongation of QT interval (long QT syndrome) is associated with an extremely high incidence of ventricular fibrillation (VF) and sudden death. Drugs that prolong the QT interval (quinidine, amiodarone, tricyclic antidepressants and others) are also associated with sudden death due to VF. A vulnerability index has been proposed based on QT interval prolongation. In experimental animals manipulation of the sympathetic nervous system affects the QT interval. Maneuvers that lengthen it, such as ablation of the right stellate ganglion or stimulation of the left, increase the incidence of ventricular arrhythmias and of VF in anesthetized animals during myocardial ischemia as well as in conscious animals during physical or emotional stresses.

To test the prognostic significance of a consistently prolonged QT, a group of patients with previous myocardial infarction and their matched controls were followed for ten years, during the first four to seven years of which repeated ECGs were recorded every two months. Approximately half of the patient group and one of the controls died suddenly during the period of study. Among both patients and controls the QT measurements were correlated with the clinical outcome.

Methods

Population Under Study

There were 134 subjects in all, 67 patients and 67 healthy controls. The patients, 53 men and 14 women, had suffered a
TABLE 1. QTc and Variability (Δ) of QTc in the Population under Study

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>QTc (msec, ± SD)</th>
<th>Significance</th>
<th>ΔQTc (msec, ± SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>55</td>
<td>418 ± 15 (±2)</td>
<td>P &lt; 0.001</td>
<td>16 ± 6 (±1)</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>Patients</td>
<td>55</td>
<td>436 ± 25 (±3)</td>
<td>P &lt; 0.05</td>
<td>24 ± 12 (±2)</td>
<td>P &lt; 0.025</td>
</tr>
<tr>
<td>Survivors</td>
<td>27</td>
<td>429 ± 20 (±4)</td>
<td></td>
<td>20 ± 10 (±2)</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>28</td>
<td>443 ± 27 (±5)</td>
<td></td>
<td>28 ± 13 (±2)</td>
<td></td>
</tr>
</tbody>
</table>

Figures are means ± sd and are expressed in msec. Values in parenthesis are as.

well-documented myocardial infarction two months to six years in the past. The study group was drawn from a consecutive series of patients seen at the University of Oklahoma Medical Center between 1962 and 1965. Selection was made only on the basis of geographic proximity to Oklahoma City. None of the patients declined to participate. The diagnosis of myocardial infarction was established by unequivocal electrocardiographic changes and elevated SGOT at the time of their acute attack. The healthy controls were drawn from more than 1,000 candidates in two industrial firms and the State Highway Department. They were selected to match individually with the patients on the basis of age (± 2 years), sex, race, height (± 2 inches), weight (± 8 pounds), educational background (years of schooling) and type of job (laborer, skilled, clerical, professional). The ages are reported as of September 1962. The subjects, patients and controls, were initially hospitalized on a research ward where psychological, sociological, physical, X-ray and laboratory data were gathered. The various tests were repeated at two month intervals on both patients and controls over a seven year period. Many of the findings have been reported elsewhere.2 This report concerns only the ECG data.

QT Interval Study

Discarded from the study together with their matched controls were ten patients because of bundle branch block or digitalis-induced changes that obscured the ECG analysis, and two others who committed suicide during the ten year period of study. Omitting these 12 patients and their matched controls reduced the total number of patients and controls to 110. The QT interval was measured from five nonconsecutive beats in each ECG tracing taken at a speed of 50 mm/sec. QTc was calculated according to Bazett's formula: QTc = QT / \sqrt{R-R'}. The five values of QTc for each subject were then averaged and the mean values ± sd were calculated along with the measurements of heart rate. All measurements were made by one of us without knowing whether the tracings were those of a patient or a control. Only when all the measurements were completed was the code broken. A QTc exceeding 440 msec was defined as prolonged.20

Statistical Analysis

The absolute values of QTc were compared between controls, survivors and deceased, using the unpaired t-test. The standard deviations were similarly analyzed to determine the variability of QTc and HR among the groups.

Comparisons between survivors and deceased with respect to QTc and premature ventricular beats (PVBs) were made using the chi square test or the Fisher exact test. The relative risk of sudden death was also calculated.21

Results

At the end of seven years of repeated observation and three additional years of follow-up study 27 of the 55 patients were still alive. The remaining 28 had died, all of them suddenly. Among the 55 controls only one had died and he died suddenly (within 24 hours following beginning of symptoms).

QTc. The QTc among the controls was 418 ± 15 msec (mean ± sd), while among the patients it was significantly longer, 436 ± 25 (P < 0.001). The QTc among the surviving patients was 429 ± 20 and among the deceased was 443 ± 27, the latter being significantly longer than the value for surviving patients (P < 0.05) and in the abnormal range (table 1, fig. 1). The fact that it is necessary to add 1½ standard deviations to the QTc of the controls in order to reach 440 msec supports the concept that 440 msec is a proper limit for QTc.

The only control whose QTc was prolonged (457 ± 14) died suddenly. A fresh myocardial infarction was found at autopsy. Among 21 patients who had a mean value greater than 440 msec, 16 (77%) died suddenly (fig. 2). The variability of QTc from month to month and year to year as determined by the mean differences in measurement ± se was least among controls (16 ± 1 msec), intermediate among surviving patients (20 ± 2) and greatest among the deceased (28 ± 2). The mean difference in QT interval variability between surviving patients and deceased was statistically significant (P < 0.025) (table 1).

A QT interval greater than 440 msec was present in 57%
TABLE 2. Risk of Sudden Death in Patients with Prolonged QT Interval

<table>
<thead>
<tr>
<th>QTc (msec)</th>
<th>Deceased</th>
<th>Survivors</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 440</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>&lt; 440</td>
<td>12</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>27</td>
<td>55</td>
</tr>
<tr>
<td>P = 0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated risk = 2.16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2. Distribution of QTc values among patients and controls.

of the deceased in contrast to 18% of the survivors; values greater than 450 msec were found in 36% of the deceased and in only 8% of the survivors. The differences are significant \((P = 0.003)\) at the 440 msec level and \(P = 0.005)\) at the 450 msec level. The calculated risk of sudden death for patients with a previous myocardial infarction and prolonged QT intervals was respectively 2.16 and 2.36 times greater than for those with a normal QT interval (table 2).

**PVBs.** The presence of premature ventricular beats (PVBs) on an eight hour ECG monitor correlated with risk of sudden death. Twenty-seven out of the 55 patients had PVBs (more than 10 per minute). The presence of such frequent PVBs increased the risk of sudden death among those who had suffered a myocardial infarction in the past by a factor of 2.19. Table 2 shows that a prolonged QT with or without PVBs carried a risk of sudden death between 5 and 6 times higher than a normal QT and no PVBs.

**Age.** Controls and patients were matched for age (± 2 years). The mean age of controls was 52 ± 12. The mean age of surviving patients was 49 ± 13 compared to 54 ± 12 for the deceased, a difference that was not statistically significant. The association between prolonged QT and sudden death was separately tested among the 26 patients between the ages of 41 and 60 years. Seven out of eight (87%) of these patients with a prolonged QT interval died suddenly. Therefore, for men aged 41–60 years who had sustained a previous myocardial infarction, we found that a prolonged QT interval enhanced the risk of sudden death during the period of study by a factor of 2.25.

**Heart Rate.** The HR in the three groups was almost identical (72 ± 9 beats/min for the control group, 71 ± 7 for the survivors and 71 ± 9 for deceased). Important differences were apparent, however, in the day-to-day variability of HR. Variability was 6 ± 1 beats/min (mean ± SD) for the controls, 7 ± 1 for the survivors and 10 ± 1 for the deceased. While the difference between survivors and controls was not significant, the difference between survivors and deceased was significant \((P < 0.01)\). In other words, the deceased had a greater variability in their HR values from day to day than the survivors who, in this sense, did not differ from the controls.

**Discussion**

Unexpected sudden death is one of the most distressing and baffling events in contemporary society. Among those most vulnerable to sudden death are individuals who have sustained a myocardial infarction and who are either in the acute stages or in the early or even late stages of recovery. Patients whose myocardial infarction occurred as long as five years ago continue to be at high risk of sudden death. The ability to predict those at greatest risk might conceivably lead to effective precautionary or preventive measures.

Of the number of risk factors for sudden death proposed in the past, many have been discarded for their lack of specificity. Frequent ventricular beats, however, remain a most important predictor, being associated with a doubling of the risk of sudden death. Our findings indicate that persistent prolongation of the QT interval constitutes a further important risk indicator in persons with ischemic heart disease. Prolongation of the QT interval is a familiar finding in the acute phase of myocardial infarction,22 whereas its presence and possible significance among those with healed myocardial infarction have not previously been explored.

QT prolongation is caused by delayed ventricular repolarization and usually leads to an increase in the degree of temporal dispersion of refractory periods.3 Such increased dispersion results in prolongation of the vulnerable period and may thereby enhance susceptibility to ventricular tachyarrhythmias,23, 24 thus providing the rationale for our study.

The findings reported here do not illuminate the mechanisms responsible for the prolongation of QT. The striking difference in QT interval between all patients and controls, however, suggests that local myocardial changes secondary to the infarction may be a critical factor. Whether or not a sympathetic imbalance comparable to that produced in experimental animals is implicated cannot be stated from the data at hand.1, 2, 3, 5

Nevertheless, the findings in man implicating prolonged
QTc as indicative of vulnerability to sudden death tend to validate studies in animals performed independently in several laboratories where experimental maneuvers leading to QT prolongation were associated with VF, an association not always stressed by the authors.1, 2, 24-26

A striking finding from the study was that the greater the variability of QT from month to month, the greater the risk of sudden death. Variability in HR was observed also to be pronounced among those destined for sudden death. Undue variability in measurements of cardiovascular functions has in previous publications been correlated with high risk of recurrent myocardial infarction or sudden death.31, 12, 14, 19, 27 The variabilities in blood clotting factors,11 in heart rate and blood pressure,12 in ballistocardiographic tracings18, 19 and other indicators had been presumed to be due to a want of stabilizing influence of autonomic inhibitory impulses, related in turn to a lack of emotional stability.17, 18

Sudden increases in sympathetic activity in the setting of an ischemic myocardium facilitate VF.24 Our data on QTc and heart rate variability suggest that the patients who died suddenly were exposed to substantial shifts in autonomic activity. The first presentation of our data19 led Cobb's group in Seattle to analyze the QTc in their unique group of patients with coronary heart disease who had been resuscitated from VF outside the hospital. They found that 37% of the patients had a prolonged QTc compared to 18% of patients with a myocardial infarction not complicated by VF, a difference significant at the 0.005 level of confidence.29 This is a very important confirmation of our data despite the fact that Cobb and his associates were able to measure only a single electrocardiogram. Our analysis was made on a very large number of ECGs; indeed, it was not uncommon for patients whose mean QTc was normal to have had occasionally a prolonged value and vice versa. A prognostic judgment of increased risk for sudden death because of prolongation of QTc should be made only on the basis of measurements of several ECGs in the same individual.

Acknowledgment

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References

QT interval prolongation as predictor of sudden death in patients with myocardial infarction.

P J Schwartz and S Wolf

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