The Effects of Coronary Artery Disease on the Ventricular Fibrillation Threshold in Man

Leonard N. Horowitz, M.D., Joseph F. Spear, Ph.D., Mark E. Josephson, M.D., John A. Kastor, M.D., and E. Neil Moore, D.V.M., Ph.D.

SUMMARY The ventricular fibrillation threshold (VFT) was measured in 28 patients at the time of cardiac surgery. The VFT was measured with a 100 Hz train of 24 rectangular pulses positioned across the ST segment and T wave. Current was applied to the epicardial surface of either ventricle with a bipolar electrode probe. In six patients, the normal right VFT was 24.3 ± 5.2 mA, and in 10 patients the normal left VFT was 33.6 ± 9.5 mA (p < 0.05). In 12 patients with ≥75% obstruction of the left anterior descending coronary artery, the left VFT was 18.6 ± 6.9 mA. This value was significantly less than the left VFT in patients without coronary artery disease (p < 0.001). This study shows that the VFT can be measured in man and that coronary artery disease reduces this parameter.

IN 1940, Wiggers and Wegria \(^1\) reported that a single electrical stimulus of appropriate intensity delivered to the ventricles during late systole could induce ventricular fibrillation. These investigators suggested that this phenomenon could be standardized to assess vulnerability of the ventricle to fibrillation. Since then, many studies \(^2\)–\(^10\) have used this technique to assess ventricular vulnerability during experimentally induced pathologic states and after the administration of antiarrhythmic drugs. However, the relationship of these studies to ventricular vulnerability to fibrillation in man is not clear.

In the present study we measured electrically induced fibrillation threshold in man to evaluate ventricular vulnerability and to evaluate the effects of coronary artery disease on ventricular vulnerability.

Methods and Materials

The ventricular fibrillation threshold (VFT), an index of ventricular vulnerability, was measured in 28 patients undergoing cardiac surgery for congenital, valvular, or coronary heart disease. All patients gave written informed consent. The VFT was defined as the minimal current (mA) required to initiate ventricular fibrillation when applied to the ventricles during the vulnerable period. The routine procedure during surgery requiring cardiopulmonary bypass at the

References

Hospital of the University of Pennsylvania includes the elective induction of ventricular fibrillation by electrical stimulation. This experimental procedure, therefore, did not represent a significant departure from the routine. After cannulation for cardiopulmonary bypass the VFT was measured during atrial pacing at a cycle length of 600 msec (100 beats/min) with a gated train of 24 rectangular pulses, 4 msec in duration at a frequency of 100 Hz delivered to the epicardial surface during the vulnerable period (fig. 1). Electrocardiographic lead V₅ was monitored. The current train was positioned in the ST segment and T wave after every twelfth QRS complex. The position of the train was adjusted to insure the stimulation of only a single premature depolarization. Current was increased in increments of 1–2 mA until ventricular fibrillation resulted (fig. 2). Cardiopulmonary bypass was initiated immediately at the onset of ventricular fibrillation. This technique allowed the induction of ventricular fibrillation with the minimum effective current. A single measurement was made in each patient.

Current was delivered from an optically isolated constant current source capable of producing 0–100 mA through a handheld probe. The probe was constructed of milled teflon with platinum electrodes embedded in the surface placed on the epicardium. The circular electrodes are 7 mm in diameter and are separated by 15 mm (center to center). The probe was held in a stable position at the site of measurement. Previous experiments in dogs had shown that passage of as much as 100 mA of current 20 times through this probe produced no gross or microscopic damage to the epicardium.

The clinical data describing the 28 patients are presented in table 1. Twelve patients had coronary artery disease (≥ 75% obstruction of the left anterior descending coronary artery) and were undergoing coronary artery bypass grafting for disabling chronic stable angina. Thirteen patients had acquired valvular heart disease and normal coronary arteries and were having either aortic or mitral valve replacement. Three patients had secundum atrial septal defects and normal coronary arteries and were undergoing closure of the defect.

In six patients the probe was positioned in the center of the anterior right ventricular wall. In 22 patients the probe was positioned on the anterior wall of the left ventricle along the interventricular groove in the area supplied by the left anterior descending coronary artery. Ten of these patients had normal coronary arteries documented by coronary angiography and normal left ventricular contractile patterns as determined by angiography. Twelve patients had ≥ 75% obstruction of the left anterior descending coronary artery; in no patient was the vessel totally occluded. Of these 12 patients the anterior wall motion was normal in eight and hypokinetic in four. No patient had electrocardiographic evidence of anterior myocardial infarction.

All cardioactive medications were discontinued at least 48 hours before surgery. During the measure-
ment of the VFT the temperature measured by a nasopharyngeal probe was 34-37°C and blood pressure never fell below 100/60 mm Hg. Serum sodium, potassium and ionized calcium, as well as arterial pH, Po2 and Pco2 were within normal limits. The anesthesia was narcotic and halothane. Electroencephalographic activity was monitored during the measurement and showed primarily alpha-wave activity. In 21 patients pulmonary artery pressure was measured with a balloon-tip catheter positioned in the pulmonary artery.

Statistical analysis was performed with the t test for unpaired data.

**Results**

In each patient ventricular fibrillation was produced by the experimental technique without complications. No gross damage to the myocardium resulted and no patient developed evidence of epicardial injury (ST-segment elevation) or significant postoperative ventricular arrhythmias. During the measurement of VFT there were no significant changes in pulmonary diastolic pressure, mean aortic pressure, or ST-segment shifts suggestive of acute coronary ischemia.

The mean right VFT measured in six patients was 24.3 ± 5.2 mA (mean ± SD). No patient in this group had electrocardiographic evidence of right ventricular hypertrophy, pulmonary hypertension or right ventricular hemodynamic dysfunction. In 10 patients without coronary arterial obstruction the left VFT was 33.6 ± 9.5 mA (table 1). The difference between the right and left VFTs was significant (p < 0.05).

In the 12 patients with coronary artery disease, the left VFT was 18.6 ± 6.9 mA. The difference between the left VFT in the groups with and without coronary arterial obstruction was significant (p < 0.001). The patients' body weight and the coupling intervals of the premature depolarizations induced by the test current were not significantly different among the three groups (table 1).

**Discussion**

The initiation of ventricular fibrillation depends on fractionated myocardial activation and the development of multiple asynchronous wavelets of depolarization. Conditions which produce an inhomogeneously excitable myocardium predispose toward this sustained asynchronous reentry. It has been previously shown that the VFT is an index of temporal dispersion of recovery of excitability.5, 10 The present experiments demonstrate that VFT can be measured in man and that significant coronary arterial obstruction reduces the threshold. The electrical threshold for the induction of ventricular fibrillation in patients with severe coronary arterial obstruction was significantly lower than in the patients without coronary artery disease. None of our patients had ventricular arrhythmias or unstable angina which might have contributed to a decrease in the VFT. Although the stress of cardiac surgery may have produced transient ischemia in the patients with severe coronary artery disease, there was no electrocardiographic or hemodynamic evidence of ischemia during the procedure.

The VFT of the right ventricle was significantly lower than that of the left ventricle in this series. This observation has been made in animals by several investigators.5-10 Although the explanation for these observations is not known, proximity of the stimulating electrode to the subendocardial Purkinje network may play a role and the thinner right ventricular wall may explain the lower VFT on that ventricle.11

The VFT has previously been measured in patients...
TABLE 1. Clinical Data

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<tr>
<th>Pt no.</th>
<th>Age (years)/Sex</th>
<th>Diagnosis</th>
<th>Weight (kg)</th>
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<td></td>
<td>76 ± 11</td>
<td>18.6 ± 6.9†</td>
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*p <0.05 (compared with LVFT - normal coronary arteries).  
†p <0.001 (compared with LVFT - normal coronary arteries).  
Abbreviations: ASD = atrial septal defect; AS = aortic stenosis; MR = mitral regurgitation; AR = aortic regurgitation; MS = mitral stenosis; TR = tricuspid regurgitation; CAD = coronary artery disease; LV = left ventricle; RV = right ventricle; VFT = ventricular fibrillation threshold.

undergoing open heart surgery. Watson et al.,12 Starmer and Whalen,13 and Kugelberg,14 using alternating current for stimulation, obtained mean epicardial VFT values of 735, 1180, and 601 mA, respectively. These results however, cannot be compared with our data because of methodologic differences, including electrode configuration7,13,14 and the type of stimulating current.16,17 In addition, the type and extent of cardiac disease in these series were not specified. No adverse effects of the measurement techniques were observed in their patients. Furthermore, there have been several case reports in which VFTs have been measured in patients with fixed-rate pacemakers.18-21 Although these represent random observations, the values are of a similar order of magnitude as our data. These data are not strictly comparable, again because of methodologic differences; however, narrow rectangular pulses have been used experimentally in animals and produce results similar to studies using trains of current pulses;10 therefore, these latter data are more comparable to our present data than those obtained with alternating current.

There are certain inherent limitations to the
measurements in this study. A single measurement of the VFT was made in each patient because the countershock which would have been required for serial measurements and the rest period between measurements would have prolonged the surgical procedure unacceptably. The control or normal group was not strictly normal, because they were undergoing cardiac surgery for organic cardiac disease and the procedure requires the measurements be performed under these conditions. Nonetheless, the results appear valid, and refinements of this technique may eventually allow serial measurements in patients with completely normal hearts.

Relationship to Experimental Reduction in Coronary Flow

Although it is well established that total coronary occlusion in experimental animals reduces the VFT in the distribution of the occluded vessel, the effects of graded reduction in coronary flow on ventricular vulnerability have received less attention. Several studies have shown that chronic ischemia produced by coronary ligation reduces the VFT, and this reduction persists for as long as 6 months. Dixon et al. found that a 50% reduction in coronary flow produced a 25% decrease in the VFT and a 75% reduction in flow lowered the VFT approximately 60%. Furthermore, endocardial and epicardial sites within the distribution of the same obstructed vessel have different VFTs which are related to the flow to those sites. Lee and co-workers have measured the VFT in swine with severe coronary atherosclerosis and found that it was significantly reduced compared with that in control animals without coronary disease.

Garza et al. have also shown that the effect of coronary occlusion on ventricular vulnerability depends on the extent of coronary collateral circulation. In their study, the anastomotic index, a measure of coronary collateral development, was inversely related to the decrease in VFT after coronary occlusion. Therefore, in experimental animal models, ventricular vulnerability is increased by partial reduction in coronary flow. This concept is compatible with the present data in man.

Mechanism of Increased Vulnerability in Coronary Artery Disease

The mechanism by which partial reduction in coronary flow increases ventricular vulnerability is speculative. Lambert et al. have shown that reduced coronary flow shortened ventricular refractoriness, but less than that associated with total occlusion. Furthermore, while the absolute refractory period was shorter, the relative refractory period was longer. During the relative refractory period there is normally a degree of electrical inhomogeneity of recovery, and further asynchrony of recovery produced by partial occlusion would predispose toward the initiation of fibrillation. In addition to the changes caused by reduced coronary blood flow, the differences between the endocardial, intramural, and epicardial circulations may cause further disparity at any given blood flow. Batsford et al. have shown that such complex relationships exist between flow and ventricular refractory periods during myocardial ischemia produced by acute coronary artery ligation.

Clinical Relevance

Although sudden cardiac death in the setting of coronary artery disease is usually secondary to ventricular fibrillation, it is not known whether an episode of acute ischemia is required to increase ventricular vulnerability or if an increased basal state of vulnerability is sufficient to initiate ventricular fibrillation. Sudden death in the absence of prior symptoms suggests the latter alternative, although asymptomatic ischemia cannot be excluded. Beta-blocking agents that in experimental animal models increase the VFT have been demonstrated in some studies to reduce the incidence of sudden cardiac death in patients with coronary artery disease. These results may be related to a direct effect of these agents to increase the VFT. Similarly, Myerburg et al. have reported that antiarrhythmic therapy prevented sudden death without abolishing complex ventricular arrhythmias in patients previously resuscitated from ventricular fibrillation. The antiarrhythmic agents used in their study have been shown to increase the VFT in experimental animals. The protection afforded by these drugs against sudden death may be due to a decrease in the asynchrony of recovery of the ventricles.

In summary, in the present study we have shown that the VFT can be measured in man and that coronary artery disease reduces the parameter. These findings may be relevant to sudden cardiac death and its prevention by antiarrhythmic drugs or coronary artery bypass surgery.

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