Impact of Myocardial Ischemia and Reperfusion on Ventricular Defibrillation Patterns, Energy Requirements, and Detection of Recovery

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Background—Shocks that have defibrillated spontaneous ventricular fibrillation (VF) during acute ischemia or reperfusion may seem to have failed if VF recurs before the ECG amplifier recovers after shock. This could explain why the defibrillation threshold (DFT) for spontaneous VF appears markedly higher than for electrically induced VF.

Methods and Results—The DFT for electrically induced VF (E-DFT) was determined in 15 pigs before ischemia, followed by left anterior ascending or left circumflex artery occlusion.VF was electrically induced 20 minutes after occlusion, followed 5 minutes later by reperfusion. Whether spontaneous or electrically induced, VF during occlusion or reperfusion was treated with up to 3 shocks at 1.5×E-DFT. If all 3 shocks failed, shock strength was increased. Thirty minutes after reperfusion, the other artery was occluded and the protocol was repeated. Defibrillation was considered successful if postshock sinus/idioventricular rhythm was present for ≥30 seconds. VF recurring within 30 seconds after the shock was considered immediate or delayed if the first postshock activation complex in a rapidly restored ECG recording was VF or sinus/idioventricular rhythm, respectively. Defibrillation efficacy at 1.5×E-DFT was significantly higher for electrically induced ischemic VF (76%) than for spontaneous VF (31%). The incidence of delayed recurrence after electrically induced nonischemic (3%) or ischemic (20%) VF was significantly lower than after spontaneous VF (75%). Mean VF recurrence time after spontaneous VF was 4.6±5.3 seconds.

Conclusions—Spontaneous VF can be halted by a shock but then quickly restart before a standard ECG amplifier has recovered from postshock saturation, making it appear that the shock failed. (Circulation. 2002;105:2537-2542.)

Key Words: ischemia  fibrillation  defibrillation

A major complication of coronary artery disease is sudden death caused by spontaneous VF secondary to acute ischemia. Although the defibrillation threshold (DFT) has been reported to be higher for spontaneous VF during acute ischemia or reperfusion than for electrically induced VF, in most studies VF was electrically induced in the absence of regional ischemia. To determine the relative roles of acute ischemia and the mode of VF induction on elevation of the DFT, Ouyang et al compared the DFTs for spontaneous VF and electrically induced VF with or without acute ischemia. Their results suggested that the DFT was determined not only by the presence or absence of regional ischemia but also by whether VF occurred spontaneously or was induced electrically. Although the myriad electrophysiological changes induced by acute ischemia may explain why the DFT is elevated in the presence of regional ischemia independent of the mode of VF initiation, it is less clear why, in the presence of ischemia, spontaneously occurring VF has a higher DFT than electrically induced VF. As one possible explanation, we hypothesized that the increased arrhythmogenic propensity of the ischemic tissue responsible for spontaneous initiation of VF remains present for some time after VF occurs so that after the original VF episode is halted by a shock, VF is rapidly reinitiated. Because of the large defibrillation shock, standard ECG amplifiers are saturated for many seconds after the shock. If VF is reinitiated during this interval, it could be falsely concluded that the defibrillation shock failed because it was too weak to halt the original spontaneous VF episode. To test this hypothesis, we determined the outcome of defibrillation shocks of the same strength in animals with acute ischemia during spontaneous and electrically induced VF episodes while recording cardiac electrical activity with amplifiers that resumed recording quickly after the shock.

Methods

Animal Preparation

The Animal Care and Use Committee at the University of Alabama at Birmingham approved this study. The guidelines in the Position of the American Heart Association on Research Animal Use were followed.

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General anesthesia was induced in 15 healthy, mixed-breed pigs (20 to 44 kg; Animal Resource Program, University of Alabama at Birmingham) of either sex with intramuscular telazol (4.4 mg/kg), xylazine (2.2 mg/kg), and atropine (0.04 mg/kg). It was maintained by continuous administration of isoflurane (1% to 4%). An intravenous bolus of succinylcholine (0.25 to 0.50 mg/kg) was given several minutes before the first defibrillation attempt and repeated as needed to suppress muscular contraction in response to defibrillation shocks.

The animal was placed in dorsal recumbency, intubated with a cuffed endotracheal tube, and ventilated with a pressure-controlled respirator (Model 2000, Hallowell EMC). The lateral aspects of the thorax were shaved for application of a pair of 115-cm² self-adhesive defibrillation patches (Quick-Combo, Physio-Control Corp). The 2 external jugular veins, a femoral vein, a femoral artery, and a carotid artery were surgically isolated for placing hemostatic sheaths (8 to 10 F) and catheters. Under fluoroscopic guidance, 3 catheters containing stimulating or recording electrodes (EP Technologies) were introduced into the coronary sinus (CS), right atrium (RA), and right ventricle (RV). Pulmonary wedge and central venous pressures were produced into the coronary sinus (CS), right atrium (RA), and right ventricle (RV). Pulmonary wedge and central venous pressures were monitored using a Swan-Ganz catheter engaged in a small distal pulmonary artery. A femoral arterial catheter was used for blood sampling and continuous arterial pressure monitoring. Blood gases were analyzed at least hourly, and corrections in PO₂, P CO₂, Na⁺, K⁺, Ca²⁺, and bicarbonate were maintained within normal ranges. Intravenous lactated Ringer’s solution was continuously administered (5 to 10 mL/kg per min). Body temperature was measured with an esophageal temperature probe and maintained at ~37°C with a heating pad beneath the animal. The pig was euthanized by electrical induction of VF at the end of the experiment.

Determination of the DFT Before Acute Ischemia

Before coronary occlusion was performed, VF was induced by a 60-Hz current delivered through an electrode on the catheter in the RV apex. VF, indicated by a rapid drop of arterial pressure and disorganized ECGs, was allowed to continue for 15 seconds before a shock. The low- and high-frequency filters were 1 and 500 Hz, respectively. To minimize signal saturation caused by electrical shocks, a relay was placed between the electrodes and the amplifiers to disconnect the recording system beginning 10 ms before and lasting until a few milliseconds after the end of a shock.

Defibrillation was considered successful if the pig remained in organized (sinus/idioventricular) rhythm for ≥30 seconds. Recurrent VF after a failed shock was considered immediate or delayed if the first postshock activation complex was VF or organized rhythm, respectively. VF recurrence time was defined as the interval between the onset of the shock and the first postshock VF complex. A perfusing beat was defined as one that produced a femoral systolic arterial pressure >30 mm Hg before any cardiac massage was attempted. The earliest postshock perfusion time was defined as the interval between the onset of the shock and the first perfusing beat.

Statistics

Quantitative data were expressed as mean ± SD and compared by the Mann-Whitney U test. χ² tests were used to compare categorical variables. Although counted in calculating defibrillation efficacy, 23 failed shocks for electrically induced nonischemic VF and 8 for occlusion VF episodes were excluded in analyzing the earliest postshock perfusion time and VF recurrence time and recurrence patterns, because the first electrogram complexes after these shocks could not be definitely interpreted as VF or sinus/idioventricular rhythm. P<0.05 was considered to be statistically significant.

Results

General Data

Twenty-four occlusions were performed in 15 pigs. Six animals completed the entire experiment, 5 died during one of the occlusion episodes, 3 died of asystole after successful defibrillation, and 1 died of VF occurring during coronary catheterization before the balloon was inflated. There were 35 spontaneous VF episodes, 17 during occlusion and 18 during reperfusion. Of 17 electrically induced ischemic VF episodes, 4 were preceded by occlusion VF whereas the other 13 were not.

The mean E-DFT was 99±43 J. The mean shock energy that defibrillated electrically induced ischemic VF, occlusion VF, and reperfusion VF was 167±54, 215±113, and 200±108 J, respectively (P=NS among the three).

Defibrillation Efficacy for Electrically Induced VF During Ischemia and Spontaneous VF During Ischemia or Reperfusion

The percent of successful shocks at 1.5×E-DFT (Figure 1) was significantly higher for electrically induced ischemic VF...
(76%) than for occlusion (23%) or reperfusion VF (40%). There was no significant difference between the percent of shocks at 1.5×E-DFT that stopped occlusion VF or reperfusion VF. Most successful shocks (73%) defibrillated within 80 seconds after spontaneous VF initiated (Figure 2).

The fraction of electrically induced ischemic VF defibrillated by 1.5×E-DFT (16 of 17) was significantly higher than that of occlusion VF (8 of 17) but did not differ from that of reperfusion VF (14 of 18). Increasing shock energy >1.5×E-DFT eventually defibrillated all electrically induced ischemic VF and reperfusion VF but failed to halt 29% (5 of 17) of occlusion VF episodes ($P<0.05$).

**VF Recurrence Patterns After Failed Defibrillation**

Figure 3 illustrates electrogram examples of immediate and delayed VF recurrence patterns. Although the longest VF recurrence time (25 seconds) occurred after a failed shock for occlusion VF (Figure 4), the interval between successful defibrillation of a spontaneous VF episode and the onset of the next spontaneous VF during the same occlusion-reperfusion episode ranged from 54 to 960 seconds, supporting the use of a recurrence time of 30 seconds as a cutoff criterion for classifying successful and unsuccessful shocks.7 VF recurred significantly earlier for electrically induced nonischemic VF (0.5±0.2 seconds) than for electrically induced ischemic VF (3.3±5.0 seconds), occlusion VF (4.1±5.3 seconds), or reperfusion VF (5.3±5.3 seconds). The mean recurrence time did not differ significantly among electrically induced ischemic VF, occlusion VF, or reperfusion VF. The incidence of delayed VF recurrence was significantly lower for electrically induced ischemic or nonischemic VF than for spontaneous VF during occlusion or reperfusion (Figure 5). The incidence of delayed recurrence after failed shocks was similar for occlusion and reperfusion VF ($P=NS$).

There was no linear correlation between VF recurrence time and shock strength for any VF types ($P=NS$). Figure 6 illustrates a scatter plot of these 2 parameters for spontaneous VF.

**Postshock Perfusion After Failed Defibrillation**

The percent of recurrent VF episodes preceded by at least 1 perfusing beat after failed defibrillation of electrically induced nonischemic VF (0%) was significantly lower than that of occlusion VF (33%) or reperfusion VF (41%) but did not differ among electrically induced ischemic VF (10%), occlusion VF, or reperfusion VF ($P=NS$). The earliest postshock perfusion, however, occurred significantly later after failed shocks for occlusion VF (1.4±0.7 seconds) than for reperfusion VF (0.8±0.3 seconds).

**Discussion**

This study confirmed the previous findings that spontaneous VF during acute ischemia or reperfusion requires significantly higher defibrillation energy than electrical VF induced in the absence of ischemia and that 1.5×E-DFT is not sufficient shock energy to defibrillate most spontaneous VF.3 In addition, this study demonstrates that the percent defibrillation success for 1.5×E-DFT energy shocks is significantly higher for electrically induced ischemic VF than for occlusion VF during ischemia or reperfusion.
Figure 3. Immediate and delayed VF recurrence after failed defibrillation in 1 pig. In each panel, the upper tracing is an electrogram recorded from the right ventricle. The arrow indicates the end of the shock. The lower tracing shows the femoral artery pressure, and the arrow denotes the end of noise caused by muscular contraction of the pig in response to the shock.

A, Immediate VF recurrence after failed defibrillation of electrically induced VF before coronary occlusion. The first discernible postshock rhythm is VF. B, Delayed VF recurrence after failed defibrillation of spontaneous VF during coronary occlusion. The first discernible postshock complex was an organized rhythm. VF recurred ~7.5 seconds after the shock. C, Delayed VF recurrence after failed defibrillation of spontaneous VF during reperfusion. The first 2 postshock beats were organized, followed by recurrent VF. The noise on the right side of the upper and lower tracings was caused by defibrillator charging.

The presence of the first of these 2 VF patterns, immediate restoration of VF on recovery of the amplifiers, suggests 2 possible mechanisms. First, the shock may have been too weak to halt the VF wavefronts. Second, VF may have been stopped, but a new VF episode could have been initiated by the shock itself via a critical point or focal mechanism. No matter which of the 2 mechanisms is operative, insufficient shock strength may explain the immediate VF recurrence pattern. Insufficient shock strength according to either mechanism, however, cannot explain the delayed VF recurrence pattern. The postshock organized rhythm, the prolonged time until VF recurrence, and, particularly, the high incidence of postshock perfusing beats all strongly suggest that shocks ≥1.5×E-DFT energy stopped most spontaneous VF episodes but that a new postshock VF episode was reinitiated.

Acute ischemia could be one factor responsible for this reinitiation, because it can cause many detrimental changes, such as increased sympathetic activity, hyperkalemia, and acidosis, which have been shown to increase vulnerability to VF. These ischemia-induced changes may have caused the reinitiation of VF within the 30 seconds after the defibrillation of spontaneous VF. Yet ischemia-induced alterations should also have existed after defibrillation of electrically induced ischemic VF. Then, why is spontaneous VF more difficult to defibrillate than electrical VF induced during occlusion? One possible reason is that ischemia was more severe when VF occurred spontaneously than when it was electrically induced. However, in a study in which the LAD and LCX were alternatively ligated with a protocol similar to ours, electrically induced ischemic VF was induced only when no spontaneous VF occurred throughout the ligation. Yet there was no significant difference in the ischemic mass among dogs with electrical VF induced during occlusion or spontaneous VF during occlusion or reperfusion. Thus, the ischemic area had little, if any, influence over the DFTs in that study.

Strong shocks may cause conduction block and prolonged depolarization, which in turn can cause VF. It is also possible that ischemic tissue is more vulnerable to the effects of strong shocks. If so, strong defibrillation shocks delivered during acute ischemia or reperfusion may contribute to the reinitiation of VF after an interval of postshock organized rhythm, leading to defibrillation failure and delayed VF recurrence. However, the lack of correlation between shock strength and VF recurrence time (Figure 6) and the substantial fractions of occlusion (4 of 12) and reperfusion VF episodes (4 of 18) defibrillated by shocks >1.5×E-DFT energy level do not support this scenario. Instead, they are consistent with another hypothesis: defibrillation outcome during spontaneous VF is determined not only by shock energy delivered to the heart but also by arrhythmogenic propensity of the acutely ischemic or reperfused tissue, particularly the original trigger responsible for the spontaneous initiation of VF.

It is possible that whatever initiates the original spontaneous VF episode is still present to induce VF recurrence during the 30 seconds after the shock. Although the exact duration of the increased arrhythmogenic propensity responsible for the initiation of spontaneous VF episodes is
not known, evidence from this study suggests that it frequently has decreased or disappeared within 80 seconds after the onset of the original VF episodes (Figure 2). The possibility that the duration and degree of the increased arrhythmogenic propensity could differ in occlusion or reperfusion episodes or during different portions of the same episode may help explain the large standard deviation in VF recurrence time for delayed recurrent spontaneous VF. The duration of increased arrhythmogenic potential may be longer during occlusion than during reperfusion, as supported by the following evidence: of the 17 occlusion VF episodes, 5 were never halted with shocks as great as 400 J, yet increasing shock strength up to 400 J eventually defibrillated 100% of reperfusion VF episodes, suggesting that the arrhythmogenic mechanism during reperfusion, which is thought to be caused by sudden release of large amounts of accumulated ischemic metabolites, is probably different from that during occlusion. The eventual successful defibrillation of reperfusion VF episodes may not be a direct result of multiple strong shocks; rather, it is possible that delivery of multiple shocks allowed time for the condition responsible for the spontaneous initiation of reperfusion VF to dissipate. Although the incidence of postshock perfusing beats is comparable after failed shocks for reperfusion and occlusion VF episodes, these perfusing beats may allow
washout of arrhythmogenic substances during reperfusion to a higher extent than during occlusion because the artery perfusing the ischemic tissue is open after reperfusion but is still occluded during occlusion VF.

Clinical Implications
These findings raise the possibility that although increasing shock strength may defibrillate a higher percentage of immediately recurrent VF episodes, multiple shocks of escalating strength may not improve defibrillation efficacy of persistently recurring VF during acute ischemia or reperfusion in all patients. Instead, a defibrillation shock of the same appropriate strength repeated after a period of cardiac massage, during which the original arrhythmogenic conditions may decrease, might be more efficacious than a shock given immediately after the recurrence of the spontaneous VF episode. Although this is an external defibrillation study, these findings probably are also applicable to selection of shock energy levels for implantable cardioverter-defibrillators (ICDs) in patients with acute ischemia or reperfusion. For example, programming ICDs to maximum output to prevent the elevated DFT during ischemia may not always be helpful or may even be harmful if the mechanisms of defibrillation are not related to insufficient shock energy. Antiarrhythmic drugs, such as intravenous sotalol, which has been shown to prevent early recurrence of atrial fibrillation after successful cardioversion and intravenous amiodarone during cardiopulmonary resuscitation, may also reduce the incidence of VF recurrence. All of these ideas require comprehensive testing before being used clinically, and it is extremely important to exercise caution when extrapolating the findings in this animal study to potential changes in the clinical protocol for shock-energy sequences.

Study Limitations
Acute ischemia was induced by an inflated balloon in a structurally normal animal, so the arrhythmogenic effects of atherosclerotic lesions and acute thrombi were not present in the study. Defibrillation was attempted within <1 minute after the onset of a spontaneous VF episode; thus, results from this study may not hold for longer durations of VF before the shock. It is possible that some VF episodes during occlusion or reperfusion could have been halted by shocks weaker than 1.5×E-DFT, but such lower shock strengths were not tested.

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