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Effects of Myocardial Ischemia on Ventricular Fibrillation Inducibility and Defibrillation Efficacy

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Objectives. **This study investigated the effects of acute global ischemia on the vulnerable window, the upper limit of vulnerability and the defibrillation threshold.**

Background. **Myocardial ischemia, an important factor for arrhythmogenesis and sudden death, may affect the inducibility of ventricular fibrillation by T wave shocks as well as the defibrillation threshold. However, studies of the effect of ischemia on the defibrillation threshold remain inconclusive, and the effect of ischemia on recently established variables of ventricular fibrillation vulnerability is still unknown.**

Methods. **Ten isolated, perfused rabbit hearts were immersed in a tissue bath between two shock plate electrodes. Truncated 5-ms biphasic shocks were used to determine the vulnerable window, the upper limit of vulnerability and the defibrillation threshold. Measurements were performed during baseline and at 10 to 15 min of acute ischemia induced by an 80% reduction of coronary flow. The effects of ischemia were monitored by measuring the dispersion of ventricular activation and repolarization using multiple monophasic action potential recordings.**

Results. **Acute ischemia caused an increase in dispersion of activation (baseline vs. ischemia [mean ± SD]: 22 ± 6 vs. 34 ± 10 ms, $p < 0.001$) and dispersion of repolarization (37 ± 16 vs. 69 ± 29 ms, $p < 0.01$). The width of the vulnerable window increased from 25 ± 22 ms during baseline to 75 ± 26 ms during ischemia ($p = 0.001$). The upper limit of vulnerability (baseline vs. ischemia: 294 ± 44 vs. 274 ± 53 V, $p = 0.21$) and the defibrillation threshold (271 ± 33 vs. 268 ± 42 V, $p = 0.74$) remained unchanged during ischemia.**

Conclusions. **Acute global ischemia caused a threefold increase in the width of the vulnerable window. This increase was associated with increased heterogeneity of ventricular activation and repolarization. Despite these marked changes, the upper limit of vulnerability and the defibrillation threshold were not affected by acute myocardial ischemia. Thus, the previously reported similarity between both measures was maintained under these adverse conditions.**

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Sudden cardiac death is often caused by acute myocardial ischemia (1). Because most patients requiring treatment with an implantable cardioverter-defibrillator have concomitant ischemic heart disease, acute ischemia may also play a role in defibrillation failure and sudden cardiac death in these patients (2). Although the underlying mechanisms of spontaneous ventricular fibrillation (3) and the fibrillation threshold (4,5) under ischemic conditions have been studied extensively (6), only a few studies, several years ago, investigated the effects of acute ischemia on the electrophysiologic responses to electrical field shocks. Two of these studies (7,8) reported a significant increase in the defibrillation threshold, whereas the other studies found either no change (9–11) or a decrease (12) in the defibrillation threshold under ischemic conditions. The effects of acute ischemia on defibrillation efficacy thus remain unclear. In addition, the electrophysiologic response to electrical field shocks during normal rhythm has not been investigated under ischemic conditions. According to the "upper limit of vulnerability" hypothesis of defibrillation (13), the upper limit of vulnerability and the defibrillation threshold might be related to a common mechanism. Thus, interventions affecting the defibrillation threshold should also affect the upper limit of vulnerability. However, it is not known whether the reported relation between the defibrillation threshold and the upper limit of vulnerability (14–16) is still present during an episode of acute myocardial ischemia.

The purpose of our study was to determine in an isolated, perfused rabbit heart model the effects of acute global ischemia on both ventricular fibrillation inducibility in response to electrical field shocks and defibrillation efficacy. Ventricular fibrillation inducibility was determined during paced rhythm by assessing the upper limit of vulnerability and the vulnerable window. Defibrillation efficacy was determined by measuring the defibrillation threshold. The effects of ischemia on the electrophysiologic state of the ventricular myocardium were monitored by monophasic action potentials recorded simultaneously from 10 widely spaced sites in both ventricles.

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Abbreviations and Acronyms
ECG = electrocardiogram, electrocardiographic
MAP = monophasic action potential

Methods

Experimental setup. Ten hearts from New Zealand White male rabbits (mean [±SD] weight 4.02 ± 0.26 kg) were investigated. Rabbits were anesthetized with intravenous pentobarbital (50 mg/kg body weight), and hearts were isolated, mounted on a vertical Langendorff apparatus (Fig. 1A) and perfused as previously described (17). The temperature of the solution was maintained at 37 ± 0.5°C. The atrioventricular node was ablated, and hearts were subsequently paced at a cycle length of 500 ms by electrical stimuli of twice diastolic threshold strength and 2-ms stimulus duration from the right ventricular apex.

Hearts were instrumented with monophasic action potential (MAP) electrodes and immersed in a tissue chamber (Fig. 1B) filled with warm Tyrode's solution. At the wall of the tissue chamber, silver–silver chloride electrodes were positioned in an approximate Einthoven position to record a volume-conducted electrocardiogram (ECG) (18). MAPs were recorded simultaneously from 10 different sites of the endocardium and epicardium of both ventricles using the contact electrode technique (19). The position of the MAP electrodes is shown in Figure 1C. Epicardial MAP electrodes were located 6 to 8 mm below the atria. Endocardial MAP recordings were obtained from the right and left ventricular apex using standard 7F MAP catheters (EP Technologies). MAP signals were preamplified by a direct current coupled amplifier with automatic offset control (EP Technologies, model 10012). Signals from the ECG were amplified by a multichannel amplifier with conventional filter characteristics (Stellartech). Both, MAP and ECG recordings were acquired digitally at a sampling rate of 1,000 Hz and backed up on magneto-optical disks for off-line computer-aided analysis.

Truncated exponential biphasic shocks, with a 2.5-ms duration of each phase and equal voltages for the trailing edge of the first and leading edge of the second phase, were delivered with an experimental defibrillator (Medtronic, model 2394, capacitance 120 μF) by means of two circular shock plate electrodes located above and below the heart within the tissue bath (Fig. 1, A and B). The distance between the two plate electrodes was 6 cm. Using this electrode configuration, the entire heart was located in the center of the electrical field between the two shock plate electrodes and was thus exposed to a relatively uniform shock field. The delivered shock waveform was displayed on a digital oscilloscope (Lecroy, model LS 140) for on-line analysis of peak and integrated shock voltages.

Experimental protocol. The protocol was started after an equilibration time of 30 min. In the first part of the protocol, the vulnerable window, the upper limit of vulnerability and the defibrillation threshold were determined under baseline conditions. For assessment of the vulnerable window and the upper limit of vulnerability, a modified protocol was used as previously described (20). The first shock was delivered at an intermediate shock strength (200 to 280 V) and a shock coupling interval of 200 ms to determine the right border of the vulnerable window. Depending on whether ventricular fibrillation was induced, the shock coupling interval was adjusted (prolonged if ventricular fibrillation was induced or shortened if no ventricular fibrillation occurred). To determine the left border of the vulnerable window, an analog procedure was repeated at the same shock strength but at a shock coupling interval of 150 ms. The step size of changes in shock coupling intervals was 10 ms. Because the width of the vulnerable window is shock-strength dependent (20–22), the procedure was repeated at various shock strengths (range 120 to 360 V, step size 40 V) to determine the true maximal extent of the

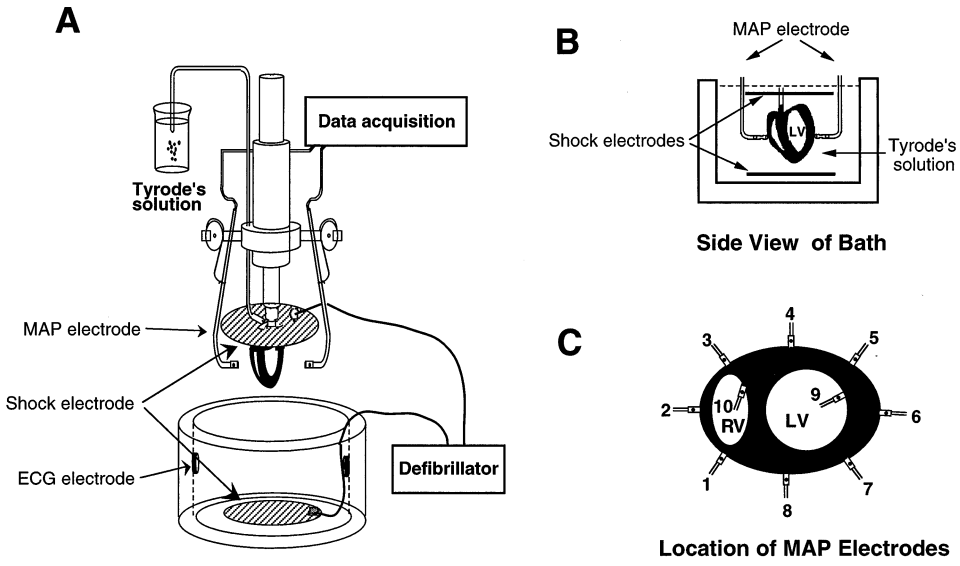

Figure 1. Experimental setup. **A,** The heart is displayed on the vertical Langendorff apparatus before its immersion into the tissue bath. **B,** Side view of the immersed heart, with two MAP electrodes in place (the other eight MAP electrodes are not shown). **C,** Location of all MAP electrodes indicated by the **numbers 1 to 10.** LV = left ventricle; RV = right ventricle.

vulnerable window. The right and left borders of the vulnerable window were defined as the longest and shortest ventricular fibrillation-inducing shock coupling intervals, respectively (20,23). To determine the upper limit of vulnerability, shocks were delivered at various shock voltages that were increased or decreased in 40-V steps depending on whether the shock induced ventricular fibrillation. This procedure was performed at various shock coupling intervals during the repolarization process (range of tested coupling intervals 150 to 200 ms, step size 10 ms) because the upper limit of vulnerability depends on the timing of the shock (15,24). The highest ventricular fibrillation-inducing shock strength was defined as the *upper limit of vulnerability* (14).

The *defibrillation threshold* was defined as a 50% probability of successful defibrillation and was determined using the delayed up–down protocol (16,25), as previously described (23). The step size between the various shock strengths tested was 40 V, and a minimum of four data points was required for the estimation of the defibrillation threshold. If shocks induced ventricular fibrillation, defibrillation shocks were delivered after 5 to 10 s to measure the defibrillation threshold and terminate ventricular fibrillation. Short episodes of ventricular fibrillation that lasted <5 s were not used to determine the defibrillation threshold. If a defibrillation shock was unsuccessful, a rescue shock of 500 to 600 V was applied to terminate ventricular fibrillation.

In the second part of the protocol, measurements were repeated under ischemic conditions. Myocardial ischemia was induced by reducing the retrograde inflow into the aorta by 80%, resulting in a flow rate of ~8 ml/min and a mean perfusion pressure of 15 to 25 mm Hg. Flow reduction was maintained for 15 min. Variables were determined between 10 and 15 min of ischemia. Because of time constraints, the vulnerable window was measured at the same shock strength as under baseline conditions. The initial coupling intervals for the determination of the right and left borders of the vulnerable window were 100 and 200 ms, respectively. The upper limit of vulnerability and the defibrillation threshold were determined as described earlier. Episodes of ventricular fibrillation that were induced during the measurements of the vulnerable window and the upper limit of vulnerability were used to determine the defibrillation threshold. The time interval between episodes was 15 s if a T wave shock resulted in nonsustained or no arrhythmias. The interval was extended to 30 s if ventricular fibrillation was induced. After a total ischemia time of 15 min, the hearts were reperfused using the baseline flow rate, and activation and repolarization measurements were repeated. The hearts were then removed from the Langendorff apparatus and weighed. The mean wet weight was 12.07 ± 2.14 g.

Data analyses and statistics. The following variables were determined from MAP recordings: *activation time,* defined as the interval between the pacing artifact and the fastest MAP upstroke; *action potential duration,* defined as the interval between the fastest MAP upstroke and 90% repolarization; *repolarization time*, defined as the sum of activation time and action potential duration; *dispersion of activation,* defined as the difference between the shortest and longest activation times; and *dispersion of repolarization,* defined as the difference between the shortest and longest repolarization times. These measurements were performed during baseline and at 5, 10 and 15 min of myocardial ischemia and after 5 min of reperfusion. Induction of ventricular fibrillation was defined if a shock initiated six or more postshock excitations with cycle lengths <160 ms (20,23,26). This definition was used because rabbit hearts, with their small myocardial mass, tend to spontaneously recover from ventricular fibrillation (27,28).

Results are expressed as mean value ± SD. The effects of ischemia on activation and repolarization and dispersion of these variables were calculated using repeated measures analysis of variance and the Scheffé F test as a multiple comparison procedure. Comparisons between data at baseline and during ischemia for the upper limit of vulnerability, defibrillation threshold and vulnerable window were performed using the paired Student *t* test. Correlations between the borders of the vulnerable window and MAP repolarization times were calculated using linear regression analyses. Statistical significance was assumed at $p < 0.05$.

Results

Effects of myocardial ischemia on MAP recordings. Figure 2 illustrates an example of 10 simultaneously recorded MAPs from a single heart during baseline and ischemia and after reperfusion. During ischemia, MAPs progressively shortened and became more triangular than those at baseline recordings. However, the magnitude of ischemia-induced alterations varied between different recording sites. Reperfusion resulted in a normalization of both duration and shape of most MAP recordings.

Activation and repolarization data obtained from all 10 experiments during baseline, ischemia and reperfusion are depicted in Figure 3. There was an ischemia-induced increase of the activation time, and both action potential duration and repolarization time shortened during ischemia compared with baseline measurements. Both dispersion of activation and repolarization increased under ischemic conditions. Five minutes after reperfusion, all measures returned to baseline values.

Effects of myocardial ischemia on upper limit of vulnerability and defibrillation threshold. Figure 4 depicts the upper limit of vulnerability and defibrillation threshold during baseline and ischemia measurements. The upper limit of vulnerability (Fig. 4A) slightly increased in three hearts and decreased in six other hearts (difference 40 to 80 V). In one experiment, the upper limit of vulnerability did not change. If calculated over all 10 experiments, there was no significant difference in the upper limit of vulnerability between baseline and ischemia measurements ($p = 0.21$). The defibrillation threshold (Fig. 4B) slightly increased in four hearts and decreased in four other experiments (difference 20 to 80 V). In two hearts, defibrillation threshold remained unchanged (difference ≤10 V).

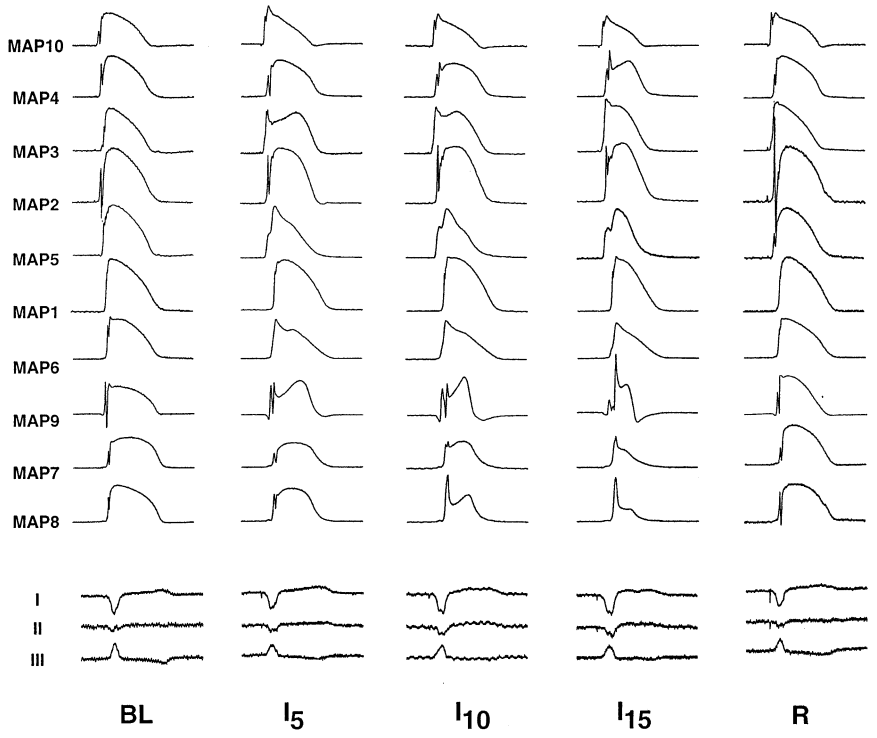

Figure 2. Original recording of 10 MAPs recorded at baseline (BL) and after 5 (I_5), 10 (I_{10}) and 15 min (I_{15}) of acute global ischemia and after 5 min of reperfusion (R). See Figure 1C for MAP locations.

On average, there was no significant defibrillation threshold difference between baseline and ischemia measurements ($p = 0.74$).

Effects of myocardial ischemia on vulnerable window. The effects of ischemia on the width and borders of the vulnerable window are illustrated in Figure 5. The width increased threefold from 25 ± 22 ms during baseline to 75 ± 26 ms during ischemia ($p = 0.001$). This increase was primarily due to a shift of the left border of the vulnerable window toward shorter coupling intervals (baseline vs. ischemia: 170 ± 26 vs. 109 ± 25 ms, $p < 0.001$). The right border of the vulnerable window remained unchanged (baseline vs. ischemia: 194 ± 15 vs. 184 ± 26 ms, $p = 0.288$).

To determine the relation between the borders of the vulnerable window and ventricular repolarization, the left border of the vulnerable window (i.e., the shortest ventricular fibrillation-inducing shock coupling interval) was correlated with the repolarization time of the shortest MAP recording of each experiment, and the right border (i.e., the longest ventricular fibrillation-inducing shock coupling interval) with that of the longest MAP recording. Correlations were calculated for data obtained during baseline and after 15 min of ischemia. The results are shown in Figure 6. There was a close correlation between the repolarization time of the shortest individual MAP recording and the left border of the vulnerable window (Fig. 6A), and both measures were grouped around the line of identity. The repolarization time of the longest individual MAP recording and the right border of the vulnerable window also showed a significant but weak correlation (Fig. 6B).

Discussion

The present study investigated the influence of acute global ischemia on myocardial vulnerability for ventricular fibrillation and the defibrillation threshold for biphasic shocks in an isolated perfused rabbit heart model. The electrophysiologic changes induced by global ischemia were directly monitored by MAPs recorded simultaneously from 10 different sites of the ventricles. The *main findings for fibrillation induction and defibrillation* are the following: 1) The width of the vulnerable window increased threefold during ischemia; 2) the ischemia-related increase in the width of the vulnerable window was associated with a leftward shift of the shortest ventricular fibrillation-inducing coupling interval; 3) the leftward extension of the vulnerable window correlated closely with the repolarization time of the MAP recording most shortened by ischemia; and 4) Despite these marked ischemia-induced changes in the vulnerable window, both the upper limit of vulnerability and defibrillation threshold remained unchanged during ischemia compared with baseline measurements.

Ischemia-related effects on ventricular activation and repolarization. Myocardial ischemia caused a prolongation of the activation time at all recording sites. This prolongation was accompanied by an increase in the dispersion of ventricular repolarization, primarily caused by disparate shortening of the action potential duration in areas most affected by ischemia. We previously demonstrated (29) that prolongation of the activation time and shortening of action potential duration can be juxtaposed to each other and thus compensate. The ischemia-induced increase in activation and repolarization heterogeneity

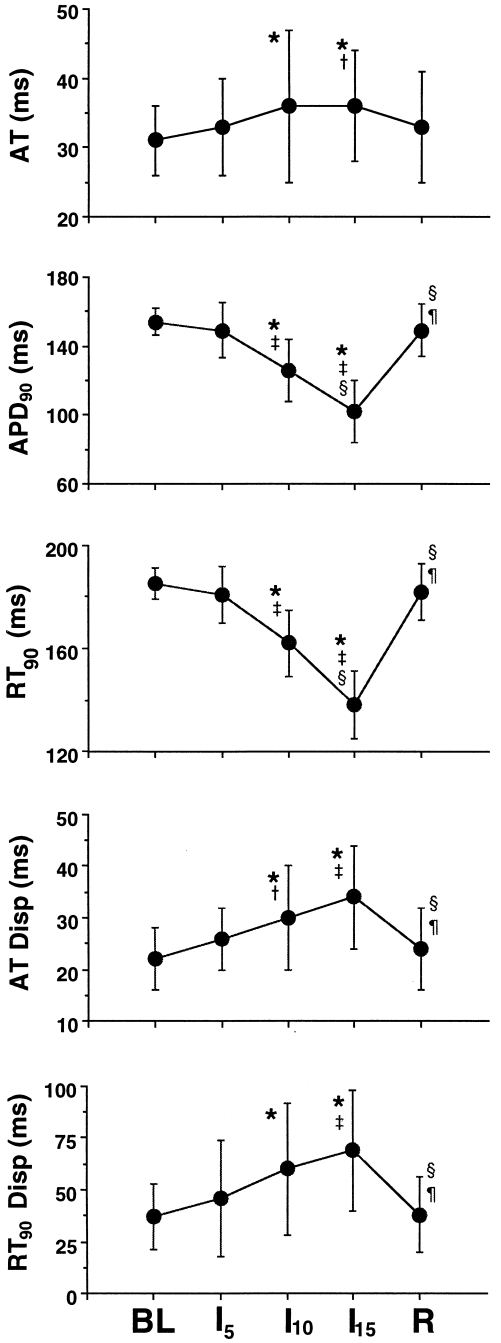

Figure 3. Effects of acute ischemia on activation time (AT), action potential duration (APD_{90}) and repolarization time (RT_{90}) at 90% repolarization and dispersion of activation (AT Disp) and repolarization (RT_{90} Disp). *$p < 0.01$ versus baseline (BL). †$p < 0.05$ and ‡$p < 0.01$ versus 5 min (I_5), §$p < 0.01$ versus 10 min (I_{10}) and ¶$p < 0.01$ versus 15 min (I_{15}) of acute ischemia.

was caused by different effects on activation and repolarization at various sites of the heart. For example, ventricular repolarization shortened substantially in some areas of the heart but only moderately in others (Fig. 2), which resulted in an increased repolarization heterogeneity that has been considered an important factor for the initiation of arrhythmias (30,31).

Ischemia widens the vulnerable window. Ischemia produced a threefold increase in the width of the vulnerable window, which indicates that acute ischemia modifies the electrophysiologic state of the ventricular myocardium so as to facilitate the initiation of ventricular fibrillation by electrical field stimuli. This finding is consistent with the fact that under ischemic conditions, the initiation of spontaneous ventricular fibrillation is facilitated as a result of slow conduction and variable degrees of conduction block in ischemic areas, thereby providing the conditions for reentry to occur (3). The increased width of the vulnerable window in response to field shocks may therefore be related to better reentry conditions within the myocardium during acute ischemia.

Role of ventricular repolarization for ischemia-related changes of the vulnerable window. The vulnerable window widened predominantly because of a leftward shift of the shortest ventricular fibrillation-inducing shock coupling interval (i.e., the left border of the vulnerable window). This led us to the hypothesis that the leftward shift may be due to action potential shortening during ischemia (29,30,32). We measured ventricular repolarization at multiple sites of both ventricles and found that the repolarization time of MAP recordings most shortened by ischemia and the left border of the vulnerable window were closely correlated ($r = 0.809$) (Fig. 6A). We found a further correlation between the longest individual repolarization time and the right border of the vulnerable window. This relation was not as strong ($r = 0.540$), possibly because these two variables were less altered during ischemia, resulting in a smaller spread of data points (Fig. 6B). These findings suggest that the maximal range between the longest and shortest repolarization time may be at least one factor in determining the width of the vulnerable window during myocardial ischemia. Thus, there appears to be a direct relation between ischemia-related effects on action potential duration and myocardial arrhythmia vulnerability. Although these findings do not prove a causal relation between both measures, they are consistent with previous reports in which ventricular repolarization heterogeneity was found to be an important factor for arrhythmogenesis (33) and arrhythmia inducibility by both electrical point (29,34) and field stimulation (20,35).

Ischemia does not change the upper limit of vulnerability and the defibrillation threshold. Acute myocardial ischemia affected neither the upper limit of vulnerability nor the defibrillation threshold. In the present study, the ischemia-related effects on both measures were determined because under normal conditions, the upper limit of vulnerability and the defibrillation threshold have been shown to be correlated (14–16). The finding that both the upper limit of vulnerability and the defibrillation threshold remained unchanged under ischemic compared with baseline conditions supports the upper limit of vulnerability hypothesis of defibrillation (13) and thus the concept of a common mechanism for both measures.

Previous studies (7–12) investigated the effects of acute ischemia on the defibrillation threshold; however, data on ischemia-related effects on the upper limit of vulnerability are lacking. Tacker et al. (8) reported a 2.5-fold increase in the

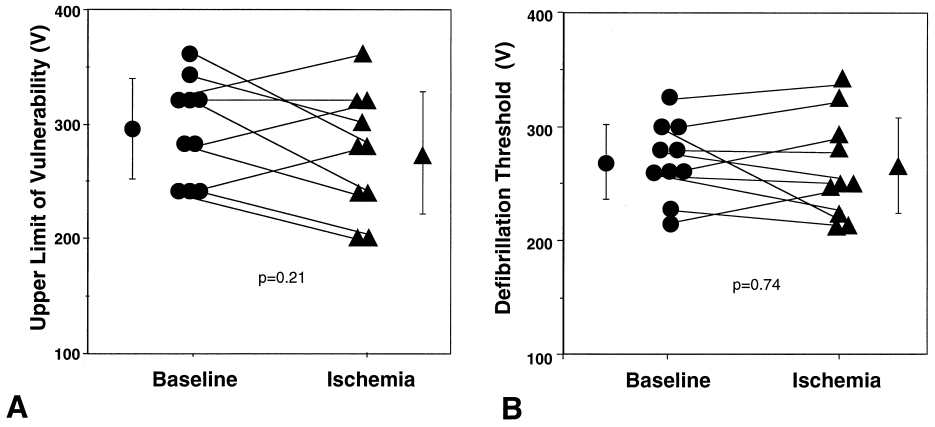

Figure 4. Effects of acute ischemia on upper limit of vulnerability **(A)** and defibrillation threshold **(B).**

defibrillation threshold. The defibrillation threshold increased immediately after occlusion of the left anterior descending coronary artery and decreased toward control values after 30 min. Tacker et al. speculated that, on average, 150% and, in individual subjects, up to 435% more defibrillation energy might be required to terminate ventricular fibrillation in patients with an acute infarction. Babbs et al. (7) also found a significant increase in the defibrillation threshold after 15 min of left coronary artery embolization. The defibrillation threshold increase was smaller (~20%) than that in the Tacker et al. (8) study and remained stable during the entire 2-h study period. In contrast, three other studies (9–11) reported no significant change in the defibrillation threshold during acute myocardial ischemia, and one study (12) found a small decrease of ~10% after coronary artery ligation.

Our findings are consistent with some previous studies (9–11). The reasons for the defibrillation threshold increase reported in two studies (7,8) remain unclear but may be related to differences in the experimental protocol. A possible explanation for the findings reported by Tacker et al. (8) could be that ventricular fibrillation episodes in that study were both long-lasting (up to 30 s before termination) and frequently induced (with a 30-s recovery period between episodes). Differences in the results of those previous studies may also be related, at least in part, to the fact that various cardiac and extracardiac factors could have changed during ischemia, thereby influencing electrophysiologic conditions and the response to electrical field shocks (36,37). We therefore investigated the effects of ischemia on the upper limit of vulnerability and the defibrillation threshold in an isolated heart model, which is not influenced by extracardiac factors, and in which cardiac factors such as hemodynamic and metabolic conditions or coronary perfusion may be better controlled than in in vivo models (38).

Methodologic considerations. The present study was performed under experimental constraints. During ischemia, the vulnerable window, the upper limit of vulnerability and the defibrillation threshold were determined over a period of time during which there were ongoing changes in MAP duration and the repolarization dispersion as a result of the constantly changing electrophysiologic state of the ventricular myocardium. It is very difficult, if not impossible, to keep myocardial ischemia at equilibrium between supply and demand over time. Measurements were begun at 10 min of ischemia because both MAP duration and repolarization dispersion were significantly altered at this time and tended toward a quasi equilibrium for the subsequent 5 min. Another limitation was that the present study investigated the effects of global rather than regional ischemia, which may not simulate the conditions of clinical events, such as an acute myocardial infarction that occurs in a

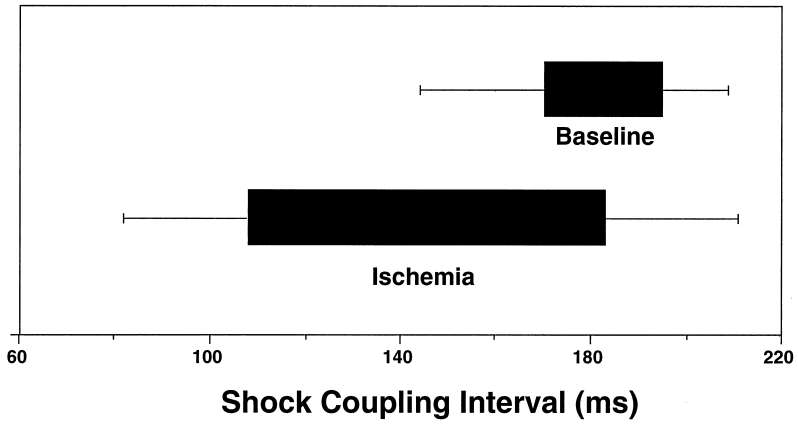

Figure 5. Effects of acute ischemia on the vulnerable window and its borders.

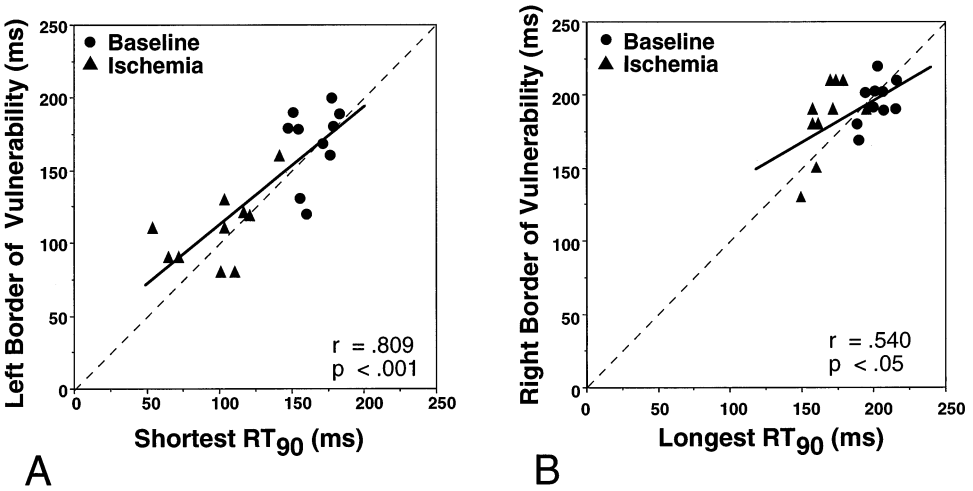

Figure 6. Correlation between (**A**) the left border of the vulnerable window and the shortest repolarization time at 90% repolarization (RT_{90}) and (**B**) the right border of the vulnerable window and longest repolarization time. The relation is depicted for baseline and ischemic conditions. See text for details.

distinct territory of the heart. Therefore, it is not clear whether the observations made in this model of global ischemia may be immediately translated to that of an ischemic event in the human heart. A third limitation was that rabbit hearts are prone to defibrillate spontaneously because of their small size (27,28). In concordance with previous reports (20,26,27), we defined ventricular fibrillation as six or more rapid postshock excitations. However, for measurements of the defibrillation threshold, only ventricular fibrillation episodes that lasted at least 5 s were included. It is unknown whether this somewhat arbitrary definition of ventricular fibrillation in the rabbit heart truly reflects an episode of sustained ventricular fibrillation in large mammalian hearts (including human hearts). Gray et al. (39) recently demonstrated in an isolated perfused rabbit heart model similar to our preparation that a single or paired ("figure of eight") meandering spiral wave may be sufficient to produce ventricular fibrillation–like activity. In contrast, multiple reentrant wavefronts may be present in larger mammalian hearts, thereby causing episodes of sustained ventricular fibrillation. A defibrillation shock thus needs to terminate multiple nonstationary scroll waves in larger mammalian hearts but only a single or paired scroll waves in the model used. The different characteristics of ventricular fibrillation may also result in a difference in the efficacy of shocks to terminate an episode of ventricular fibrillation in various species.

Conclusions. In this isolated Langendorff perfused heart model, acute global ischemia significantly altered the electrophysiologic state of the ventricular myocardium and substantially increased the width of the vulnerable window. This finding confirms previous reports that acute ischemia facilitates the initiation of ventricular fibrillation. Despite the facilitation of ventricular fibrillation induction by ischemia, the defibrillation threshold remained essentially unchanged during ischemia. This finding is of clinical importance for patients with ischemic heart disease treated with an implantable cardioverter-defibrillator. Some patients may develop ventricular tachyarrhythmias during episodes of acute myocardial ischemia, and our data suggest that defibrillation success should not be affected under these circumstances. We also found no change in the upper limit of vulnerability between baseline with ischemic conditions. Finally, the finding that both the upper limit of vulnerability and the defibrillation threshold remained unchanged during ischemia supports the validity of the concordance between the two measures and suggests that the upper limit of vulnerability may still be a valid surrogate for the defibrillation threshold under these adverse, ischemic conditions.

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