Electrophysiological Deterioration During Long-Duration Ventricular Fibrillation

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Background—Probability of survival from sudden cardiac arrest caused by ventricular fibrillation (VF) decreases rapidly with fibrillation duration. We hypothesized that cellular ischemia/fibrillation-induced electrophysiological deterioration underlies decreased survival.

Methods and Results—We determined fibrillation monophasic action potential (MAP) morphology including action potential frequency content, duration, cycle length, developing diastolic intervals, and amplitude as a function of ischemic fibrillation duration in 10 isolated rabbit hearts. We also correlated ECG frequency (used clinically) and MAP amplitude and frequency. Fibrillation cycle length and diastole duration increased, whereas APD[100] shortened significantly with time (P<0.001). Between 1 and 3 minutes, diastole appeared primarily as the result of APD[100] shortening, with only small changes in cycle length. Between 2 and 5 minutes, diastole increased primarily as the result of increased cycle length. Diastole developed progressively from 5% of VF cycles at 5 seconds to =100% of VF cycles by 120 seconds (P<0.001). Diastole increased from 1% of cycle length at 5 seconds to 62% at 5 minutes. Its duration increased from 4.7 ms at 5 seconds to 90 ms at 5 minutes (P<0.001). Both MAP and ECG 1/frequency closely correlated with fibrillation cycle length.

Conclusions—These results show a rapid and progressive electrophysiological deterioration during fibrillation, leading to electrical diastole between fibrillation action potentials. This rapid deterioration may explain the decreased probability of successful resuscitation after prolonged fibrillation. Therefore, a greater understanding of cellular deterioration during fibrillation may lead to improved resuscitation methods, including development of specific defibrillator waveforms for out-of-hospital cardiac arrest. (Circulation. 2000;102:2886-2891.)

Key Words: death, sudden ■ defibrillation ■ electrophysiology ■ resuscitation ■ fibrillation

The duration of fibrillation is a critical determinant of successful resuscitation, defined as defibrillation with restoration of perfusing rhythm, as well as survival. Internal defibrillation with implantable cardioverter-defibrillators, in which the defibrillation shock is delivered within 30 seconds, has reduced the sudden death mortality rate to 1% per year.1 In contrast, after out-of-hospital cardiac arrest, survival is poor, either because the shock fails to defibrillate, because the successful shock is followed by asystole or electromechanical dissociation rather than a perfusing rhythm,2 or because of late deaths occurring after hospital admission. Survival to discharge decreases dramatically to 43% after 4 minutes of fibrillation, 18% at 5 to 9 minutes, 8% at 10 to 14 minutes, and only 5% for times >14 minutes.3

A review of out-of-hospital cardiac arrest studies from 1967 to 1988 in 29 cities (worldwide)4 suggested that without cardiopulmonary resuscitation, survival decreases by 10% for each minute from the time of collapse until 10 minutes of fibrillation. A study of cardiac arrest in Las Vegas casinos showed that the time from the 911 call to shock was 3 minutes longer for nonsurvivors (12.46±9.58 minutes) than for survivors (9.88±5.88 minutes).5 Even at 4 minutes, only 36% survived. This probability decreased 5% for each minute without defibrillation. A recent and comprehensive study of 39 emergency medical service systems and 33 124 patients showed higher survival for defibrillation response times of <6 minutes than for times of 6 to 11 minutes.6

During prolonged ventricular fibrillation (VF), substantial metabolic changes occur in myocytes exposed to high-frequency activations characteristic of fibrillation and ischemia. These changes in electrophysiological properties of myocytes can result in defibrillation failure or postdefibrillation asystole or contractile dysfunction (including electromechanical dissociation) leading to resuscitation failure even if the heart is "successfully" defibrillated.2 To understand cellular mechanisms underlying the ECG deterioration produced by long-duration VF that is associated with decreased probability of successful defibrillation and survival,7,8 we corre-
related changes in the ECG with alterations in cellular electrophysiology, including fibrillation action potential morphology, amplitude, and frequency content, as a function of ischemic fibrillation duration.

**Methods**

**Characterization of Fibrillation**

We determined time-dependent changes in cycle length (CL), action potential duration (APD\textsubscript{50}), and the development of “electrical diastole” during ischemic VF. In this study, we used the term diastole to describe phase 4 of the action potential (commonly called diastole).\textsuperscript{9} We correlated fibrillation action potential amplitude and frequency and verified the agreement between the frequency analysis of monophasic action potential (MAP) and ECG and manual measurements of local MAP recordings.

**Isolated Heart Preparation**

The Langendorff preparation for the isolated heart model has been previously described.\textsuperscript{10} In brief, 10 French Lop rabbits weighing between 3.9 and 5.7 kg (4.9±0.14 kg) were anesthetized intravenously with pentobarbital (50 mg/kg) followed by 1000 IU of heparin. Heart weight ranged from 10.7 to 18.8 g (14.8±0.7 g, mean±SEM). Intracavitary temperature was monitored by a thermocouple placed in the right ventricle and was maintained at 37.0±0.5°C. Hearts were perfused with a modified Krebs-Henseleit bicarbonate buffer containing (in mmol/L) NaCl 110, NaHCO\textsubscript{3} 32, NaH\textsubscript{2}PO\textsubscript{4} 1.2, Na pyruvate 2, KCl 4, dextrose 5.5, MgSO\textsubscript{4} 1.2, CaCl\textsubscript{2} 2.5, and 10 IU/L regular pork insulin. The perfusate was gassed with 95% O\textsubscript{2}, 5% CO\textsubscript{2} to achieve pH 7.4, Po\textsubscript{2} 600 mm Hg, and PCO\textsubscript{2} 40 mm Hg. Per fusate pH, Po\textsubscript{2}, and PCO\textsubscript{2} were monitored throughout the experiment and maintained within optimal limits.

**Instrumentation and Experimental Protocol**

A catheter was placed in the right ventricle for inducing fibrillation. Two custom platinum platinum-black epicardial patch electrodes (Guidant Corp) were placed on the epicardial surface for defibrillation. The heart was then submerged into Krebs solution in a glass chamber. Distant electrodes were placed on the walls of the container for recording a bipolar ECG. The ECG was filtered by setting the high- and low-pass filters at 1 and 300 Hz, respectively. Epicardial MAPs (EP Technologies) were recorded from the base of the right or left ventricular free wall with a MAP electrode placed halfway between the defibrillating electrodes. All data were recorded and stored digitally on a PC computer.

VF was induced with a 1- to 2-second, 60-Hz AC pulse and was defined by chaotic irregular ECG recordings. Ischemia was produced by stopping the Langendorff perfusion immediately after fibrillation induction.

**Definitions**

The following definitions have been previously used and described.\textsuperscript{11} Fibrillation CL was defined as the time between the upstroke of one action potential and the upstroke of the next action potential. Fibrillation APD\textsubscript{50} was defined as the time between the action potential upstroke and the intersection of a hand-drawn extrapolated slope of maximum repolarization (the steepest slope during repolarization) with the baseline. Diastole was defined as the average time interval (with only those diastolic intervals >0 ms) between the end of one action potential (measured as described under APD) and the upstroke of the next action potential included in a 1-second segment of fibrillation (≈10 action potentials).

**Measurements and Data Analysis**

In 5 hearts, the parameters of CL, APD\textsubscript{50}, and diastole were determined by averaging measurements from 5 successive action potentials at 5 seconds and 1, 2, 3, 4, and 5 minutes of VF for each episode.

Correlation between local MAP fibrillation amplitude and frequency was determined by averaging the peak-to-peak amplitude of each action potential (measured manually) during the first 10-second segment of each minute of VF. The first measurement was obtained 10 seconds (0.16 minutes) after the onset of VF when fibrillation was well established. Later measurements were normalized to the 10-second amplitude measurement. Frequency analysis of MAP recordings was performed with the use of fast Fourier transforms during the first 10 seconds of each minute of VF between 10 seconds and 5 minutes.

In another 5 hearts, a more detailed analysis of the development of diastole during the first 2 minutes of fibrillation was obtained by counting the number of diastoles during 1-second segments of VF every 20 seconds until diastole was completely established (a period of diastole followed each action potential). The results were expressed as a percentage of fibrillation cycles containing diastole. In the same segments, CL, APD, and the duration of any occurring diastoles were measured from 5 action potentials and then averaged for each episode. This analysis was complemented with spectral analysis of the MAP and ECG recordings by means of fast Fourier transforms of a 10-second window every 20 seconds, and dominant frequencies were determined.

To minimize subjectivity in the measurements, a second investigator repeated all measurements in 20% of episodes selected randomly. Results are expressed as mean± SEM. Statistical differences were determined with 1- and 2-way ANOVA. Differences were considered significant at \(P<0.05\).
Results

Figure 1A shows MAPs during 5 minutes of VF. The upper panel shows a 1-second recording during normal sinus rhythm (NSR) just before induction of VF. The second panel shows VF at 5 seconds (0.08 minutes), when fibrillation was well established. The following panels show recordings at the beginning of each minute.

At 5 seconds of fibrillation, action potentials immediately followed repolarization from the previous action potential. At 1-minute fibrillation, action potentials were slightly shorter and were occasionally followed by short periods of diastole. By 2 minutes, CL was longer and action potentials continued to shorten, thereby producing regular intervals of diastole. During the next 3 minutes of fibrillation, CL increased progressively with time, whereas APD decreased. This produced increasingly long diastolic intervals. Simultaneously with the prolongation of diastole, a progressive decrease of voltage amplitude occurred. The correlation between mean normalized MAP amplitude and mean normalized MAP frequency as function of fibrillation duration was linear ($R=0.96$, $P<0.001$), but the slope differed from the unity line because MAP frequency decreased more rapidly than MAP amplitude.

Examples of the ECG recorded during NSR and at 0.08 and 5 minutes of fibrillation are shown in Figure 1B. The ECG tracings in the figure confirm that the heart remains in fibrillation at 5 minutes and show the decrease in both frequency and peak-to-peak amplitude observed after long-duration fibrillation. The MAP signals show the corresponding action potential shortening and development of diastole.

Figure 2 shows CL, APD, and diastolic interval as a function of time in fibrillation. At up to 2 minutes of fibrillation, diastole increased primarily because of action potential shortening, with only a small change in CL. APD decreased significantly from $87.6\pm2.7$ ms at 5 seconds to $54.5\pm2.2$ ms at 5 minutes ($P<0.001$). Between 2 and 3 minutes, diastolic intervals continued to increase rapidly, but now the change was due primarily to a sudden change in CL. After 3 minutes, CL increased slowly with time, whereas APD simultaneously decreased. CL increased significantly from $88.6\pm2.6$ ms at 5 seconds to $144.9\pm4.3$ ms at 5 minutes ($P<0.001$). The combined effect produced diastolic intervals that increased continuously from $4.7\pm1.7$ ms at 5 seconds to $90.4\pm4.0$ ms at 5 minutes ($P<0.001$).

Figure 3 shows the percentage of total CL spent in diastole as a function of ischemic fibrillation duration. At short fibrillation durations (5 seconds), little or no time was spent in diastole. However, by 5 minutes of fibrillation, 62% of the total CL was spent in diastole.

Diastole after each fibrillation action potential was completely established by 2 minutes of fibrillation. To examine
the time course for diastole development in more detail, we examined tracings at shorter intervals during this time. Figure 4 shows 1-second tracings of MAPs recorded during NSR and every 20 seconds for the first 2 minutes of fibrillation. At 5 seconds, short periods of diastole appeared only twice. Both probability of occurrence and duration of diastole increased as fibrillation continued. After 100 seconds of fibrillation, a significant period of diastole was present after almost every action potential.

Diastole occurred in 5% of fibrillation cycles at 5 seconds and became completely established (100% of fibrillation cycles) by 100 to 120 seconds \( (P<0.001) \). Mean diastole duration increased from 3.4±2.2 ms at 5 seconds to 48.4±6.4 ms at 2 minutes \( (P<0.001) \), as shown in Figure 5.

As shown in Figure 6, the manually measured VF CL (MAP) increased significantly from 82.3±2.4 ms at 5 seconds to 111±5.4 ms at 2 minutes \( (P<0.05) \). The inverse of the ECG and MAP mean dominant frequencies were statistically similar to the manually measured MAP CL \( (P=\text{NS} \text{ by ANOVA}) \).

**Discussion**

**Out-of-Hospital Survival After 5 Minutes of Fibrillation**

Approximately 1000 patients daily have sudden cardiac arrest caused by VF in the United States, \(^{12}\) and \( \approx 90\% \) of these cases occur out of the hospital. \(^{11}\) Despite the proven efficacy of fast defibrillation with conventional systems (emergency medical service), even patients defibrillated at 4 minutes from the emergency call have only 36% to 43% probability of survival.\(^{3,5}\) Every minute counts in out-of-hospital defibrillation. However, there is a limit to shortening time from collapse to shock, and even within 5 minutes, many lives are lost.\(^{5,6}\) An understanding of how VF changes as a function of time can lead to improved methods to counteract its deterioration and improve success of resuscitation and survival.

**ECG Changes During First 5 Minutes of Fibrillation**

During VF in swine, the median ECG frequency decreases from 13.5 Hz at the beginning of VF to \( \approx 4 \) Hz at 10 minutes.\(^{14}\) ECG frequency alone may predict the outcome of defibrillation in humans. Swartz et al\(^{15}\) showed that in the early seconds of fibrillation, in which defibrillation with implantable cardioverter-defibrillators usually succeeds, fibrillation frequency (inverse of MAP CL) is 4.7 Hz. Stewart et al\(^{8}\) showed that in humans, decreased VF frequency is associated with decreasing probability of survival. In that study, the ECG mean dominant frequency of survivors was 5.2±0.3 Hz and of nonsurvivors was 3.1±0.3 Hz. Another clinical study that used semiautomatic defibrillators showed that successful shocks were associated with an ECG dominant frequency of 4.56±0.99 Hz compared with 3.31±1.57 Hz for unsuccessful shocks.\(^{7}\)

In addition to the predictive value of ECG frequency for successful resuscitation, higher ECG amplitudes have been associated with a greater probability of defibrillation and restoration of spontaneous circulation.\(^{7,16}\) In one study, the VF amplitude was 1.40±0.50 mV for successful shocks versus 1.16±0.68 mV for unsuccessful shocks. A problem with ECG amplitude is that this depends on the direction of the main fibrillation vector, producing a wide intersubject variability.\(^{7}\) The combination of the ECG frequency and amplitude has also been used to predict the probability of successful defibrillation and restoration of circulation.\(^{17}\)

Our present results are consistent with the above studies. We found that fibrillation frequency decreased from 11.8 Hz at 10 seconds of fibrillation to 7.1 Hz at 5 minutes of fibrillation. This decrease in frequency with fibrillation duration is similar to that in pigs.\(^{14}\) As shown in Figure 1, there was also a progressive decrease in MAP amplitude during fibrillation similar to that observed in the ECG. Mean epicardial action potential amplitude decreased linearly with mean excitation frequency during the 5 minutes of VF.

In our study, the inverse of the dominant frequency of both MAP and ECG recordings and manual measurements of fibrillation CL were consistently similar and demonstrated a significant difference between 5 seconds and 2 minutes of fibrillation (Figure 6). However, our manual measurements of
MAP recordings added a new dimension to our understanding of electrophysiological deterioration during fibrillation by showing that the frequency changes observed in situ signify the development of large diastolic intervals between fibrillation action potentials. This additional information could not be obtained with the use of conventional analysis in the frequency domain of MAP and ECG signals alone.

Cellular Electrophysiological Deterioration During First 5 Minutes of Fibrillation

At the onset of VF and during the first few seconds, action potentials are activated one after another with little or no period of diastole in humans as well as in animal models. However, we showed that significant changes in fibrillation action potential characteristics take place during the first minute after the onset of fibrillation and that these changes affect defibrillation efficacy.

In the present study, we showed that during the first 5 minutes of VF, a progressive action potential shortening accompanied by lengthening of CL and diastole occurs. Diastole is very rare and of short duration during the first seconds of fibrillation, a time when clinical resuscitation is likely to be successful and survival is high. During the first 2 minutes, diastole occurrence and duration increase (Figure 5) as a consequence of APD shortening with only a small change in cycle length. Between 2 and 3 minutes, there is a marked prolongation in CL (Figure 2). After 3 minutes, CL and diastole continue to increase progressively, whereas APD decreases slowly. After 5 minutes of fibrillation, a time when clinical resuscitation is likely to fail and survival is poor, diastole has reached 62% of the total CL (Figure 3).

During prolonged VF, substantial metabolic changes occur in myocytes exposed to ischemia and the high-frequency activations characteristic of fibrillation, including intracellular/extracellular ionic imbalances and opening of KATP sarcolemmal channels. During ischemia alone in the absence of fibrillation, these cellular alterations produce slowed conduction and postrepolarization refractoriness. During ischemic fibrillation, these alterations can be expected to develop more rapidly because of continuously occurring fibrillation action potentials.

In the absence of ischemia, the refractory period ends during repolarization. However, as ischemia develops during prolonged fibrillation, postrepolarization refractoriness develops and the refractory period continues long after repolarization. The prolonged refractory period can now be the limiting factor in determining the rate of fibrillation action potential formation. Because repolarization takes place before the end of the refractory period, the resulting interval before the next action potential may become the period of diastole.

Clinical Implications

An understanding of how VF evolves with time can lead to improved electrical and pharmacological methods, for example, improved defibrillator waveforms specifically designed for cells with deteriorated electrophysiological characteristics, to counteract its deterioration and prevent postshock dysfunction and therefore improve the success of defibrillation and resuscitation. Biphasic defibrillation shocks are more effective than monophasic shocks at fibrillation durations of 1 minute in rabbits, 5 minutes in dogs, and in humans for out-of-hospital defibrillation. Biphasic waveform success at long fibrillation durations can be explained in part by its better ability to stimulate at low intensities during the refractory period as well as its better ability to excite depolarized cells. Because 62% of the fibrillation CL is spent in diastole by 5 minutes of fibrillation, the probability that the shock interacts with cells during diastole and probably during periods of postrepolarization refractoriness increases significantly during long-duration fibrillation. Under each of these conditions, the first phase of the biphasic waveform causes membrane hyperpolarization/repolarization either when delivered during the action potential or during the depolarized diastolic period between action potentials, thereby allowing sodium channel recovery from inactivation. The second pulse then creates a well-formed response to terminate fibrillation at much lower intensities than could the monophasic depolarizing pulse alone.

However, after long-duration fibrillation, even when defibrillation is successful it may not lead to a perfusing rhythm or to survival because of shock-induced and/or ischemia-induced dysfunction. Low-intensity biphasic shocks, when compared with high-intensity monophasic shocks, produce fewer postshock ECG abnormalities in humans at short fibrillation duration, better postresuscitation myocardial function in pigs after 4 to 7 minutes of fibrillation, and less cellular dysfunction.

Limitations

Most of the research to improve our understanding of VF is conducted in animal models because of obvious limitations for conducting the same research in humans. The extension of the present results to humans should be considered cautiously because of the differences in species. However, significant similarities in ionic currents and cellular kinetics between human ventricular myocytes and rabbit ventricular myocytes, in addition to the similarities in the patterns of decreased fibrillation frequency and amplitude with increasing fibrillation duration observed in humans and rabbits, suggest that the rabbit heart can provide a realistic model to help us understand deterioration of VF as a function of time.

A second limitation is the possible subjectivity in determining fibrillation APD and diastolic intervals manually. However, control measurements by a second investigator showed agreement within 10% of the total measurements.

Summary

These results show that during VF, cellular electrophysiology deteriorates rapidly and progressively with time. This rapid deterioration can explain the rapidly increasing difficulty for defibrillation and resuscitation with increasing fibrillation duration. Therefore, an improved understanding of cellular electrophysiological deterioration can contribute to optimization of electrical and pharmacological interventions during VF and increase the probability of successful resuscitation during out-of-hospital cardiac arrest.
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References
