Characterization of Ventricular Fibrillation Based on Monophasic Action Potential Morphology in the Human Heart

John F. Swartz, MD; Janice L. Jones, PhD; and Ross D. Fletcher, MD

Background. Recent studies examining mechanisms of defibrillation have focused on prolongation of graded cellular response duration during refractory period stimulation. This mechanism assumes that defibrillation shocks interact with ventricular cells during the process of repolarization.

Methods and Results. To test this assumption, we examined monophasic action potentials (MAPs) from 171 episodes of induced ventricular dysrhythmia associated with loss of systemic perfusion pressure in 22 patients undergoing nonthoracotomy defibrillator implantation. Ventricular fibrillation (VF)/polymorphic ventricular tachycardia (PVT), defined by an irregular limb lead I morphology, was present in 156 dysrhythmia episodes. Monomorphic ventricular tachycardia (VT), present in the remaining 15 episodes, was associated with regular limb lead morphology. All episodes were examined for MAP cycle length, variation, fractionation, and repolarization. VF/PVT cycle length was 215±28 msec, with a 14±7% (33±20-msec) cycle length variability. Nonfractionated MAP recordings were found in 122 of 156 VF/PVT episodes. Episodes characterized as VF by ECG criteria (n=136) showed lack of MAP diastole and had a mean cycle length of 213±27 msec. Episodes characterized as PVT (n=20) were associated with amiodarone therapy and had occasional MAP diastole and a significantly longer mean cycle length of 257±22 msec (p<0.001). Monomorphic VT had a mean cycle length of 261±29 msec, minimal cycle length variation (1±3%), absence of MAP fractionation, and consistent degree of repolarization before restimulation.

Conclusions. These results suggest that human VF cycle length is limited by cellular refractory periods so that defibrillating shocks interact with cells primarily during their refractory period. (Circulation 1993;87:1907–1914)

Key Words • defibrillation • death, sudden • fibrillation, ventricular

Internal defibrillators, in combination with epicardial patches, are now widely implanted clinically and have a proven history of saving lives.1–4 Implantation of these devices, however, requires a surgical approach such as thoracotomy or median sternotomy; therefore, they are withheld from many patients because of concerns about operative morbidity and mortality. Recent advances have led to development of transvenous lead systems that do not require a major surgical intervention for implant. Although these lead systems greatly expand the number of patients eligible for implantation, defibrillation thresholds with the new leads are higher than those for epicardial leads, probably because of unevelectric fields produced by these defibrillators.5 In fact, the very uneven electric fields produced by these defibrillators have resulted in extremely high defibrillation thresholds when they are used with the standard truncated exponential monophasic waveform, precluding implantation in approximately 30% of patients.6,7 The uneven fields also produce high shock intensities in regions near the electrodes and may cause dysfunction at both the cellular and organ levels and decrease defibrillation efficacy.8,9 Similar factors may be responsible for the relatively high energy requirements and low efficacy of transthoracic defibrillation. These problems have encouraged intense investigation into defibrillation mechanisms with the goal of reducing energy requirements for epicardial, transvenous, and transthoracic defibrillation. In spite of these efforts, electrophysiological characteristics of ventricular fibrillation and mechanisms underlying defibrillation remain poorly understood, which impedes new waveform development. The most recently proposed mechanisms, the upper limit of vulnerability and the extension of refractoriness hypotheses, both are based on the assumption that defibrillation shocks interact with most ventricular cells during the process of repolarization.10–14

A significant limitation of these hypotheses is a lack of direct knowledge concerning the electrophysiological characteristics of individual myocardial cells during...
human ventricular fibrillation and the electric state of these cells at the time of the defibrillating shock. Therefore, the goal of this study was to determine whether, during clinical fibrillation episodes, myocardial cells are restimulated before achieving electric diastole, so that fibrillation cycle length is controlled by action potential duration and the cellular refractory period.

**Methods**

**Patient Selection**

Patients included in this study were referred to our institution for clinical defibrillator system implant because of medically refractory, recurrent, sustained monomorphic ventricular tachycardia or aborted sudden cardiac death. Medtronic model 7217B or 7217B pacer/cardioverter/defibrillator systems were implanted according to a protocol approved by the Veteran's Administration Medical Center, Washington, D.C. Institutional Review Board and Protection of Human Subjects Committee. All study data were acquired during acute defibrillation threshold determination for nonthoracotomy defibrillation lead system implants in 22 patients. Demographic data of these patients are listed in Table 1. Mean patient age was 59±12 years (range, 23–73 years). Thirteen patients were taking antiarrhythmic agents at the time of system implant. Six patients were taking amiodarone, four mexiletine, three procainamide, two sotalol, one quinidine, and one diphenhydantoin. Four patients were taking a combination of antiarrhythmic agents. Nine patients were on no cardioactive medications at the time of device implant. Clinically detectable cardiac disease was present in 20 patients. Atherosclerotic coronary artery disease affected 18 patients; 17 were status post remote myocardial infarction, and seven were status post coronary artery bypass grafting procedures. Idiopathic dilated cardiomyopathy was present in two patients.

**Monophasic Action Potential Fibrillation Recordings**

Ventricular fibrillation was induced with 60-cycle/sec AC, decremental ramp pacing, or a ventricular extra-stimulus pacing protocol. Each patient underwent multiple fibrillation/defibrillation cycles during the course of defibrillation threshold testing and device implantation. Defibrillation thresholds were determined to the nearest 5 J according to an up–down protocol. Monophasic action potentials (MAPs) were recorded from the right ventricle in all patients by a 7F combination pacing/recording catheter (EP Technologies, Inc., Mountain View, Calif.). Specific MAP recording site varied between patients but was maintained at a fixed site for each individual case. Recordings were bandpass filtered (0.05–5,000 Hz), amplified, and displayed on a standard physiological recorder (VR-16, Pittsburgh Plate Glass Inc., Biomedical Systems Division, Lenexa, Kan.). Limb leads I, II, and III were recorded simultaneously with the MAPs, as were arterial blood pressure and an intracardiac right ventricular apex bipolar electrogram from the sensing lead of the clinical defibrillation system. MAP recordings were evaluated for cycle length, variation, degree of repolarization, and action potential fractionation after 3 seconds of ventricular fibrillation. Dysrhythmia cycle length was calculated as the average of seven consecutive action potential up-
stroke intervals. Maximum and minimum intervals occurring between the seven measured action potentials were also recorded. Cycle length variation was then determined as the absolute difference between maximum and minimum intervals and as a percentage of the average cycle length for each episode. Consistency and degree of action potential repolarization was determined by direct comparison of each fibrillation action potential to the baseline resting membrane potential established during normal sinus rhythm immediately before fibrillation induction. MAP fractionation was defined as the presence of abortive, chaotic upstrokes interrupting the plateau or early repolarization zones of the action potential recordings.

**Data Analysis**

Data are expressed as mean±SD. Nonpaired Student’s t test was used to determine differences among parametrically distributed data populations. Differences were considered statistically significant at p<0.05.

**Results**

MAP recordings were evaluated from 171 induced dysrhythmia episodes in 22 patients. The initial criterion for dysrhythmia episode inclusion in this study was that no measurable systemic blood pressure accompanied the episodes. One hundred fifty-six dysrhythmia episodes were classified as ventricular fibrillation or polymorphic ventricular tachycardia according to their irregular limb lead I morphology. Fifteen dysrhythmia episodes were defined as monomorphic ventricular tachycardia because they had a regular limb lead I morphology, according to the classification scheme outlined in Figure 1.

**Monomorphic Ventricular Tachycardia**

A typical fast monomorphic ventricular tachycardia episode with a cycle length of 230 msec is shown in Figure 2. MAP recordings in these dysrhythmia episodes are characterized by uniformly shaped action potentials without apparent electric diastole. The 15 episodes of monomorphic ventricular tachycardia that resulted in the loss of systemic perfusion pressure had a mean cycle length of 261±29 msec, with a very low cycle length variation of 1±3%. The mean maximum dysrhythmia cycle length was 263±29 msec, and the mean minimum cycle length was 259±29 msec. Although slower ventricular tachycardias associated with preserved systemic perfusion pressure were not included in this study, an example of MAPs during a typical episode is shown in Figure 3 to illustrate the distinct resting membrane diastolic phase separating each MAP.

**Ventricular Fibrillation/Polymorphic Ventricular Tachycardia**

Ventricular fibrillation/polymorphic ventricular tachycardia was characterized by a random limb lead I morphology. A typical example of MAPs recorded during a ventricular fibrillation episode is shown in Figure 4. The mean dysrhythmia cycle length in 156 episodes with irregular limb lead I morphology from the 22 patients was 215±28 msec, with a mean maximum interval of 233±36 msec and a mean minimum of 199±26 msec. The subgroup of nine patients on no antiarrhythmic drug therapy had 89 dysrhythmia episodes, with a mean cycle length of 197±20 msec. In contrast, the subgroup of six patients on amiodarone therapy had 28 dysrhythmia episodes, with a mean cycle length of 244±15 msec (p<0.001 between patients on no drug therapy and patients on amiodarone therapy). The shortest individual fibrillation interval identified in the 156 dysrhythmia episodes was 140 msec. Overall fibrillation cycle length variation was 33±20 msec, and percent fibrillation cycle length variation was 14±7%. MAPs recorded during ventricular fibrillation demonstrated consistent restimulation before a resting membrane potential was achieved.

In seven of the 156 dysrhythmia episodes with an irregular limb lead I morphology, occasional discrete
MAP diastolic intervals occurred, as shown in Figure 5. The seven episodes with MAP diastole had a longer mean cycle length (257±22 m/sec) than episodes without MAP diastole (213±27 m/sec, p<0.001). Five of the seven episodes with MAP diastolic intervals were distributed among four of the six patients on amiodarone therapy. For patients receiving amiodarone therapy, dysrhythmias with identifiable MAP diastole also had a longer mean cycle length (262±12 m/sec) than dysrhythmias without MAP diastole (240±12 m/sec, p<0.001). The presence of MAP diastole occurred primarily (six of seven) in dysrhythmia episodes having limb lead I characteristics commonly associated with the clinical diagnosis of polymorphic ventricular tachycardia. However, the converse was not true. MAP diastolic intervals were identifiable only during six of 20 dysrhythmias having limb lead I morphological characteristics of polymorphic ventricular tachycardia. Although dysrhythmia episodes with a clinical diagnosis of polymorphic ventricular tachycardia (n=20) were associated with longer cycle length (263±11 m/sec) than those episodes associated with the clinical diagnosis of ventricular fibrillation (p<0.001), they mimicked ventricular fibrillation with respect to cycle length variation (56±24 m/sec, 18±7%).

MAPs during fibrillation, similar in morphology to those expected from transmembrane action potentials, were observed in 122 of 156 episodes. However, a fractionated action potential appearance, such as that shown in Figure 6, occurred in 34 of the 156 dysrhythmia episodes. Fractionated MAPs were observed in 12 of the 22 patients. Therefore, fractionated MAP recordings were found in 54.5% of patients but represented only 23.5% of all ventricular fibrillation episodes. Most episodes in which fractionation occurred were fractionated during the entire episode. However, waxing and waning MAP fractionation was observed during nine fibrillation episodes in three patients (6.7% of total fibrillation episodes). MAP fractionation was always accompanied by endocardial bipolar sensing electrogram fractionation when the recording sites were in close proximity. However, MAP fractionation did not correlate temporally with bipolar electrogams when the recording sites were distant from one another, as shown in Figure 7. In this tracing, the MAP catheter was positioned in the right ventricular outflow tract, and the bipolar sensing catheter was placed at the right ventricular apex. Figure 7 also shows that the “fineness or coarseness” of fibrillation in the limb lead ECG did not correlate with the occurrence of MAP fractionation.

**Discussion**

**In Situ Defibrillation**

Although defibrillation was originally thought to occur when a critical mass of the ventricle was depolarized, recent studies have shown that the mechanisms are more complex. Several mechanisms have been proposed, including the upper limit of vulnerability hypothesis and the extension of refractoriness hypothesis. Both of these proposed mechanisms focus on the interaction of defibrillating shocks with cells that are in the process of

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**Figure 3.** Tracings showing monophasic action potentials (MAPs) during “slow” ventricular tachycardia. Baseline limb lead (I, II, III) morphology and MAP recording during sinus rhythm are shown on the left. In this episode, the tachycardia cycle length was 360 m/sec without measurable cycle length variation. Complete MAP repolarization with intervals of resting membrane potential are consistently evident for 30 m/sec before each action potential upstroke.

**Figure 4.** Tracings showing nonfractionated monophasic action potentials (MAPs) during ventricular fibrillation. Reference sinus rhythm ECG (I, II, III), MAP, and bipolar electrogram (EGM) recordings are shown on the left. Ventricular fibrillation cycle length varies between 200 and 220 m/sec with a mean cycle length of 210 m/sec (9.5% variability). Incomplete action potential repolarization is present throughout the fibrillation episode. Random limb lead morphology is present in spite of a regular MAP appearance.
repolarization. The underlying assumption that most cells are restimulated before complete repolarization during fibrillation has never been directly demonstrated in humans. The need for confirming this assumption in humans is important because most defibrillation studies have been carried out in the canine model, in which fibrillation cycle length is approximately 100 msec.\(^{17,18}\) Yet both common clinical knowledge based on right ventricular bipolar electrograms and the results of this study using both bipolar electrograms and MAP recordings show that fibrillation cycle length in humans is approximately 200 msec. If this difference in cycle length reflects a difference in the electrophysiology of the underlying arrhythmia, then findings from the canine model might not be applicable to human fibrillation. For example, canine fibrillation cycle length may be determined by the cellular refractory period rather than by conduction velocity of fibrillation wave fronts, whereas in humans, delayed conduction of fibrillation wave fronts may control cycle length rather than cellular refractory period. Therefore, an improved understanding of fibrillation mechanisms in these models can be obtained by examination of not only activation patterns but also individual cellular behavior, including action potential morphology, duration, and the prevalence of complete cellular repolarization intervals.

**Ventricular Action Potentials During Fibrillation**

There are only a few studies in which intracellular transmembrane action potentials have been observed during fibrillation.\(^{19-23}\) Ventricular fibrillation induced with transient ischemia followed by reperfusion in both porcine and canine models was characterized by incomplete repolarization and a complete absence of resting membrane potential.\(^{21,22}\) Although these studies varied with respect to species and fibrillation induction method, ventricular fibrillation was uniformly characterized by irregularly occurring action potentials with depressed upstroke velocities, decreased amplitude, and variable degrees of repolarization before restimul-

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**FIGURE 5.** Tracings showing monophasic action potentials (MAPs) recorded during polymorphic ventricular tachycardia. Baseline sinus rhythm ECG (I, II, III) and MAP recordings are shown on the left. The mean tachycardia cycle length is 282 msec with a minimum interval of 240 msec and a maximum interval of 370 msec. The cycle length variation for this episode of polymorphous ventricular tachycardia was 46%. Intervals of resting membrane potential, as shown in the middle of this tracing (arrow), were unusual occurrences during polymorphous ventricular tachycardia. EGM, bipolar electrogram.

**FIGURE 6.** Tracings showing fractionated monophasic action potentials (MAPs) during ventricular fibrillation. Baseline sinus rhythm recordings of the surface ECG (I, II, III), MAP, and bipolar endocardial electrogram (EGM) are shown on the left. In this tracing, a tachycardia cycle length of approximately 200 msec is associated with a severely fractionated appearance of the monophasic action potential recording. Immediate restoration of a stable MAP recording after the defibrillating shock and simultaneous fractionated appearance of the bipolar electrogram recorded from a nearby position during fibrillation suggest that MAP fractionation accurately reflects local activation events and was not a result of inadequate catheter contact.
Origin of Monophasic Action Potential Recordings

The method of catheter-based MAP recording to record the in situ cellular effects of physiological interventions was originally reported in 1983. Since its inception, MAP recording has become a widely accepted method of elucidating knowledge of local cellular effects of antiarrhythmic agents, heart rate, and cardiac arrhythmias. The assumption that MAP recordings accurately parallel individual cellular events during these interventions seems justified, given the high degree of correlation with simultaneous intracellular microelectrode recordings. Takeshi et al. identified a very close relation between midmyocardial transmembrane action potential duration and endocardial contact nonsuction electrode MAP duration. In contrast, Purkinje fiber transmembrane action potential duration at both 50% and 90% repolarization was significantly longer than the endocardial contact electrode MAPs in the same study. The midmyocardial origin of endocardial contact electrode MAP recordings is also suggested by the substantially greater amplitudes of recordings obtained from thick tissue segments, such as the left ventricle, as opposed to thinner tissue segments, such as the right ventricular free wall or atrial tissues.

Characteristics of Human Ventricular Fibrillation

Although ventricular fibrillation appears disorganized at the organ level, we found that the majority of episodes are actually quite organized when examined locally with MAP recordings. Further, MAP recordings confirm the commonly held belief that cells rarely achieve complete repolarization during ventricular fibrillation. This was true not only for fibrillation but also for polymorphic ventricular tachycardia and short cycle length monomorphic ventricular tachycardia associated with loss of systemic perfusion pressure. In contrast, slow monomorphic ventricular tachycardia was characterized by well-defined periods of a resting membrane potential before restimulation.

Ventricular fibrillation was most frequently associated with nonfractionated MAP activity in this study. This finding differs from results previously published by Liem et al., in which ventricular fibrillation was defined by the presence of MAP fractionation. Although these authors concluded that human fibrillation is characterized by fractionated MAP morphology, they illustrated well-defined and regular MAP morphology during fibrillation in the final figure of their article. Because fractionated MAP recordings were observed in 23.5% of 177 fibrillation episodes during the present study, it is possible that the small number of experimental observations (n=6) in the Liem study prevented recognition of the statistical significance of their observed nonfractionated MAP characteristics.

Although the mechanistic basis for fractionated and nonfractionated MAP recordings during fibrillation is unknown, it is likely that multiple fibrillation wave fronts near the recording catheter cause fractionation. The occurrence of MAP fractionation invariably correlated with the appearance of nearly continuous low-amplitude baseline activity as recorded by the actively fixed endocardial
bipolar sensing electrode when both were placed in close proximity at the right ventricular apex, as seen in Figure 6. However, in recordings such as shown in Figure 7, in which the MAP catheter was placed in the right ventricular outflow tract, action potential fractionation occurred while bipolar recordings from the right ventricular apex remained regular. Correlation between MAP fractionation and bipolar electrogram irregularity when the two electrodes are in close proximity and the lack of correlation when they are separated suggest that the fractionation phenomenon is not artifactual and strengthen the hypothesis that multiple local activations are the basis for this phenomenon.

Although ventricular fibrillation was usually associated with well-defined MAP morphology in this study, modest fibrillation cycle length variation was always present. Ventricular fibrillation and polymorphic ventricular tachycardia were similar with respect to MAP excitation interval variation. In accordance with the difference in dysrhythmia cycle lengths, maximal cycle length difference and percent interval variation were slightly less for ventricular fibrillation than polymorphic ventricular tachycardia. In contrast, monomorphic ventricular tachycardia was characterized by extremely stable MAP excitation intervals. These contrasting properties of monomorphic ventricular tachycardia and polymorphic ventricular tachycardia or ventricular fibrillation are in agreement with the results of other studies.19,24

The regularity and relatively slow rate of monomorphic ventricular tachycardias that do not produce loss of systemic perfusion pressure result in consistent and complete repolarization of MAP. This uniform achievement of a stable diastolic interval during slower monomorphic ventricular tachycardias and the resulting low cellular excitation threshold probably serve as the basis for low energy levels required for tachycardia termination compared with defibrillation.30,31 The lack of recognizable diastolic intervals during ventricular fibrillation and their occasional occurrence during polymorphic ventricular tachycardia are consistent with the higher energies required to terminate both of these arrhythmias because the stimulation threshold is high for partially refractory cells, which must be shocked to terminate these arrhythmias.12,13,32

Summary

This study shows that nonfractionated MAPs, similar to intracellular action potentials previously recorded in canines, can be recorded in humans during fibrillation, as well as polymorphic ventricular tachycardia. Although human ventricular fibrillation cycle length is twice that observed in the canine model, the lack of MAP diastole observed in this study strengthens the hypothesis that human fibrillation cycle length is controlled by the cellular refractory period and not by fibrillation wave-front conduction properties. The need to stimulate cells during their refractory period is consistent with the high energy required for termination of ventricular fibrillation and polymorphic ventricular tachycardia.

Acknowledgments

We gratefully acknowledge the outstanding support received from the Cardiac Catheterization Labo-

ratory staff at VA Medical Center, Washington, D.C.; Frankie Hayes, RN, Herman Rogers, and Bill Finch.

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Characterization of ventricular fibrillation based on monophasic action potential morphology in the human heart.

J F Swartz, J L Jones and R D Fletcher

Circulation. 1993;87:1907-1914
doi: 10.1161/01.CIR.87.6.1907

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/6/1907

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