Evolution of activation patterns during long-duration ventricular fibrillation in dogs

Jian Huang, Jack M. Rogers, Cheryl R. Killingsworth, Karan P. Singh, William M. Smith, and Raymond E. Ideker

Cardiac Rhythm Management Laboratory, Department of Medicine, Department of Biomedical Engineering, Department of Biomathematics and Biostatistics, and Department of Physiology, University of Alabama, Birmingham, Alabama 35294-0019

Submitted 11 August 2003; accepted in final form 29 October 2003

Evolution of activation patterns during long-duration ventricular fibrillation in dogs. Am J Physiol Heart Circ Physiol 286: H1193–H1200, 2004; 10.1152/ajpheart.00773.2003.—Although resuscitation for sudden cardiac arrest attempts are frequently not instituted for several minutes after the onset of ventricular fibrillation (VF), previous mapping studies have examined only the first 40 s of VF or have involved isolated perfused hearts that did not become ischemic during VF. We applied quantitative pattern analysis to mapping data throughout the first 10 min of VF acquired from a 21×24 unipolar electrode array located on the ventricular epicardium of six open-chest dogs. The following twelve descriptors were continuously quantified: 1) number of wavefronts, 2) incidence of reentry, 3) wavefront propagation velocity, 4) incidence of breakthrough/ focus, 5) incidence of block, 6) mean area activated by the wavefronts, 7) wavefront fractionations, 8) wavefront collisions, 9) multiplicity index, 10) repeatability, 11) negative peak rate of voltage change, and 12) peak frequency of activation. Cluster analysis of these descriptors divided VF into five stages (stages i–v). The values of most descriptors (except block and breakthrough incidence) increased during stage i (1–11 s after VF induction) and maintained high values with rapid dynamic fluctuations during stage ii (12–62 s). Descriptors changed quickly to values indicating greater organization during stage iii (63–86 s), decreased steadily during stage iv (87–310 s), and approached zero during stage v (311–600 s). There was a high incidence of reentry just before, during, and after stage iii. In conclusion, during the first 10 min, VF can be divided into five stages according to the evolution of electrophysiological characteristics. All of the parameters show a rapid deterioration during VF, except for a temporary reversal during stage i and a brief period of increased organization after stage iii. These changes, particularly the increased organization of stage iii, have clinical consequences, such as an alteration in defibrillation efficacy.

An early study by Wiggers (41) used high-speed cinematography to observe ventricular mechanical contraction from which he identified four stages of ventricular fibrillation (VF). More recently, electrical and optical mapping techniques have assessed the evolution of activation sequences during VF and have found that wavefronts move regularly and with high repeatability at the start of VF but then quickly break down into an irregular rhythm (18, 20, 44). However, most optical mapping studies focused on reentrant circus movement in the isolated perfused heart, in which VF was maintained without ischemia (18, 44) and electrical mapping studies analyzed only short segments of data every 5 or 10 s during the first 20 or 40 s after VF induction (20). Nonetheless, these approaches have monitored the evolution of VF continuously past this short period although resuscitation from sudden cardiac death is typically not initiated for several minutes after the onset of VF and, although uncommon, individuals can be successfully resuscitated after 10 min of VF (5).

VF is highly dynamic with activation patterns that change quickly. To better understand the nature of the activation sequences and how they change during VF, activations should be analyzed continuously and described by several variables that represent the important characteristics of the wavefronts. Accordingly, we (20, 33–35) have recently developed a set of robust algorithms that analyze large volumes of electrical mapping data automatically and quantify many of the electrophysiological aspects of VF.

The objective of this study was to describe quantitatively the activation fronts beneath a large electrode array covering ~20% of the canine epicardium and to characterize continuous temporal changes during the first 10 min of VF. We applied cluster analysis to divide the activation patterns into stages. We hypothesized that the quantification of the evolution of VF obtained from electrical activation would not be the same as that from mechanical contraction obtained by Wiggers and would provide additional information toward better understanding the mechanisms of VF maintenance. While the first 20 s of VF, as analyzed in our previous study, is the time during which shocks from implantable defibrillators are delivered, most external shocks for sudden cardiac arrest are delivered after several minutes of VF. Although rare, survival is occasionally possible even after 10 min of VF (38). Therefore, the knowledge about how VF changes during the first 10 min is important.

METHODS

All of the animals were managed in accordance with the guidelines established by the American Heart Association on research animal use (1) and the protocols were approved by the University of Alabama at Birmingham’s Institutional Animal Care and Use Committee.

Animal preparation. Six 27–32 kg (30 ± 4 kg, means ± SD) mongrel dogs were anesthetized with 25 mg/kg iv thiopental sodium,

Address for reprint requests and other correspondence: J. Huang, Cardiac Rhythm Management Laboratory, Volker Hall B140, 1670 University Blvd., Birmingham, AL 35294-0019 (E-mail: jh@crml.uab.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.ajpheart.org 0363-6135/04 $5.00 Copyright © 2004 the American Physiological Society
INTRODUCTION

Crolia et al. (20) recently reported that the number of wavefronts within a reentry pattern is a parameter that measures the number of distinct wavefront activation pathways. Descriptors 1 through 6 are used to measure the number of wavefronts in a reentry pattern and the spatial distribution of wavefronts. Descriptors 7 through 12 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 13 through 14 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 15 through 16 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts.

METHODS

Crolia et al. (20) used a two-dimensional map of wavefronts to measure the number of wavefronts within a reentry pattern. The two-dimensional map of wavefronts is composed of a grid of nodes, each of which represents a point on the surface of the heart. The grid of nodes is divided into two-dimensional regions, each of which represents a point on the surface of the heart. The number of wavefronts within a reentry pattern is the number of points on the surface of the heart that are within the reentry pattern.

RESULTS

The results of the study by Crolia et al. (20) showed that the number of wavefronts within a reentry pattern is a parameter that measures the number of distinct wavefront activation pathways. Descriptors 1 through 6 are used to measure the number of wavefronts in a reentry pattern and the spatial distribution of wavefronts. Descriptors 7 through 12 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 13 through 14 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 15 through 16 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts.

DISCUSSION

Crolia et al. (20) used a two-dimensional map of wavefronts to measure the number of wavefronts within a reentry pattern. The two-dimensional map of wavefronts is composed of a grid of nodes, each of which represents a point on the surface of the heart. The grid of nodes is divided into two-dimensional regions, each of which represents a point on the surface of the heart. The number of wavefronts within a reentry pattern is the number of points on the surface of the heart that are within the reentry pattern.

CONCLUSION

Crolia et al. (20) showed that the number of wavefronts within a reentry pattern is a parameter that measures the number of distinct wavefront activation pathways. Descriptors 1 through 6 are used to measure the number of wavefronts in a reentry pattern and the spatial distribution of wavefronts. Descriptors 7 through 12 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 13 through 14 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts. Descriptors 15 through 16 are used to measure the number of wavefronts within a reentry pattern and the spatial distribution of wavefronts.
Examples of VF activation sequences during the five stages are shown in Fig. 1. The broad picture of the dynamics are the following: stage i, regular and repeatable activation pattern (Fig. 1A); stage ii, large spatial and temporal variation (Fig. 1B); stage iii, return to a highly repeatable activation pattern (Fig. 1C); stage iv, irregular and fragmented wavefronts; and stage v, small, slow moving, short-lived wavefronts. The time course of the multiple parameters was consistent for five of the six dogs studied. One dog did not show the increased organization of stage iii.

Wavefront number, fractionation, and collision. There were rapid temporal fluctuations in activation (Fig. 2). The number of wavefronts in stage i increased rapidly (Fig. 3). The number of wavefronts maintained a high level during stage ii with large spatial and temporal fluctuations. The maximum difference for the number of wavefronts between sequential 1-s epochs in a single animal was 69. The number of wavefronts continuously declined during stages iv and v. Also, the variation in the number of wavefronts between successive 1-s epochs decreased as VF continued. The changes in the number of fractionations and collisions were similar to that of the number of wavefronts (not shown).

Repeatability and multiplicity. Multiplicity increased quickly in stage i and showed rapid fluctuations during stage ii (Fig. 4A). However, repeatability changed less during stages i and ii than did multiplicity (Fig. 4B). Multiplicity decreased suddenly during stage iii, whereas repeatability markedly increased, indicating increased organization with fewer distinct pathways with more wavefronts following each pathway. Both multiplicity and repeatability then decreased continuously during stages iv and v.

Propagation speed and peak frequency. Wavefronts propagated quickly at the beginning of VF but slowed as VF continued, except for an increase in conduction velocity during stage iii, when the number of wavefronts decreased and repeatability increased (Fig. 5A).

The changes in peak frequency were relatively smooth with a rapid increase during stage i, reaching a maximum during stage ii and decreasing during stages iii and iv (Fig. 5B). However, the peak frequency increased at the end of stage iv and throughout most of stage v. The high peak frequency during stages iv and v appeared to be caused by small rapid undulations in the signal rather than the larger slower complexes that may have represented true activation on the epicardium (Fig. 1, D and E).

Breakthrough/focal and block incidence. The changes in breakthrough/focal and block incidence over time were similar (Fig. 6). There were fewer wavefronts that blocked or broke through to the epicardium during the first three stages. The incidence of block and breakthrough increased during stage iv as VF continued.

Fig. 1. Snapshots of activation during stages i–v of ventricular fibrillation (VF) in one dog. Each colored pixel is an electrode site at which the rate of voltage change (dV/dt) is less than or equal to −0.5 V/s sometime during the 5-ms interval represented by each frame. The numbers show the time from the beginning of each VF stage. Different-colored pixels indicate distinct isolated wavefronts. The arrows in stage iv indicate the direction of wavefront movement. Recordings from the same four electrodes are shown below the activation maps for each stage. A: during stage i, the wavefronts are large and coherent and in this particular example repeatedly propagate from right to left. B: during stage ii, there are large spatial and temporal variations in the number of wavefronts and extent of the area swept out by each wavefront. C: during stage iii, the wavefronts become more regular. D: a reentrant wavefront rotates counterclockwise in this particular example during stage iv. E: there are few wavefronts in stage v, which is characterized by slow conduction and small wavefront areas.
Area swept out by wavefronts. The pattern of evolution for the area swept out by VF wavefronts was similar to that of propagation speed. In general, the wavefronts activated smaller epicardial areas as VF continued. Consistent with the decreased number of wavefronts and increased propagation speed during stage iii, the area swept out increased in this time period (Fig. 7A).

Peak negative dV/dt. The peak dV/dt was most negative during the first three stages after VF induction and then gradually became less negative during stages iv and v (Fig. 7B).

Reentrant circuits. Only 9.4% of wavefront families formed reentrant circuits during the first stage of VF on the epicardium. Throughout the 600 s of VF, 16.3% of wavefront families were involved in reentrant pathways with the highest rate, 23%, during the second, third, and early fourth stages of VF (Fig. 8).

DISCUSSION

VF is a complex cardiac rhythm disorder with rapid temporal and spatial variations in activation patterns. The evolution of VF involves changes of excitability, conduction velocity, repeatability, and other electrophysiological features. During the first 10 min of VF, we found: 1) a distinct increase in wavefront conduction velocity and organization during the
brief third stage beginning ~1 min after VF induction and lasting ~30 s, 2) a high variation for most descriptors from second to second during VF, especially during the second stage, and 3) an increased incidence of reentry beginning ~40 s after VF induction and lasting for ~2 min.

To our knowledge, the present study is the first to make continuous observations of dynamic VF changes using multiple descriptors that quantify several aspects of the electrophysiological features during VF. As discussed below, our five stages based on observation of the electrically mapped epicardial activation patterns during VF are not completely consistent with Wiggers’ four stages based on observation of epicardial movement.

Comparison of present study with previous studies. Several studies have been performed to observe the evolution of VF. In 1940, Wiggers (40) reported that four stages of electrically induced VF were visible by cinematography. The first was the undulatory or tachysystolic stage, which consisted of three to six undulatory contractions lasting <1 s. The second stage, called the convulsive incoordination stage, lasted for 15–40 s. This stage was characterized by more frequent waves of contractions that sweep over smaller sections of the ventricles. In this stage, synchronous contractions of the ventricles were lost. The third stage, that of tremulous incoordination, lasted 2 to 3 min, during which the surface of the ventricles appears to be broken up into progressively smaller and smaller independently contracting areas. The final stage was that of atonic fibrillation, with complete failure of contractility.

On the basis of electrical wavefront activation, we partitioned VF into five stages, which somewhat interface with Wiggers’ four stages. Our stage i is longer than Wiggers’ stage I, in which the clustering algorithm not only included the VT-like activation period, but also included the first part of Wiggers’ stage II. Although a wavebreak is present during this time (Fig. 6) (27), it is fairly constant, as is the number of different activation patterns as indicated by multiplicity (Fig. 4). Our stage ii covers the remainder of Wiggers’ stage II and part of stage III. The number of wavefronts was greatest during this period. Several of the quantitative variables exhibited a plateau throughout stage ii. Stage iii was a period of increased organization as indicated by a decrease in repeatability (Fig. 4), an increase in conduction velocity (Fig. 5), and an increase in the area swept out by each wavefront (Fig. 7). Wiggers’ stages do not include such a period of increased organization.

Electrical and optical mapping studies have demonstrated that reentry is present during Wiggers’ stages I and II VF but does not involve the majority of wavefronts (8, 9, 14, 18, 27, 44). Our previous study showed that ~30% of wavefront families exhibit reentry (34). With the use of a robust reentrant

Fig. 5. The evolution of propagation speed (A) and peak frequency (B) during VF. The format is the same as in Fig. 3.

Fig. 6. The evolution of breakthrough/focal (A) and block incidence (B) patterns during VF. The format is the same as in Fig. 3.
analysis algorithm for continuous VF analysis in the present study, we demonstrated a large variation from second to second in the incidence of reentrant excitation during VF. The present study found that the highest incidence of reentry occurred 40 s after induction, which is beyond the time period examined by most previous studies.

Spectral correlation and coherence analysis (4, 22, 36), as well as nonlinear dynamical approaches (4, 17), have been used to study VF organization. Recently, the application of the theory of wave propagation in excitable media to the study of VF (43) with high-resolution mapping techniques (11, 18) has enabled investigators to demonstrate that self-organization of nonlinear electrical waves with both deterministic and stochastic components exists in VF. Altogether, these studies provide strong evidence that VF is not an entirely random phenomenon. In this study, we continuously traced activation pathways and quantified the similarity of activation sequences and found that many wavefronts traveled similar pathways during VF for approximately the first 5 min of VF (stage i–iv, Fig. 4).

Activation patterns during VF time course. The evolution of activation patterns during the different stages of VF could be caused by several factors, including 1) alterations independent of changes in the intrinsic cardiac state such as accommodation and restitution of electrophysiological characteristics, 2) alterations in the cardiac state caused by changes in autonomic tone due to hypotension and cardiac stretch, and 3) alterations in the cardiac state caused by ischemia due to lack of coronary perfusion. The quick dynamic increase in wavefronts and other descriptors during stage i of VF may be independent of any underlying change to the intrinsic state of the heart. This possibility is supported by computer modeling studies of excitable systems, in which the underlying properties of the media are held constant (10, 13, 15, 25, 29, 30).

There was a rapid change in waveform conduction and organization between 63 and 86 s of VF in stage iii, which returned those descriptors to near the stage i values. This may be related to the “dip” in extracellular K⁺, which was shown by Wilde et al. (42) during global ischemia in isolated guinea pig hearts. A decrease in K⁺ efflux combined with an unaltered active K⁺ influx caused by the Na⁺/K⁺ pump and by a release of endogenous catecholamine (42) during this particular period would greatly reduce the extracellular K⁺, which in turn would increase the resting potential and improve propagation by increasing excitability. The decreased multiplicity and increased repeatability, velocity, and area swept out by each wavefront during stage iii support the assumption that activation temporarly improves. However, the dip in extracellular K⁺ was observed after 10 min of global ischemia in isolated guinea pig hearts. Because ischemic myocardium exhausts its energy stores more rapidly during VF than during sinus rhythm because of the rapid activation rates in VF (24), it is possible that the dip in extracellular K⁺ would occur much earlier during VF. However, this interpretation is highly speculative and additional experiments are needed to verify the cause of the increased organization of stage iii.

The continuous deterioration in metabolic state caused by ischemia as VF progresses may increase asynchronous depolarization and decrease the size of the activation fronts, indicated by the decreased area swept out by the wavefronts (Fig. 7). By stage v, ~70% of wavefronts appear on the epicardium in a breakthrough/focal pattern and ~70% of wavefronts are extinguished by conduction block (Fig. 6). The Purkinje fibers are more tolerant to ischemia than is the working myocardium (2) and triggered activity has been shown to occur in Purkinje fibers exposed to high K⁺ and acidosis (31, 39). Thus it is possible that after 5 min of VF, most activation fronts breakthrough to the epicardium after arising intramurally from
Purkinje fibers, either by triggered activity or reentry within the specialized conduction system.

Clinical relevance. This study shows that there are rapid temporal and spatial changes in the number of wavefronts and all other parameters during VF. This may explain in part the probability of defibrillation success. Although the exact mechanism for defibrillation is still unclear, evidence suggests that a certain minimum strength shock electric field must be achieved in the region of the heart exposed to the weakest electrical field intensity to halt activation in this region and avoid reinitiation of VF (23). The characteristics and timing of activation in the weakest electrical field region immediately before the shock may be critical for the success of defibrillation (12, 19). When a shock is delivered during the interval when this region is vulnerable to the stimulation of new activation fronts that reinitiate VF, the shock will fail to defibrillate. Thus defibrillation may require a relatively lower shock energy to defibrillate when VF is more organized so that the entire region exposed to the weak shock field spends a smaller fraction of time in its vulnerable period.

Evidence of a critical time for resuscitation success during prolonged VF has been provided by Geuze et al. (16). After 60–90 s of VF in the dog, the time of the first rapid fall in the number of wavefronts in our study (Fig. 3), spontaneous recovery of blood pressure after successful defibrillation was rare. The declining number of wavefronts and other concurrent electrophysiological changes may mirror a decline in cardiac mechanical function, raising the possibility that if these electrophysiological changes can be detected in the ECG they may be used to predict the state of cardiac mechanical function following defibrillation during cardiac resuscitation. Furthermore, the scaling structure of the ECG, a measure of organization, has been investigated to estimate the duration of VF (7), which could provide a useful stratifying variable in clinical studies of outcome after sudden cardiac death for which the onset of VF was not witnessed. Quantifying the organization and reentry circuits during VF could contribute to a better understanding and interpretation of the scaling exponent measured from the surface ECG. Because our results indicate that organization does not monotonically decrease throughout the time course of VF.

Increasingly sophisticated computer models of normal and abnormal cardiac electrophysiological states are being developed. The quantitative results of our study provide a benchmark for the mathematical simulation of ventricular fibrillation.

Limitations. The limitations for extracellular electrical mapping studies from epicardial arrays described in our previous study (21) are also present in this study. We mapped only 20% of the epicardial area and performed no transmural mapping so that complete activation pathways could not always be determined and all reentrant circuits were probably not detected. The evolution of VF described in this study used anesthetized dogs with normal hearts, which may differ from clinical VF, which most often occurs in cardiac ischemia or heart failure patients without anesthesia. The evolution of VF in diseased hearts may differ from that in normal hearts.

REFERENCES