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The effect of ischemia on ventricular fibrillation as measured by fractal dimension and frequency measures

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Abstract

Introduction—Most animal studies of VF waveform characteristics involve healthy animals with VF initiated by electric shock. However, clinical VF is usually the result of ischemia. The waveform characteristics in these two types of VF may differ. The angular velocity (AV), frequency ratio (FR) and median frequency (MF) are three frequency based measures of VF. The scaling exponent (ScE), the logarithm of the absolute correlations (LAC) and the Hurst exponent (HE) are three measures of the fractal dimension of VF.

Hypothesis—We hypothesized that these quantitative measures would differ between ischemic and electrically initiated VF.

Methods—VF was induced in 14 swine by electric shock and in 12 swine by ischemia. For ischemia induced VF animals, an angioplasty catheter was positioned in the mid-LAD and the balloon inflated. A mean of 891 +/- 608 (SD) seconds later, VF occurred. For electrically induced animals, an AC current was passed through a catheter in the RV. Following initiation by either method, VF was recorded for 7 minutes. Sequential 5 second epochs were analyzed for AV, FR, MF and fractal dimension measures.

Results—Ischemic VF demonstrated a significantly higher fractal dimension as estimated by the ScE for the first 0 to 90 seconds ($p = 0.021$) and for 90 to 180 seconds ($p = 0.016$). The Hurst exponent was significantly higher for ischemic VF for both 0 to 90 seconds ($p < 0.0001$) and 90 to 180 seconds ($p < 0.0001$). The fractal dimension as estimated by the LAC method was not significantly different for 0-90 seconds ($p = 0.056$) but was highly significant for 90-180 seconds ($p = 0.001$). During the initial 90 seconds the groups did differ in all measures of frequency as follows: AV ($p < 0.001$), FR ($p < 0.001$), MF ($p < 0.001$). These differences did not persist beyond 90 seconds except for a mild elevation of the FR after 270 seconds ($p < 0.02$).

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Conflict of interest statement

L.D. Sherman and J.J. Menegazzi hold patents of the scaling exponent and Hurst exponent and have applied for patents using the angular velocity method for use in VF waveform analysis. L.D. Sherman has applied for patents using the logarithm of the absolute correlations and the frequency ratio methods for the same purpose.

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Conclusion—Fractal based measures indicate an increase in the fractal dimension of ischemia induced VF for the first 180 seconds when compared to electrically induced VF. Frequency based measures uniformly demonstrate a pattern of higher frequencies for electrically induced VF for the first 90 seconds. The increased fractal dimension and decreased frequencies associated with ischemia induced VF may reflect changes in the underlying myocardial physiology that can be used to guide therapies.

Keywords

Arrhythmias; clinical electrophysiology; drugs; CPR emergency cardiac care; Electrocardiology; Electrophysiology; Basic Science Research Animal models of human disease

INTRODUCTION

Ventricular fibrillation (VF) is the first recorded electrocardiographic rhythm in approximately 30% of sudden cardiac death events in the out-of-hospital setting [1,2]. Three large studies of cardiac arrest have demonstrated that when cardiopulmonary resuscitation (CPR) is performed for one and one half to three minutes prior to defibrillation there is an associated increase in survival of over 10% percent [1-3]. The increased survival is due almost exclusively to greater survival (approximately 15%) in the group of patients with VF duration of over 4 to 5 minutes. In these studies, patients with shorter VF durations did not show an increase in survival when CPR was performed prior to defibrillation.

The findings of these clinical trials, as well as laboratory investigations, have led to the search for a method which would discriminate VF of over 5 minutes duration (prolonged VF) from VF of under 5 minutes duration (early VF). Such a method would allow the application of CPR prior to defibrillation for those patients with prolonged VF and potentially increase the likelihood of survival. It would also identify those patients early VF who would benefit from immediate defibrillation.

Earlier laboratory studies have demonstrated that VF waveform analysis methods can provide an estimate of the duration of VF from the recorded electrocardiogram for use in treatment algorithms [4-10]. These methods exploit the two main features of the VF waveform, namely, frequency and roughness. Frequency is most often measured by Fourier analysis techniques and roughness is estimated by the use of the fractal dimension. The fractal dimension is based on chaos theory and is a quantitative measure of the roughness of a line [11]. A straight line has a dimension of 1. Early VF which has large smooth contours has a dimension near 1.1 and this gradually increases with VF duration to a dimension of 1.5 or greater as the waveform becomes more irregular.[7,9]

The three frequency based measures have been studied extensively and include median frequency, angular velocity, and frequency ratio [4-8,12,16]. Measures of the fractal dimension have also been developed to analyze VF and include the scaling exponent (ScE) [9,13-15] and the logarithm of the absolute correlations (LAC) [17]. Another measure of fractal dimension is the Hurst exponent [7,18-20]. The Hurst exponent indicates the degree to which the values in a waveform deviate from being random. In random Brownian motion the Hurst exponent is 0.5. Hurst exponents less than this indicate a waveform that is significantly more 'rough' than a brownian path. All three fractal measures therefore estimate the roughness of the VF waveform.

Methods to estimate the duration of VF have been derived from VF waveform recordings from healthy swine in which VF was induced by brief AC current electrical stimulation of the myocardium. However, VF in the clinical arena is often preceded by ischemia. It is likely that

measures of VF frequency and roughness result from alterations in the underlying myocardial physiology and that these measures would demonstrate differences between electrically induced VF and that produced by ischemia. In other words, ischemically induced VF may appear to be more prolonged in duration compared to electrically induced VF. We sought to determine whether VF produced by electrical shock differed from that produced by ischemia in terms of measures based on frequency and fractal dimension. Differences would have implications regarding estimation of VF duration and could affect decisions regarding initial therapy, namely, CPR versus immediate countershock. Specifically, if ischemically induced VF deteriorates more quickly than electrical VF, it would indicate that patients with ischemic VF should receive CPR earlier than those with other types of VF. Patients with other types of VF would be responsive to electric shock for a longer period of time. The difference between the two would be determined directly by these methods of waveform analysis. We hypothesized that quantitative measures of VF would differ when electrically induced VF was compared to ischemically induced VF.

METHODS

This investigation was approved by the Animal Care and Utilization Review Committee of Harbor-UCLA Medical Center and conformed to the position of the American Heart Association on research animal use.

Domestic swine ($n = 28$) of both sexes weighing 34 to 47 kgs were premedicated with ketamine (20 mg/kg) and xylazine (2 mg/kg). General anesthesia was induced with isoflurane via nose cone, and following tracheal intubation, maintained with inhaled isoflurane (MAC 1.0-2.5%) and nitrous oxide in a 1 to 1 mixture with oxygen. End-tidal CO_2 was continuously monitored and minute ventilation was adjusted to maintain a value of 35-45 mm Hg. Standard lead II of the surface ECG was monitored during instrumentation and throughout the study protocol.

Under fluoroscopic guidance, a high fidelity, micro-manometer tipped catheter (Millar Instruments, Houston, TX) was positioned in the ascending aorta. Following instrumentation, animals were randomized by permuted block design to undergo electrically induced VF or ischemically induced VF. A standard 7F bipolar pacing catheter was introduced into a jugular vein and positioned in the apex of the right ventricle (RV) in contact with the RV endocardium for animals randomized to electrically induced VF. VF was induced by passing 60 Hz AC current for approximately 0.5 sec through the electrodes of the RV bipolar catheter. A standard PTCA catheter and balloon (3 mm $\times$ 10 mm), introduced into a guiding catheter inserted via a carotid artery, was used for left anterior descending (LAD) coronary artery occlusions in those animals randomized to ischemically induced VF. The site of coronary occlusion and the occurrence of complete cessation of coronary flow were confirmed with manual contrast injections.

VF was recorded for 7 minutes following the initiation of VF by either method. Recording was performed with PowerLab (ADInstruments, Castle Hill, Australia) in Chart format at a sampling rate of 1000 samples/second. Analysis of recordings was performed by conversion to text files for analysis using custom routines developed in MATLAB (Release 12, The Mathworks, Inc.). There were 14 recordings of electrically induced VF and 12 of ischemia induced VF. These recordings were then analyzed without filtering for calculation of the median frequency, angular velocity, frequency ratio, scaling exponent, LAC, and Hurst exponent. Recordings were analyzed sequentially using 5-second intervals consisting of 5000 points each for the 7 minute duration of VF. A total of 84 epochs were analyzed for each of the 26 recordings for all 5 measures.

The results of the calculations from the seven minute recordings were divided into intervals of 90 seconds each for statistical analysis. Each 90 second interval was analyzed with longitudinal data analysis methods using SAS Statistical Software (SAS 9.1.3) and repeat measures ANOVA in a factorial design. We employed an alpha error rate of 0.05 for all comparisons.

RESULTS

Onset of VF was immediate in the electrically induced group. In the ischemia induced group, the onset of VF occurred an average of 14.8 (+/- 10.1) minutes after balloon inflation. VF could not be induced in two of the 14 animals randomized to the ischemic group.

Fractal Dimension Measures

The scaling exponent (ScE) (Figure 1) demonstrated an increased fractal dimension for ischemic VF with a significant difference between the two curves noted for the first 180 seconds (0-90 sec. $p=0.021$, 90-180 sec. $p=0.016$). This increase in roughness occurred very early after initiation of VF, and, while not statistically significant after 180 seconds, it persisted for 7 minutes. The Hurst exponent (Figure 2) has a similar pattern with significantly higher values for ischemia induced VF for 0 to 90 seconds ($p<0.0001$) and 90 to 180 seconds ($p<0.0001$). After 180 seconds this difference between the two curves is no longer present. The logarithm of the absolute correlations (LAC) (Figure 3) also shows an increase in the fractal dimension (a lower LAC value). The difference between the curves for ischemic and electrical VF is significant only for the 90-180 second interval ($p = 0.001$). The difference between the curves for the 0-90 second interval does not achieve significance ($p = 0.056$). In summary, fractal based measures indicate an increase in the fractal dimension of ischemia induced VF for the first 180 seconds when compared to electrically induced VF.

Frequency Based Measures

The median frequency of electrically induced VF demonstrated an increased frequency during the first 90 seconds ($p < 0.0001$) compared to ischemia induced VF (Figure 4). This elevation in frequency showed a rapid decline with no difference after the first 2 minutes. The angular velocity (Figure 5) also showed this pattern of higher frequency for electrically induced VF with a significant difference between the curves during the 0-90 second interval ($p = 0.021$), but not thereafter. This pattern is repeated for the frequency ratio (Figure 6) with a higher ratio for the 0-90 second interval for electrically induced VF ($p < 0.0001$). Thus frequency based measures uniformly demonstrate this pattern of higher frequency for the electrically induced VF for the first 90 seconds.

DISCUSSION

Waveform analysis has been developed in order to select those patients who have a high probability of responding to defibrillation so that this therapy may be applied immediately. Human and animal studies have established that the probability of successful defibrillation decreases with VF duration and that subjects with early VF (less than 4 to 5 minutes) have a higher probability of successful defibrillation than those with prolonged VF [21,22]. Algorithms to differentiate early from prolonged VF have sought to use waveform analysis to select patients with early VF so that defibrillation may be used as the initial therapy [4,12, 13]. A central aspect of these algorithms is that they should have a high sensitivity so that most patients with early VF may receive shock appropriately while they also should have high specificity guaranteeing that those patients with prolonged VF receive CPR which has been demonstrated to improve their chances of survival. These are competing goals in the design of algorithms to increase survival and are perhaps best evaluated through the use of receiver operating characteristic (ROC) curves. It appears that characteristics of a measure or set of

measures to differentiate early from prolonged VF which will be clinically safe and effective should have an area under the ROC curve of approximately 90% with an ability to predict the outcome of defibrillation attempts of 90% [23]. Selection of the sensitivity and specificity points at which the algorithms would operate will then depend on the EMS response times and specific features of the environment in which the algorithms will be utilized.

This study extends previous observations and refines understanding of these measures. The scaling exponent (ScE), LAC, and Hurst exponent have been well characterized in a large group of swine in earlier experimental work [7,9,14]. They show an increase in the fractal dimension over time. An increased fractal dimension observed in this study suggests that there is abnormal myocardial physiology. In the present work we see the fractal dimension is increased in animals which experience ischemia prior to onset of VF. We believe that this supports the use of the fractal dimension as a measure of underlying myocardial physiology and hence the probability of successful defibrillation. Of importance for algorithms using this measure, the range of fractal dimension values indicating that early VF is present may require adjustment to a higher level to account for the effects of ischemia which are most marked during the first 3 minutes. The Hurst exponent increases over time and approaches 0.5, which is characteristic of a random signal. This increase in the random nature of VF over time is supported by studies of VF mechanism in which “rotors” are seen to break down into disorganized wave fronts [24,25].

In prior studies the frequency based measures have shown a clear tendency to decrease with the duration of VF [4,5,7,8,16]. This implies that decreasing frequency is an indicator of prolonged VF. The current study confirms this result with the additional observation that ischemia produces a significant decrease in frequency for the first 90 seconds. This supports the ability of the frequency based measures to detect abnormal physiology. All three measures appear to be approximately equivalent over the period examined here. Algorithms which employ frequency based measures should take into account the lower frequencies of ischemic VF as compared to electrical VF. Frequencies which indicate early VF will be lower during the first 90 seconds in ischemic patients.

The findings of this study suggest that research involving VF therapies should be also be performed on animals in which VF is induced by ischemia. Electrically induced VF differs from ischemic VF during the first 3 minutes and may not be an adequate model for the type of VF encountered clinically. It should be noted that the deterioration in electrical VF to fractal dimension and frequency levels indistinguishable from ischemic VF occurs rapidly. This suggests that the changes induced by ischemia occur within 3 minutes. Identification of the etiology for these changes may be aided by identifying substrates which coincide with these waveform changes.

Finally, an important objective of waveform research is to guide therapy. Because ischemic VF appears to be more abnormal in the early phase, CPR would be indicated as first therapy sooner or more often in patients with ischemia prior to the onset of VF. In cases of witnessed arrest where ischemia preceded the onset of VF, it might be appropriate to provide CPR as the first treatment if the measures presented here indicate that sufficiently abnormal physiology is present. Also, if decreased frequency and increased fractal dimension are an approximate measure of abnormal myocardial electrophysiology indicating a decreased probability of successful defibrillation, then an obvious consideration is whether these methods can be used to follow the progress of therapies such as CPR, epinephrine (adrenaline), vasopressin, etc. One expectation would be that as the therapy is applied, the waveform would be sampled continuously until the desired values of frequency and fractal dimension are reached indicating a reasonable probability of successful defibrillation. This would lead to the use of waveform analysis as a monitor of VF duration resuscitation.

Limitations

This work establishes the effect of ischemia on frequency and fractal dimension measures of VF in the swine model. Application of these results to human subjects will require confirmation that they also apply to human subjects. The animal model described here is acute ischemia in otherwise healthy animals. Patients will often have chronic ischemia as an underlying factor with other co-morbid conditions present. The acquisition of a large database of VF recordings from human subjects in which the outcome of defibrillation attempts is known would provide the opportunity to determine if the probability of successful defibrillation directly correlates with these measures.

Conclusions

We have demonstrated that early after the onset of VF, quantitative measures of electrically induced VF and ischemically induced VF are different. This information will be useful when these measures are incorporated into the next generation of defibrillators.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Cobb LA, Fahrenbruch C, Walsh T, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA* 1999;281(13):1182–8. [PubMed: 10199427]
2. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation. *JAMA* 2003;289(11):1389–95. [PubMed: 12636461]
3. Vilke GM, Chan TC, Dunford JV, et al. The three-phase model of cardiac arrest as applied to ventricular fibrillation in a large, urban emergency medical services system. *Resuscitation* 2004;64:341–6. [PubMed: 15733764]
4. Callaway CW, Menegazzi JJ. Waveform analysis of ventricular fibrillation to predict defibrillation. *Curr Opin Crit Care* 2005;11:192–9. [PubMed: 15928465]
5. Dzwonczyk R, Brown CG, Werman HA. The median frequency of the ECG during ventricular fibrillation: its use in an algorithm for estimating the duration of cardiac arrest. *IEEE Trans Biomed Eng* 1990;37:640–6. [PubMed: 2354846]
6. Berg RA, Hilwig RW, Kern KB, Ewy GA. Precountershock cardiopulmonary resuscitation improves ventricular fibrillation median frequency and myocardial readiness for successful defibrillation from prolonged ventricular fibrillation: a randomized, controlled swine study. *Ann Emerg Med* 2002;40(6): 563–70. [PubMed: 12447331]
7. Sherman LD, Callaway CW, Menegazzi JJ. Ventricular fibrillation exhibits dynamical properties and self-similarity. *Resuscitation* 2000;47(2):163–73. [PubMed: 11008154]
8. Sherman LD, Flagg A, Callaway CW, Menegazzi JJ, Hsieh M. Angular velocity: a new method to improve prediction of ventricular fibrillation duration. *Resuscitation* 2004;60:79–90. [PubMed: 15002486]
9. Callaway CW, Sherman LD, Menegazzi JJ, Scheatzle MD. Scaling structure of electrocardiographic waveform during prolonged ventricular fibrillation in swine. *Pacing Clin Electrophysiol* 2000;2:180–91. [PubMed: 10709226]
10. Hayes MM, Berg RA, Otto CW. Monitoring during cardiac arrest: are we there yet? *Curr Opin Crit Care* 2003;9:211–217. [PubMed: 12771672]

11. Peitgen, H.; Jurgens, H.; Saupe, D. *Chaos and Fractals: New Frontiers of Science*. Springer-Verlag New York Inc.; 1992. p. 202-212.
12. Brown CG, Dzwonszyk R. Signal analysis of the human electrocardiogram during ventricular fibrillation: frequency and amplitude parameters as predictors of successful countershock. *Ann Emerg Med* 1996;27(2):184–8. [PubMed: 8629749]
13. Menegazzi JJ, Callaway CW, Sherman LD, et al. Ventricular fibrillation scaling exponent can guide timing of defibrillation and other therapies. *Circulation* 2004;109:926–31. [PubMed: 14757695]
14. Menegazzi JJ, Wang HE, Lightfoot CB, et al. Immediate defibrillation versus interventions first in a swine model of prolonged ventricular fibrillation. *Resuscitation* 2003;59:261–70. [PubMed: 14625118]
15. Callaway CW, Sherman LD, Mosesso VN, Dietrich TJ, Holt E, Clarkson C. Scaling exponent predicts defibrillation success for out-of-hospital ventricular fibrillation cardiac arrest. *Circulation* 2001;103:1656–61. [PubMed: 11273993]
16. Sherman LD. The frequency ratio: An improved method to estimate ventricular fibrillation duration based on Fourier analysis of the waveform. *Resuscitation* 2006;69:479–486. [PubMed: 16563594]
17. Sherman, L. The LAC: An Improvement in the Scaling Exponent Method of Ventricular Fibrillation Duration Estimation Based on Autocorrelation of the Waveform, methodology. available on website: “<http://shermld.home.comcast.net>”
18. Falconer, K. *Fractal Geometry: Mathematical Foundations and Applications*. Wiley and Sons Ltd; West Sussex, England: 2003. p. 258-276.
19. Feder, J. *Fractals*. Plenum Press; New York, NY: 1988. p. 149-183.
20. Peitgen, H.; Jurgens, H.; Saupe, D. *Chaos and Fractals: New Frontiers of Science*. Springer-Verlag New York Inc.; 1992. p. 481-505.
21. Larsen MP, Eisenberg MS, Cummins RO, et al. Predicting survival from out-of-hospital cardiac arrest: a graphic model. *Ann Emerg Med* 1993;22:1652–1658. [PubMed: 8214853]
22. Yakaitis RW, Ewy GA, Otto CW, et al. Influence of time and therapy on ventricular defibrillation in dogs. *Crit Care Med* 1980;8:157–163. [PubMed: 7363631]
23. Hayes MM, Berg RA, Otto CW. Monitoring during cardiac arrest: are we there yet? *Curr Opin Crit Care* 2003;9:211–217. [PubMed: 12771672]
24. Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. *Nature* 1998;392:75–8. [PubMed: 9510249]
25. Witkowski FX, Leon LJ, Penkoske PA, Giles WR, Spano ML, Ditto WL, et al. Spatiotemporal evolution of ventricular fibrillation. *Nature* 1998;392:78–82. [PubMed: 9510250]

Figure 1.

Scaling Exponent over 7 minutes showing the increased fractal dimension of ischemia induced VF as compared to electrically induced VF. There is a significant difference in the curves for 0-90 seconds ($p=0.021$) and 90-180 seconds ($p=0.016$). Differences are not significant beyond 180 seconds. Standard deviation bars are shown at selected points.

Figure 2.

Hurst Exponent over 7 minutes showing the increased value for ischemia induced VF as compared to electrically induced VF. There is a significant difference in the curves for 0-90 seconds ($p < 0.0001$) and 90-180 seconds ($p < 0.0001$). Differences are not significant beyond 180 seconds. Standard deviation bars are shown at selected points.

Figure 3.

LAC over 7 minutes showing an increased fractal dimension (lower LAC value) for ischemia induced VF. The curves are not significantly different at 0-90 seconds ($p=0.056$) but are significantly different at 90-180 seconds ($p=0.001$). They show no significant differences after 180 seconds. Standard deviation bars are shown at selected points.

Figure 4. Median Frequency over 7 minutes demonstrates a significantly higher frequency for electrically induced VF for the 0-90 second interval ($p < 0.0001$). There is no significant difference between the curves after 90 seconds. Standard deviation bars are shown at selected points.

Figure 5. Angular Velocity over 7 minutes demonstrates a significantly higher frequency for electrically induced VF for the 0-90 second interval ($p = 0.021$). There is no significant difference between the curves after 90 seconds. Standard deviation bars are shown at selected points.

Figure 6.

Frequency Ratio over 7 minutes demonstrates a significantly higher frequency for electrically induced VF for the 0-90 second interval ($p < 0.0001$). There is no significant difference between the curves after 90 seconds. Standard deviation bars are shown at selected points.