Endocardial activation during ventricular fibrillation in normal and failing canine hearts

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Pierpont, Gordon L., Sumeet S. Chugh, John A. Hauck, and Charles C. Gornick. Endocardial activation during ventricular fibrillation in normal and failing canine hearts. Am J Physiol Heart Circ Physiol 279: H1737–H1747, 2000.—Because congestive heart failure (CHF) promotes ventricular fibrillation (VF), we compared VF in seven dogs with CHF induced by combined myocardial infarction and rapid ventricular pacing to VF in six normal dogs. A noncontact, multielectrode array balloon catheter provided full-surface real-time left ventricular (LV) endocardial electrograms and a dynamic color-coded display of endocardial activation projected onto a three-dimensional model of the LV. Fast Fourier transform (FFT) analysis of virtual electrograms showed no difference in peak or centroid frequency in CHF dogs compared with normals. The average number of simultaneous noncontiguous wavefronts present during VF was higher in normals (2.4 ± 1.0 at 10 s of VF) than in CHF dogs (1.3 ± 1.0, P < 0.005) and decreased in both over time. The wavefront “turnover” rate, estimated using FFT of the noncontiguous wavefront data, did not differ between normals and CHF and did not change over 5 min of VF. Thus the fundamental frequency characteristics of VF are unaltered by CHF, but dilated abnormal ventricles sustain fewer active wavefronts than do normal ventricles.

Studies of VF activation patterns in normal hearts have demonstrated relatively large, distinct reentrant wavefronts during early-onset VF (25). Interaction between wavefronts at a vulnerable period may be responsible for the production of new wavefronts and subsequent perpetuation of VF. Quantification of these patterns and identification of possible patterns in the sequence of activation may be crucial to our understanding of onset, maintenance, and subsequent therapy of VF in CHF. Despite evidence for a dominant role of the LV endocardial surface in the maintenance of VF (54), previous mapping studies of VF have utilized recordings from limited sections of myocardium. The study reported herein was designed to compare full-surface endocardial mapping data of VF in dogs with CHF to VF in dogs with normal hearts. Because ischemic heart disease is the most common cause of CHF, we used a model of myocardial infarction followed by rapid ventricular pacing to induce congestive heart failure (15).

MATERIALS AND METHODS

This study was approved by the Animal Studies Subcommittee of the Minneapolis Veterans Administration Medical Center, conformed to the Federal Animal Welfare Act administered by the United States Department of Agriculture, followed the guidelines of the National Research Council’s Guide for Care and Use of Laboratory Animals, and was performed in laboratories approved by the American Association for Accreditation of Laboratory Animal Care.

Two groups of dogs were studied: six normal dogs and seven dogs with CHF induced by ischemic injury followed by rapid ventricular pacing. Normal dogs were anesthetized with the use of intravenous pentobarbital sodium induction (25 mg/kg) with halothane maintenance. A pacing catheter was placed in the right ventricular apex via a femoral vein, and a noncontact, multielectrode catheter (EnSite; Endocardial Solutions, St. Paul, MN) was introduced via a femoral artery, advanced retrograde across the aortic valve, and positioned in the mid-LV. After baseline recordings were made in sinus rhythm, VF was induced by either brief application of current from a 9-V battery or by rapid pacing.

IN 35–50% OF PATIENTS who succumb to congestive heart failure (CHF), the mode of death is sudden and unexpected (22, 32). The majority of these sudden deaths are likely due to ventricular fibrillation (VF). Recent clinical trials showing improved survival using internal defibrillators in high-risk patients with CHF (30, 48) underscore the importance of attaining a clear understanding of the mechanisms of initiation and maintenance of VF, some of which remain elusive. Although mapping studies of ventricular activation during VF in animals have enhanced our understanding of many basic properties of this arrhythmia (19), equivalent data in animal models of chronic CHF are lacking. Consequently, relatively little is known about how VF in dilated hearts with left ventricular (LV) dysfunction may differ from VF in normal hearts.
delivered via the right ventricular pacing electrode. Continuous recordings were made for at least 5 min.

CHF dogs had myocardial infarction induced under surgical anesthesia with the use of a coronary angioplasty catheter. The balloon was positioned in the midvessel (or slightly distal) of either the circumflex or the anterior descending coronary artery, inflated for 90 min, and then removed. A unipolar pacing lead was positioned under fluoroscopic guidance in the right ventricular apex and tunneled to a modified high-rate pacemaker generator (Medtronic, Minneapolis, MN) in a subcutaneous pocket in the neck. After a minimum 2-wk recovery period, the pacemaker was programmed to 250 beats/min, and the animals were paced continuously for 3 wk. At the end of 3 wk, the pacemaker was deactivated, the animals were again anesthetized, and the multi-electrode catheter was positioned in the LV as described above. Baseline recordings were made, VF was induced, and endocardial activation maps were recorded continuously for at least 5 min.

The catheter used in this study has an array of 64 electrodes positioned around a balloon that, when inflated within the cardiac chamber, provides an ellipsoid 1.8 cm in diameter and 4.6 cm long. These electrodes are connected to a computer system through a breakout box that also accommodates signals from three separate ring electrodes attached to the catheter shaft, a 12-lead surface electrocardiogram, and up to 32 standard electrophysiology electrodes. The electrode signals are amplified and digitized in an interface unit and fed into a computer workstation that can display individual electrograms as well as a real-time dynamic display of endocardial activation patterns projected onto a three-dimensional model of the LV.

The model of the LV is created by “tracing” the endocardium with a standard electrophysiology (EP) catheter. Fluoroscopic guidance is used to manipulate the tip of the EP catheter into as many positions as possible within the ventricle. The position of the EP catheter tip is continuously monitored relative to the balloon electrode array over a nominal 2-min time period by use of a 50-μA 5.68-kHz current delivered through the tip electrode while the potential on the array electrodes is sensed. Because the coordinates of the array electrodes are predetermined, the position of the roving electrode can be determined by use of a point-source model (United States patent 5662108). A smooth spline fit of the most distal locations of the EP catheter tip are used to reconstruct a model of the LV (14).

Chamber geometry, known locations of the array electrodes, and passive noncontact measured endocardial potentials at each electrode on the array are combined by use of a boundary element inverse method to solve LaPlace’s equation and reconstruct potentials for the endocardial surface. This system computes 3,360 endocardial (virtual) potentials, with the virtual potential at each site refreshed at a rate of 1,280/s. The potentials are color coded by amplitude and displayed on the three-dimensional model of the LV to produce a high-resolution, full-surface real-time electroanatomic map of endocardial activation. The potentials can also be translated into virtual electrograms by displaying potential amplitude at each site versus time.

The computerized mapping technique used in this study has previously been validated in the LV during normal sinus rhythm by Gornick et al. (14) and in the right atrium during sinus rhythm, atrial flutter, and atrial fibrillation by Kadish et al. (21). To insure the technique is useful in VF, we compared virtual electrograms with contact electrograms in three normal anesthetized dogs during VF. A multielectrode catheter (Crista Cath; Cordis Webster, Diamond Bar, CA) was placed in the LV together with the EnSite system, and unipolar endocardial electrograms were compared with their corresponding virtual electrograms for each of 16 separate sites. After induction of VF, the endocardial electrograms from the tip electrode of the multielectrode catheter were recorded for 3 min, and then the 15 other endocardial electrodes were recorded sequentially for a minimum of 15 s each. The individual recordings from each site were analyzed in 2-s segments by use of cross correlation to compare the endocardial electrograms with the corresponding virtual electrograms. Because the sampling rate was 1,200 Hz, this produced 2,400 x-y pairs per sample segment. The correlation coefficients for each sample segment were averaged to get a mean correlation coefficient for each of the 16 individual sites. All 16 sites were then averaged to provide a grand mean, felt to be a fair representation of how well virtual electrograms match directly recorded endocardial electrograms. This grand mean, including all three dogs, was 0.724 ± 0.155, with a median of 0.723. If only those sites within 34 mm of the center of the EnSite catheter are included, the grand mean is 0.781 ± 0.141, with a median of 0.777. The three dogs used here for system validation were not included in the group of normal dogs used for comparison to CHF dogs.

In both the normal and CHF dogs, 2 s of VF were analyzed at two different times, the first beginning 10 s after the onset of VF (Wiggers’ stage II) and the second 5 min later. The fundamental frequency components of the VF waveforms were calculated with the use of fast Fourier transform (FFT) over a range of 2–20 Hz for selected surface leads and virtual endocardial electrograms. The peak frequency and centroid frequency of the power spectrum were determined for each FFT at the time points of interest. Centroid frequency represents that frequency for which the area under the power curve for all frequencies above that point would equal the area under the power curve for all frequencies below that point (4). It is defined as

$$\sum (f_i \cdot p_i) / \sum p_i$$

for i = 1 to n, where f is frequency and p is power.

To quantify the number of distinct wavefronts present at any time on the endocardial surface of the LV, color potentials projected onto the electroanatomic map of the LV were set such that white represented a small range of amplitude representing the most negative potentials present, and a rainbow spectrum represented progressively more positive potentials. The scale was adjusted for each animal during sinus rhythm to provide the most optimal view of normal depolarization. This generally resulted in the white color representing approximately the most negative 15% of the voltage range for each dog. The scale was not adjusted subsequently during VF. This process is analogous to producing a color contour map of a mountain range, with the colors representing voltage amplitude instead of mountain altitude. The number of simultaneous noncontiguous wavefronts present at any given time was determined by counting the number of distinct, separate white areas present on the endocardial surface. These noncontiguous wavefronts were manually counted every 10 ms for a 2-s period 10 s after the onset of VF and again at 5 min. FFT analysis of the number of noncontiguous wavefronts present over time was performed to provide an estimate of the dominant frequency with which individual wavefronts emerged and dissipated, or the “turnover” rate of VF.

Enlargement of the LV and decreased LV function in response to the infarction and rapid pacing in the CHF dogs...
were documented by obtaining echocardiograms before intervention and again at the terminal study after 3 wk of rapid pacing. Echocardiograms were performed in the right lateral position, using an HP Sonos 1000 phased array two-dimensional imaging system (Hewlett-Packard, Andover, MA). For the preterminal study, the echocardiograms were obtained after the pacemaker had been turned off. Internal diameters of the LV in systole and diastole (LVIDs and LVIDd, respectively) were measured from the septum to posterior wall in the short-axis view at the level of the chordae tendineae. Ejection fraction was estimated with the use of planimetry to calculate ventricular end-systolic and end-diastolic areas in the short-axis view at the level of the chordae tendineae and by applying the single-plane ellipse formula to transpose to systolic and diastolic volumes. Postmortem examinations of the hearts of the CHF dogs quantified the extent of myocardial infarction induced by the intracoronary 90-min balloon inflation. The LV was trimmed and cut into transverse sections at 5 mm-intervals and stained with tetrazolium blue, and the area of scar was obtained by planimetry. The percent area for each slice (except base and apex) was averaged, and the average was multiplied by the weight of the slice to get the amount of scar in each slice. These were then summed and divided by the total LV weight to get the percentage of ventricle that is scar.

Data are presented as means ± SD, and differences were considered significant for \( P < 0.05 \). Student’s unpaired t-test was used for comparisons between groups (normal vs. CHF), and Student’s paired t-test was used for within-group comparisons. When multiple comparisons were made within a group, i.e., in comparing several endocardial electrograms to surface electrograms for each animal, analysis was done using analysis of variance for repeated measures on the same elements.

RESULTS

LV function. The dogs in the CHF group developed significant LV enlargement and dysfunction in response to the intervention. Baseline LV short-axis LVIDd before any intervention in the seven CHF dogs was 2.8 ± 0.2 cm. This increased to 4.3 ± 0.6 cm at the final study, i.e., after induction of a myocardial infarction followed by 3 wk of rapid ventricular pacing (\( P < 0.005 \)). Ejection fraction decreased from 68.8 ± 13.3 to 22.1 ± 4.1% (\( P < 0.001 \)) as a result of the infarction and rapid pacing. LV damage induced by the 90-min coronary balloon occlusion resulted in scar tissue ranging from 0 to 1.5% of the total LV myocardium in the seven CHF dogs, with a mean of 0.6 ± 0.6%. The single dog with no infarction on pathological examination had ventricular tachycardia during angioplasty balloon inflation, requiring premature reperfusion before completion of 90 min of occlusion. Echocardiograms were not performed in the six normal dogs in which VF was induced without prior intervention.

Full-surface endocardial mapping. The real-time color-coded display of virtual potentials provided a dynamic view of endocardial events during ventricular activation that cannot be fully represented with static images; however, Figs. 1 and 2 present snapshot photos of several relevant time points. Ventricular activation in a normal dog during sinus rhythm is seen in Fig. 1. As noted in MATERIALS AND METHODS, the color coding is scaled such that white is maximum negative voltage. Early septal breakthrough in normal sinus rhythm can be seen in Fig. 1A at the onset of the QRS. Figure 1, B–D, shows subsequent spread of depolarization throughout the endocardium at 6-ms intervals. Figure 2 shows a representative time sequence from the same normal animal in VF. In Fig. 2, the panels are at 30-ms intervals. Note that several wavefronts are evident at once and that the number of noncontiguous wavefronts varies with time.

It became readily evident while watching the dynamic display that the ventricular wavefronts seemed fairly well organized. Indeed, occasionally the endocardial surface patterns appeared more like ventricular tachycardia or ventricular flutter than VF. Because these dynamic images cannot be presented, Fig. 3 provides an example of the high degree of organization occasionally observed by showing virtual endocardial electrograms along with a simultaneous surface electrocardiogram (ECG) lead for two different animals. In Fig. 3A, the surface ECG indicates that the animal is clearly in VF, whereas the virtual endocardial electrograms mimic ventricular tachycardia or ventricular flutter. Figure 3B illustrates a more classic case, where both the virtual endocardial electrograms and surface ECG demonstrate classic fibrillation waves.

Surface leads versus endocardial electrograms. The occasional disparity between the appearance of the virtual endocardial electrograms and the surface ECG raised the possibility that the basic characteristics of the two waveforms (surface vs. endocardial) might differ. We therefore performed FFT on two surface ECG leads (II and V2) and four representative endocardial virtual electrograms (at midventricle on the septum, anterior, lateral, and posterior walls) over the same 2-s time period beginning 10 s after the onset of VF. An example for a typical case demonstrating the results for both a surface and virtual endocardial lead is presented in Fig. 4.

In the six normal dogs, the peak frequencies in the power spectrum for leads II and V2 were 6.2 ± 1.7 and 7.4 ± 0.4, respectively. This did not differ significantly from the peak frequencies of the four endocardial sites (6.9 ± 0.5, 7.4 ± 0.4, 7.2 ± 0.5, and 7.3 ± 0.4). Similarly, in the seven CHF dogs, the peak frequencies of the surface lead power spectra were not different in surface leads II and V2 (7.2 ± 0.8 and 7.2 ± 0.9, respectively) compared with the virtual endocardial sites (7.4 ± 0.6, 7.5 ± 0.6, 7.1 ± 0.9, and 6.9 ± 0.9).

In contrast, the centroid frequencies determined 10 s after the onset of VF were different for the surface leads compared with the endocardial virtual sites. In the normal dogs, the centroid frequencies for leads II and V2 (7.2 ± 0.7 and 7.2 ± 0.6, respectively) were less than for the virtual sites (8.9 ± 0.9, 8.2 ± 0.6, 8.0 ± 0.6, and 8.0 ± 0.5) for \( P < 0.01 \). This finding was also consistent in the CHF dogs, where the centroid frequencies of the surface leads (7.6 ± 0.5 and 7.3 ± 0.6) were less than the virtual endocardial sites (7.9 ± 0.6, 7.8 ± 0.6, 8.0 ± 0.9, and 8.3 ± 0.7) for \( P < 0.01 \). These findings are illustrated in Fig. 5, where the power spectrum for both a surface
and a virtual endocardial site from each animal in the CHF group is normalized, and all curves are then combined by summation.

**Effects of CHF on frequency spectra.** To determine whether development of CHF alters the fundamental frequency characteristics of fibrillation waveforms, the same leads as noted above were compared in CHF dogs and normal dogs. During early-onset VF (10 s), neither the peak nor centroid frequency differed in CHF compared with normal dogs for any of the two surface or four virtual sites (i.e., all $P$ values > 0.05 by use of Student’s unpaired $t$-test).

**Quantitative assessment of ventricular wavefronts.** The full-surface real-time three-dimensional computerized display of endocardial potentials allowed us to observe the emergence, dispersion, and dissipation of wavefronts over time. We quantitated the number of active wavefronts by counting the number of distinct noncontiguous wavefronts present at 10-ms intervals for all dogs over a 2-s period at 10 s after the onset of VF and again 5 min later, with no interim therapy other than continuing ventilator support. The results are presented in Table 1. The average number of wavefronts present after 10 s of VF was decreased after 5
min of VF for every dog in the normal group, and this decrease was statistically significant for $P < 0.05$. These data are more completely presented in the histogram of Fig. 6, which shows the downward shift in the distribution of number of wavefronts present at any given time as VF progresses from 10 s to 5 min. The average number of wavefronts present at any time decreased from 10 s to 5 min in the CHF dogs as well, but this change did not reach statistical significance ($P = 0.18$). Most interestingly, the number of wavefronts present in the CHF dogs at the onset of VF (10 s) was significantly less ($P < 0.005$) than in the normal dogs (Table 1 and Fig. 7). The CHF dogs appear at the onset of fibrillation to be somewhat similar to the normal dogs after the latter have been fibrillating for 5 min.

**Fibrillation turnover.** As the quantitative data were being tabulated, it became evident that there was a general pattern to the way in which the number of wavefronts appeared and disappeared. This prompted us to apply FFT to the number of wavefronts present over time to obtain an assessment of the turnover rate of VF, i.e., the frequency with which wavefronts emerge and dissipate. The raw data (obtained every 10 ms for a 2-s period beginning 10 s after the onset of VF) for a representative animal are shown in Fig. 8, along
with the FFT analysis on that series of numbers. The peak frequency for all normal dogs 10 s after the onset of VF was 9.0 ± 1.3 Hz, and this was unchanged 5 min later (7.9 ± 3.4 Hz, \( P = 0.26 \)). Centroid frequency was also unchanged from 10 s (10.0 ± 0.3 Hz) to 5 min (10.2 ± 0.6 Hz, \( P = 0.99 \)). Similar results were seen in the CHF dogs, where peak frequency at 10 s (8.0 ± 1.6 Hz) remained unchanged at 5 min (9.0 ± 2.5 Hz, \( P = 0.37 \)), and centroid frequency was also unchanged (9.6 ± 1.3 to 9.6 ± 0.7 Hz, \( P = 0.99 \)). At 10 s after the onset of VF, there was no significant difference between normal and CHF dogs for either peak frequency or centroid frequency. Thus the turnover rate for VF wavefronts does not change after 5 min of sustained fibrillation and is not different in normal ventricles compared with failing ventricles.

**DISCUSSION**

**Methodology.** Gornick et al. (14) demonstrated that the system used in this study provides anatomically accurate endocardial maps of the LV that allow identification and location of endocardial pacing sites to within 4.0 ± 3.2 mm of their pathologically confirmed source. Correlation of timing and morphology of computed electrograms compared with contact electrograms was 0.97, and timing difference between computed and contact electrograms for best fit was 0.64 ± 2.48 ms. This methodology has also been validated for endocardial mapping of the right atrium during sinus rhythm, atrial flutter, and atrial fibrillation (21), where the correlation coefficients between contact and virtual electrograms were 0.80 ± 0.12, 0.85 ± 0.17, and 0.81 ± 0.18, respectively, without any correction for timing differences between systems. Our correlation coefficient between virtual and directly recorded endocardial electrograms during VF was slightly lower (0.72). This may be due in part to the larger size of the ventricle compared with the atrium, for the ability of the system to accurately reproduce electrograms is

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**Table 1. Average number of wavefronts present after onset of VF**

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<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CHF</th>
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<tbody>
<tr>
<td>Dog</td>
<td>10 s</td>
<td>5 min</td>
</tr>
<tr>
<td>1</td>
<td>3.4 ± 1.1</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>2</td>
<td>2.1 ± 0.8</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>3</td>
<td>2.2 ± 1.1</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>4</td>
<td>2.6 ± 1.1</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>2.2 ± 0.8</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>6</td>
<td>2.0 ± 0.7</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>All</td>
<td>2.4 ± 1.1</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>2.4 ± 1.1</td>
<td>1.8 ± 0.8</td>
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Average no. of wavefronts present for a 2-s period starting 10 s and 5 min after onset of ventricular fibrillation (VF). Values for no. of wavefronts are means ± SD. For normal group, \( n = 6 \) dogs. For congestive heart failure (CHF) group, \( n = 7 \) dogs, with CHF induced by combined myocardial infarction and rapid ventricular pacing.
expected to diminish as the distance between the source and the recording electrodes increases. This is supported by the increase in correlation coefficient we noted when analysis was limited to sites within 34 mm of the center of the EnSite catheter (0.78). It is also possible that degeneration of the magnitude of electrograms with progressive VF could contribute to variation between recorded and virtual electrograms, and these correlations were calculated without any corrections for possible timing differences between the directly recorded and calculated (virtual) electrograms.

More recently, this system has been used to accurately reproduce endocardial electrograms (42), characterize successful LV ablation sites (40), and map atrial fibrillation (41) in humans. The degree of spatial resolution found by Gornick et al. (14) is in the range within which there is a high degree of local spatiotemporal correlation between electrograms, as demonstrated by Bayly et al. (3). Bayly et al. (3) recorded electrograms from electrodes 1.12 mm apart on the surface of pig hearts during VF. The degree of correlation between electrograms decayed as a function of the distance between electrodes, and the “correlation length” ranged from 4 to 10 mm. Successful spatial location of endocardial activation sites has also been reported by Khoury et al. (24). By use of a boundary element inverse solution and a multipolar olive-shaped noncontact probe in isolated perfused dog heart, their location accuracy was 10 mm.

Previous studies of myocardial activation in VF have generally been restricted to recordings from a limited number of sites in a local array. The noncontact mapping system employed in this study has the advantage of providing data projected over the entire LV endocardial surface. On the other hand, given the limits of spatial resolution of the mapping system used, the extent to which very focal electrophysiological events may alter the global pattern of wavefront activity in VF cannot be discriminated in this model. Microminiature electrode arrays (0.003-mm-diameter electrodes spaced from 0.2 to 3 mm apart) have been used to record activation in VF to differentiate true propagating electrical activity from electrotonic signals and fractionated electrograms (53). The problem of determining local activation from complex electrograms can be difficult in ventricular (1, 53) or atrial (43) fibrillation. Although our method may have some loss of fine spatial resolution, we avoided the necessity of defining local activation from electrograms by displaying directly the color-coded amplitude of generated potentials in constructing the activation maps. This method has an additional advantage of avoiding bias introduced when individual electrograms are edited to determine activation times, as is often required in constructing isochronal maps. When comparing our results with previous studies using isochronal maps, it is important to remember that our data are presented as isopotential maps.

We chose to compare VF in CHF and normal hearts, both at 10 s and 5 min of sustained VF. The pattern of VF in the first few seconds after onset (Wiggers’ stage I) is unstable (1, 3, 8, 18, 38, 43, 50, 52). Although this early period is certainly of interest in assessing mechanisms of onset of VF, difficulties in analyzing transient patterns between hearts led us to use the more stable Wiggers’ stage II for comparison between CHF and normals. Wiggers’ stage II (50) is pertinent for study because it is within the time frame where detection and treatment algorithms for automatic implantable cardioverter defibrillators are activated. The analysis at 5 min was chosen because this is the outer limit of time during which treatment would likely be of benefit.

The model of tachycardia-induced heart failure has been well characterized (44). We modified the usual
model by including a small myocardial infarction before the onset of rapid pacing. This was done in an attempt to mimic as closely as possible VF as it occurs in most patients with CHF by providing an ischemic substrate with low mortality while still developing heart failure in a reasonable period of time. It is entirely possible that electrophysiological conditions in patients who respond to myocardial damage by gradually developing CHF over months or years may differ from those that we observed, but this type of limitation is present in most any animal model. It would have been of interest to include a group of dogs with rapid pacing-induced CHF but no infarction for additional comparison, but limits on time and resources made this impractical.

Effects of CHF on frequency components of VF waveforms. FFT of electrograms recorded during early-onset VF from two representative surface leads showed a peak frequency in the power spectrum similar to that of four virtual endocardial sites. The peak frequency at these six sites ranged from 6.2 to 7.4 Hz. These peaks occur in the same range as those reported by others for dogs (13, 29) and swine (5) and did not differ between normal animals and those with CHF.

Presence of multiple peaks, or multiple components of a single peak, can sometimes make peak frequency a poor choice for describing the power spectrum obtained by FFT. Because centroid (or median) frequency avoids this problem, it has been promoted as a better descriptor for the dominant frequency components of the power spectrum in VF than peak frequency. Centroid frequency may be clinically useful, as it can help predict successful cardioversion in both animal models (6, 47) and human patients (2, 4, 45, 46). We found that centroid frequency, like peak frequency, did not change in CHF compared with normal dogs. It is of interest that the centroid frequency in the power spectra from virtual endocardial sites was slightly less than that from surface leads. The reason for this discrepancy is not totally clear. One possibility is that contributions of the right ventricle would alter the dominant frequencies slightly and be more apparent on the surface-lead recordings than those made from within the LV.

We did not analyze changes in centroid frequency repeatedly during sustained VF because that has been quite thoroughly studied previously. Brown et al. (5) described a bimodal change in centroid frequency over time in swine, with an initial decrease over the first 1–2 min of VF followed by a return to baseline at 3–5 min and then a progressive decrease thereafter up to the 10-min duration of their study. Our quantitative analysis of wavefront activity at 5 min thus corresponds to a time when the centroid frequency in the power spectrum of the fibrillation waveforms would be similar to that seen in early-onset VF.

Wavefront activity. Mapping of myocardial activation has been examined by recordings from right and left ventricular epicardial (2, 19), endocardial (49), and intramural (35) electrode arrays and more recently by use of optical recordings from epicardial surfaces stained with voltage-sensitive dye (17, 52). Such studies have excluded VF as being random and rather have described varying degrees of organization with constantly changing wavefronts that evolve as VF persists, leading to postulation that VF is “deterministic chaos” (11). The occasional disparity we noted, where the surface electrocardiogram appears disorganized whereas the activation patterns recorded directly from the heart appear well organized, is consistent with the previous findings of Ideker et al. (18). We have not analyzed our data to determine whether CHF hearts differ from normal hearts in specific patterns of wavefront activity such as spirals (9, 33) or rotors (16, 17), the degree to which the complexity of activation patterns differ (39), or the extent to which reentrant versus nonreentrant pathways appear (20, 25). However, our method of mapping over the full endocardial surface allowed us to quantitate ventricular electrical activity in VF in a manner previously not possible. As a result, we were able to determine that the number of
active wavefronts declines over 5 min of VF and that fewer wavefronts are active at any given time during VF in CHF than in normal hearts. A comparison of our activation maps to isochronal maps obtained from portions of intact ventricles or isolated tissue blocks is difficult at best. However, if the sizes of the distinct wavefronts of other studies are extrapolated to a full surface of ventricle in proportion to the area of tissue studied, a quantification of wavefronts produces numbers consistent with our findings. For example, Witkowski et al. (52) recorded from ~30% of the surface of the heart, and their isochronal maps show one or two distinct wavefronts present in the example frames. This would suggest that up to six wavefronts may be present at one time over the entire epicardial surface. Of course we recognize that the right ventricle may be importantly involved in the onset and/or maintenance of VF, and we did not include the right ventricle in our analysis.

It would be of great interest to record simultaneous epicardial and endocardial activation maps to ascertain the degree of similarity or disparity between them. There is evidence that epicardial recordings may produce different activation patterns and larger numbers of wavefronts than endocardial recordings, perhaps because of the presence of endocardial-epicardial activation gradients (54). In addition to overall size (12), the thickness of the ventricle may be critical in onset and maintenance of VF (51), although this latter concept has been disputed (16).

It is well recognized that the longer VF is sustained, the more resistant it is to treatment (10, 55). It has also been shown that CHF alters the energy required to terminate VF (defibrillation threshold). In the canine rapid-pacing cardiomyopathy model, Lucy et al. (28) found a fourfold increase in defibrillation threshold in CHF animals compared with controls. In humans, there is both prospective as well as retrospective evidence that diminished ejection fraction and higher New York Heart Association (NYHA) class in CHF correlate with a higher defibrillation threshold (26, 31, 34). Mechanisms responsible for the increased defibrillation threshold in CHF are largely unknown, but increased ventricular mass and dilatation, altered myocardial refractoriness or excitability, and shunting of defibrillating currents have been put forward as possible explanations (36). It is provocative that the only significant difference we were able to demonstrate in failing hearts in CHF compared with normal hearts was a decrease in the average number of wavefronts active at any given time. Moreover, it was found that the number of wavefronts decreases with duration of VF. Thus, both in CHF and in longer-duration VF, where defibrillation threshold increases, the number of active wavefronts is diminished.

Of course the association of fewer endocardial wavefronts with higher defibrillation thresholds does not prove cause and effect. It is quite possible that those factors allowing fewer wavefronts to remain active at once also contribute to the relative resistance to cardioversion. Reentrant wavefronts with the presence of an excitable gap have been demonstrated in VF (7, 23, 25). Because reentrant wavelength is the product of conduction velocity and effective refractory period, altered refractoriness or changes in conduction velocity may effect the genesis and/or maintenance of wavefronts in VF. In the presence of LV dysfunction and dilatation, monophasic action potentials are prolonged, and the effective refractory period increases (27, 56). Effects of CHF on conduction velocity are less clear, as both a decrease in conduction velocity (27) and no change (56) have been described in dogs with rapid pacing-induced heart failure. Acute dilatation of the rabbit heart does not alter ventricular conduction properties (37). A longer refractory period would increase wavelength (conduction velocity times refractory period), whereas slower conduction velocity would shorten wavelength. It is conceivable that wavelength is increased in CHF because of a predominant effect of an increase in refractory period. A longer wavelength would require a larger surface area to maintain a reentrant circuit and thus potentially decrease the number of wavefronts that could be simultaneously active despite the cardiac enlargement seen in CHF.

**Turnover rate of wavefronts.** We have described the dominant frequency in the FFT performed on the number of wavefronts present as they emerge and dissipate with time during VF as the “turnover rate.” This turnover rate is similar to the peak frequency of the power spectrum performed on the endocardial electrograms and surface leads. It is not surprising that the rate at which wavefronts emerge and dissipate on the endocardial surface is linked to the fundamental frequency at which individual areas of the endocardium activate. Like the peak and centroid frequencies of the virtual electrograms, the turnover rate was no different in CHF than in normal hearts, despite the fact that fewer wavefronts were present in CHF.

**Conclusions.** The effectiveness of internal defibrillators in preventing sudden death in high-risk patients with CHF emphasizes the need to better understand the mechanisms involved in initiation and maintenance of VF. The finding in this study that wavefront activity is decreased in CHF in a way similar to that seen late in progression of VF in normal hearts is provocative. With fewer active wavefronts at the onset of VF, CHF hearts appear to begin VF with the same disadvantage for therapy as hearts that have already persisted in VF for ~5 min. The exact metabolic/electrophysiological changes causing the decrease in wavefront activity and resistance to defibrillation remain to be elucidated.

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