Mechanisms of Ventricular Fibrillation in Canine Models of Congestive Heart Failure and Ischemia Assessed by In Vivo Noncontact Mapping

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Background—Much of the research performed studying the mechanism of ventricular fibrillation (VF) has been in normal ventricles rather than under a pathological condition predisposing to VF. We hypothesized that different ventricular substrates would alter the mechanism and characteristics of VF.

Methods and Results—Three groups of dogs were studied: (1) control (n=8), (2) pacing-induced congestive heart failure (n=7), and (3) acute ischemia produced by 30 minutes of mid left anterior descending artery ligation (n=5). A noncontact mapping catheter (Ensite 3000, ESI) was placed via transseptal into the left ventricle (LV), along with an electrophysiology catheter. A multielectrode basket catheter (EP Technologies) was placed in the right ventricle, along with an electrophysiology catheter. Several episodes of VF were recorded in each animal. In addition to constructing isopotential and isochronal maps of the VF episodes, signals underwent frequency domain analysis as a fast Fourier transform was performed over a 2-second window every 1 second. From the fast Fourier transform, the dominant frequency was determined, and the organization was calculated. In control dogs, meandering, reentrant spiral wave activity was the main feature of the VF. The congestive heart failure group showed evidence of a stable rotor (n=3), evidence of a focal source (n=3), or no evidence of a driver in the LV (n=1). The ischemic group showed evidence of an initial focal mechanism that transitioned into reentry. In the control and ischemic groups, the LV always had higher dominant frequencies than the right ventricle.

Conclusions—Different ventricular substrates produced by the different animal models altered the characteristics of VF. Thus, different mechanisms of VF may be present in the LV, depending on the animal model. (Circulation. 2005;112:1532-1541.)

Key Words: fibrillation ■ Fourier analysis ■ mapping

The mechanism of ventricular fibrillation (VF) remains a controversial topic, with several theories—multiple wavelet reentry,1 a single stable dominant rotor, a mother rotor with other wave fronts spinning off the dominant one, or daughter wavelets2 with the mechanism of the mother rotor being a spiral wave—still being investigated.3–6 Evidence for these theories stems largely from the in vitro setting with structurally normal hearts. All in vivo recordings have been localized to specific regions in the ventricles.7–13 To date, there has been little in vivo, whole-heart analysis performed under pathological conditions known to predispose to VF.

We hypothesized that conditions such as acute ischemia and dilated cardiomyopathy, which are clinically associated with VF, may have underlying remodeling that affects the substrate and thus the mechanism of VF. We used noncontact mapping in the left ventricle (LV) and multielectrode contact mapping in the right ventricle (RV) to record VF in vivo in 2 canine models to analyze detailed activation maps and dominant frequency (DF) information to study the nature of VF with various underlying substrates.

Methods
All animal protocols were reviewed and approved by the Institutional Animal Care and Use Committee at the University of California San Francisco Laboratory Animal Resource Center, conformed to the regulations for humane care and treatment of animals established by the National Institute of Health, and were conducted with the assistance and supervision of the Animal Resource Department veterinary staff.

Twenty mongrel dogs weighing 25 to 30 kg were randomly divided into 3 different groups: (1) control group (n=8), (2) congestive heart failure (CHF; n=7) group, and (3) acute ischemia group (n=5). One dog in the CHF group and 3 in the ischemia group died before the study or induction of VF.

Heart Failure
CHF was induced in 7 dogs via 4 weeks of rapid ventricular pacing through a lead placed in the RV apex.14 The ventricular pacemakers...
were programmed to a rate of 240 bpm and at 4 times the capture threshold. Ventricular function was monitored weekly with transthoracic echocardiography, and after 4 weeks of rapid ventricular pacing, animals were brought back to the laboratory for a final study (see below).

Acute Ischemia
Acute ischemia was produced in 5 normal dogs. Once catheters were placed for mapping of VF, as described below, a left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. The mid left anterior descending artery was isolated and occluded for 30 minutes. After the occlusion period, if VF had not occurred spontaneously, VF induction was attempted with programmed stimulation. The mid left anterior descending artery remained occluded during VF recording.

Mapping of VF
Animals were intubated, mechanically ventilated, and anesthetized with isoflurane (2%). Two transeptal catheterizations were performed with a Brockenbrough needle; then, 2 sheaths were placed in the LV. A noncontact balloon mapping catheter (Ensite 3000, ESI) was positioned in the LV, along with a standard electrophysiology (EP) catheter. A 64-electrode basket catheter (EP Technologies) was inserted into the RV with a standard EP catheter.

Noncontact mapping was performed with the Ensite 3000 mapping system, which is described in detail elsewhere.15–17 The EP catheter that was also inserted into the LV was used to create a geometry of the LV in the ESI software with a methodology that has been described elsewhere.18–20 Detailed geometries (>500 points) of the LV were obtained before mapping and initiation of VF. Anatomic structures were marked on the reconstructed image. The noncontact mapping system samples all 64 cavitory potentials on the balloon at 1200 Hz and inversely applies them through the Laplace equation in real time. This method generates >3000 unipolar electrograms projected onto the geometry of the LV. The methodology has been described extensively and validated previously.18,21,22

A multielectrode basket catheter23 was used to record 32 unipolar contact electrograms from the RV simultaneously with the noncontact mapping signals. In addition to the endocardial mapping signals from the RV and LV, wide bipole signals were recorded between the distal electrodes of the standard EP catheters each placed in the RV free wall and left atrial free wall.24

Once catheters were in place and detailed LV geometries were obtained, episodes of VF were mapped. If VF did not occur spontaneously, it was initiated with programmed ventricular stimulation and burst pacing (cycle length, 50 ms). VF was defined as rapid, irregular ventricular activations resulting in variable and complex QRS morphologies on the surface ECG, along with a drop in blood pressure to 0. Only episodes that did not spontaneously terminate were analyzed. Episodes of monomorphic ventricular tachycardia were excluded from analysis. The VF was allowed to last at least 20 seconds before cardioversion with a defibrillation shock. At least 5 minutes lapsed between episodes of VF. To determine the activation of the VF, isopotential movies of activation were analyzed, and isochronal maps were constructed with local activation determined by the maximum dV/dt of the virtual electrogram. Conduction velocity was measured as the difference in activation times over a measurable distance on the LV geometry. Episodes of VF were categorized as focal or reentrant on the basis of the characteristics of activation in the isopotential movies and isochronal maps. Focal activation was defined as repetitive activation occurring in a radial fashion away from a source; reentrant activation was defined as repetitive activation over the entire cycle in which the latest activation neighbored the area of earliest activation. If the mechanism of the VF was determined to be a rotor, the area of the core of the rotor was measured as the area of continuous depolarization around which the rotor rotated.

Validation of Noncontact Electrograms
To validate the noncontact electrograms, the position of the EP catheter was labeled on the LV geometry created with the EnGuide location signal. The signals recorded from the EP catheter at that particular site were then cross-correlated with the noncontact signal calculated for that same site (Figure 1). This same procedure was done for both sinus rhythm and VF signals in each animal. The cross-correlation method was calculated over a range of lag intervals for each electrogram combination, and the peak value was considered the correlation coefficient, representing the degree of correlation between the 2 signals. In addition, activation times measured from the actual contact electrogram were compared with that of the estimated noncontact virtual electrogram during sinus rhythm and VF (Figure I in the online-only Data Supplement). Activation time points were determined as the point of maximal negative dV/dt.

Signal Processing and Frequency Domain Analysis
Thirty-two unipolar signals were obtained from the basket catheter, and an RV-LV wide bipole signal was acquired between the standard EP catheters. Surface leads I, II, III, aVL, aVR, and aVF were also recorded. All unipolar, wide bipolar, and ECG signals were filtered at 0.5 to 500 Hz and sampled at 1000 Hz. (Cardiolar, PRUCKA GE). Signals from the ES catheter were filtered at 2 to 300 Hz and sampled at 1200 Hz. For frequency domain analysis, 2048 virtual electrograms were exported. The location of each signal on the ventricular geometry was also downloaded so that the spatial distribution of frequency and orientation (OI) could be determined.

A fast Fourier transform (FFT) was calculated on the digitally filtered waveform over a sliding 2-second window every 1 second for a frequency resolution of 0.5 Hz. The data were detrended by removing the linear trend (from baseline wander resulting from DC offset) from the signal and multiplied by a Hamming window. The largest peak of the resulting magnitude spectrum was identified and defined to represent the DF of the electrogram. OI was calculated from the magnitude spectrum as the ratio of the area under the dominant peak and its harmonics to the total power of the spectrum.24 To calculate the variance of the DFs and OIs, the spatial coefficient of variance (SD/mean) was calculated during a single episode of VF among all recording sites. Temporal coefficient of variance was calculated between 2-second analysis windows for each VF episode.

Statistical Analysis
Data are expressed as mean±SD or median. Comparisons among conditions were performed with 1-way ANOVA, and between-group comparisons after ANOVA were made with Scheffe’s method. A 2-tailed Student t test was performed when appropriate. Fisher’s exact test was used to test for differences in VF activation between the animal models by categorizing the activation into single-type (focal or reentrant) or multiple-type (multiple mechanisms seen within the same VF episode) categories in a 2-way table. Statistical significance was defined as P<0.05.

Results
VF, either spontaneous or induced, was obtained in every animal. Several VF episodes were analyzed in each dog: 21 in 8 controls, 17 in 7 CHF, and 14 in 5 ischemic dogs. Signals from the EP catheter were cross-correlated with its corresponding noncontact signal (Figure 1). During sinus rhythm, the correlation coefficients were 0.94±0.01 and 0.90±0.05 for VF. In addition, activation times were determined for the signals from the EP catheter and compared with the activation times from its corresponding noncontact signal (Figure I in the Data Supplement). During both sinus rhythm and VF, the activation times were highly correlated (correlation coefficient, 0.99).

Control Group
VF was initiated with burst pacing in all control dogs. On examination of the isopotential maps, all episodes of VF in 7
of 8 control dogs demonstrated reentrant rotors that captured most of the LV. An example isopotential movie is shown in the Data Supplement (Movie I); corresponding isochronal maps are shown in Figure 2A. These show 1 dominant wavefront around the lateral wall of the LV with reentrant characteristics. The wave front circulates around a core area, which migrates around the posterior LV. This is shown in Figure 2A in the maps representing activation from 0 to 150 ms and 150 to 300 ms. In these isochronal maps, the central core is represented by the confluence point of all activation times, and the maps show this central core shifting to a lower part of the ventricle. Occasionally, the rotor terminates through wave collision and then reforms in another part of the ventricle. After a couple of rotations at this location, the rotor terminates again and reforms in the same location as at the start of the recording. Similar activation characteristics were seen in all animals with reentrant mechanisms in this group. The 1 control dog that did not show reentrant activation as a mechanism showed consistent focal activation in the apex with the emanating wave fronts traveling toward the base of the LV. From the isochronal maps, conduction velocity in the LV was measured as 129±57 cm/s (median, 150 cm/s), and if a rotor was present, its core area was measured to be 0.81±0.28 cm² (median, 0.87 cm²). When these 3 measurements were correlated, there was a linear relationship between conduction velocity and rotor core area ($R^2=0.91$) (Figure II in the Data Supplement).

To quantify the activation, frequency domain analysis was performed on the VF electrograms. For each VF recording, DF and OI maps from each sliding 2-second window were compiled into movies, examples of which are shown in the Data Supplement (Movie IVA). Static DF maps for a 2-second period of VF are shown in Figure 3A, top. Each panel shows a view of the 3D geometry of the LV rotated 90°. The distribution of frequencies follows patterns similar to those demonstrated in the isopotential sequences. In the second panel (View 90), the DF map shows a large high-frequency area originating from the lateral wall and encircling a core of lower frequencies. An arrow points to the low-DF area. In each control dog, the DFs were transient and dynamically changing, which is demonstrated in the DF movie in the Data Supplement. As the reentrant rotor meandered around the LV, the DFs changed according to its location. The DFs also altered with rotor breakup and reformation because the high-DF areas were not stable.

Figure 3A (bottom) shows the static OI maps from a 2-second FFT window of VF. As this figure shows, there is a line of low OI around the low-frequency area that is the core of the rotor. This low-OI boundary indicates block into this low-DF area. In each control dog, the DFs were transient and dynamically changing, which is demonstrated in the DF movie in the Data Supplement. As the reentrant rotor meandered around the LV, the DFs changed according to its location. The DFs also altered with rotor breakup and reformation because the high-DF areas were not stable.

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Summary data for DF and OI parameters are shown in Figure 4. Figure 4A shows the average DFs for all of the VF episodes recorded in the control group. The LV tended to have higher DFs than the RV, but the difference was not statistically significant ($P=0.2$). The DFs of the wide bipolar were similar to the LV DFs. Figure 4B shows that in the control group, the highest DFs were located in the LV because the LV had higher maximum DFs than the RV.
(7.7±2.7 versus 5.8±1.8 Hz; median, 7.1 and 4.7 Hz), but this difference was not significant ($P=0.19$). Figure 4C shows the average measured OI levels for all recorded VF episodes. The control group had similar OI levels for the LV, RV, and wide bipole. Figure 5A shows the characteristics of the DFs for an episode of VF in a control dog. The values of the average and maximum DFs for the 2-second FFT window for the 2048 signals are shown. Each second, a new calculation is made. In this example, the activation movies showed evidence of an unstable rotor that repeatedly breaks and reforms. As shown, during this type of activation, the highest DF was also unstable. Fluctuations in the highest DF corresponded to rotor breaks and reformation. Late in the VF episode, the activation stabilizes, corresponding to a stabilization of the highest DF. Although the highest DF varied, the average DF remained consistent throughout the VF episode.

Figure 2. Isochronal maps from control (A), acute ischemia (B), and CHF (C) corresponding to isopotential movies shown in the Data Supplement. The surface ECG of the VF episode represented by the isochronal maps is shown at the bottom of each part. The time label for each sequence of the isochronal maps does not directly correlate to the time of the VF episode (The first displayed isochronal map is always labeled as starting at 0 ms but may not necessarily correlate to the initiation of VF). On the maps, the colors indicate the timing of activation, with white representing the earliest activation and purple representing the latest. Curved arrows indicate the direction of reentry; straight arrows, the earliest activation of a focus. Reentry is determined by areas of earliest activation meeting areas of latest activation. In the example from the control group (A), 3 sequential maps are shown at 150-ms intervals. A reentrant pattern is seen in each map. Also seen is the shift of the core of reentry between 0 and 150 ms and 150 and 300 ms as the rotation moves to a lower position in the LV lateral wall. For the acute ischemia example (B), examples of focal and reentrant activation are shown from the same episode of VF. A stable, focal source is shown on the left; a stable reentrant wave front is shown on the right side. For both the focal and reentrant mechanisms, the activation is consistent between each time window. For the CHF example (C), focal (left) and reentrant (right) examples are shown from different episodes of VF. For each mechanism, the activation was consistent between time windows.
The characteristics of the maximum DF for each mechanism are summarized in Figure 6. As shown, when the VF activation is unstable, the coefficient of variation of the maximum DFs is higher than that for the stable activations of the focus and reentry. Thus, when the activation is unstable, the maximum DF changes at a higher degree than the stable focal and reentrant activations.

Acute Ischemia Group
In the acute ischemia group, 14 VF episodes were analyzed, and in all the ischemic dogs, a form of both reentry and focal activation was seen in the same animal. Each ischemic dog had 1 VF episode that showed both activation types. This occurred in the first VF recording in each dog. Subsequent VF episodes had reentry as the mechanism of the VF. In 4 of the 5 ischemic dogs, during episodes of VF with reentry, the reentrant rotor broke through wave collision with daughter wavelets and reformed in the same location but rotated in the opposite direction of the original rotor. An example of this type of activation behavior is shown in the Data Supplement as Movie IIA–IID. Isochronal maps of activation are also shown in Figure 2B. All maps were generated from the same

Figure 3. Static DF (top) and OI (lower) maps of noncontact signals from the LV during VF in control (A), acute ischemia (B), and CHF (C). The DFs and OIs shown are from an FFT performed on a 2-second window of VF. Each panel shows the 3D LV geometry rotated 90°. In A, the area of lowest frequency represents the core around which the reentrant wave rotated in the activation sequence shown in the Data Supplement Figure IA. In B, the DF map shown during a period of reentry in the acute ischemia model. In C, a focal area of higher frequency is seen with the remainder of the LV at a lower DF. The high-frequency area was remarkably stable throughout the VF episodes.
episode of VF. The 3 panels on the left show focal activation every 150 ms. The 3 panels on the right show reentrant activation every 150 ms during a later stage of the VF episode. There was a significant difference when the activation types were compared with that of the control group (P = 0.0008). The conduction velocity was measured to be 95 ± 21 cm/s (median, 98 cm/s), and the rotor core area measured 0.56 ± 0.26 cm² (median, 0.50 cm²). During a VF recording, each DF map from the sliding 2-second window was compiled into a DF and an OI movie; these movies are shown in the Data Supplement as Movie IVB. The movies indicate the transition from focal to reentry, and the core of the rotor is clearly visible in the OI map. Static DF maps from a representative 2-second window of VF are shown in Figure 2B. Similar to the DF maps from reentrant characteristics in the control group, the high-DF area indicates the region where the rotor originates and goes around a lower-frequency area. The corresponding static OI maps are shown in Figure 3B (bottom). The core of the rotor is seen in the second panel (view 90). There is a line of low OI around the low-frequency area that is the core of the rotor. Summary data are shown in Figure 4. On average, the ischemia group had similar frequencies between the LV, RV, and wide bipole. However, the ischemia group had higher frequencies than the control and CHF groups (6.2 ± 0.8 versus 4.9 ± 0.7 and 4.6 ± 0.7 Hz; ANOVA, P < 0.007; medians, 6.6, 4.8, and 4.5 Hz). The maximum DFs in the LV tended to be higher than those found in control (7.7 ± 2.7 versus 10.7 ± 2.0; P = 0.16; median, 7.1 and 10.3). The LV also had higher OI levels than the control LV as shown in Figure 4C. Figure 4 also shows that the LV had higher frequencies than the RV (10.7 ± 2.0 versus 7.4 ± 1.3; P < 0.02; median, 10.3 and 7.3). This finding, consistent for every ischemic dog, supports the finding that the driving source of the VF is in the LV. Figure 5B shows an example of the average and highest DFs recorded in an episode of VF in a dog with acute ischemia. As the figure shows, for each 2-second window, the average DF remains stable throughout the VF episode, but the maximum DF varies at a 2:1 ratio to the average. When the variation in the maximum DF is correlated to the activation, the behavior of the highest DF indicates the termination, reformation, and stabilization of the reentrant wave front, as labeled in the figure. These data are then summarized for all dogs in Figure 6. As the figure shows, similar to the control group, the ischemia group had a higher coefficient of variation of maximum DFs during unstable activation as opposed to stable focal or reentrant activation (0.32 ± 0.08 versus 0.08 ± 0.09 and 0.05 ± 0.01; ANOVA, P < 0.0001; median, 0.31 versus 0.03 and 0.04).

In the ischemia group, 4 episodes of VF occurred spontaneously (1 episode in 4 of 5 dogs). The characteristics and activation maps were not different from those induced with programmed stimulation.

**CHF Group**

VF was spontaneous in 4 of 7 dogs. In these dogs, the VF could not be terminated with repeated defibrillation attempts, and it was allowed to continue. Focal activation was seen in 2 of the 4 dogs; 1 dog had reentry; and the remaining dog showed no evidence of a driver in the LV. Overall, reentry was seen in 3 of 7 dogs. Focal activation with fibrillatory conduction was seen in 3 other dogs, and 1 dog had no evidence of a driver in the LV. An example of both focal activation (Movie IIIA) and stable reentry (Movie IIIB) is shown in the Data Supplement and in Figure 2C. In contrast to the control group, focal or reentrant sources were stable throughout the duration of the VF. In addition, only 1 type of activation was seen per dog in the CHF group. If the initial activation was reentrant, it remained reentrant for every episode of VF in that animal. In 1 animal in this group, no driver (reentrant or focal) was found in the LV. Isochronal maps of activation are shown in Figure 2C. The panels on the left show an example of VF in which the mechanism was focal. For each time window (200 ms), the focus originates in the same location in the lateral wall of the LV near the apex. The panels on the right show an example of VF from a different dog in which the mechanism is reentry. As shown, the activation is very consistent for every 200-ms window.
When the activation sequences for the CHF dogs were compared with those of the ischemia dogs, there was a significant difference ($P=0.0022$) between the VF mechanisms in these models. Also, the CHF model had the slowest conduction velocity compared with the control and ischemia models (65 ± 13 versus 129 ± 57 and 95 ± 21 cm/s; ANOVA, $P=0.05$; median, 63, 150, and 98 cm/s). DF and OI movies are also shown in the Data Supplement as Movie IVC. Static maps of the DF and OI generated from a 2-second FFT window are shown in Figure 3C. As the DF maps show, there is an area of higher frequencies, whereas the rest of the ventricle is composed of lower frequencies. The boundaries between DF areas are clearly seen in the OI map because the transition from 1 DF area to another alters the FFT.13,25 These DF and OI patterns were similar for dogs in the CHF group with a stable, focus source as the mechanism of VF. In the CHF animals in which reentry was the main mechanism, the DF maps showed higher-frequency areas around a low-frequency core. The OI maps showed low-OI areas around the low-frequency area that is the core of the rotor. In the 1 dog in which no LV driver was observed, there were no stable DFs or any distinguishable DF pattern in the LV. In this dog, the RV had a higher frequency with a RV-to-LV frequency gradient (8.3 ± 0.8 versus 4.6 ± 1.2 Hz; $P<0.0001$). Summary DF and OI data are shown in Figure 4. As Figure 4A shows, the LV of the CHF group had lower DFs than the other models on average. The RV tended to have higher average frequencies than the LV, and the RV also had DFs similar to those of the wide bipolar. This could be due to the 1 animal in which no driving source for the VF was found in the LV, and there was a RV-LV frequency gradient.

Figure 5C shows an example of an episode of VF with a stable, focal source. The maximum DF and average DF are very similar. The period of VF when the maximum DF was the same for each 2-second FFT window corresponded to a stable, focal source as the mechanism of the VF. For this VF episode, the shock was unsuccessful, and both the maximum and average DFs lost their stability. Figure 5D shows an example of an episode of VF with a stable, reentrant driver. There is a large difference between the frequency of the rotor and the average DF, and the frequencies remain stable for a long time. When the data are summarized for all the CHF dogs (Figure 6), the variance of the maximum DFs was higher during unstable activation than during the stable activation of a focus or reentry (0.25 ± 0.07 versus 0.03 ± 0.05 and 0.03 ± 0.04; ANOVA, $P=0.009$; median, 0.25 versus 0.03 and 0.03).

**Discussion**

This study has shown that VF does have an underlying organized rhythm, and although several other studies have also demonstrated a spatiotemporal organization during VF,4,7,26–28 the debate has continued as to whether the mechanism behind the organized rhythm is a focal source, a mother-rotor, or microreentry. In this study, we have shown that all of these mechanisms of VF do exist but that the substrate in which the VF is induced plays a key role in its mechanism. In control animals with structurally normal hearts, there are reentrant wave fronts, with the wave front capturing most of the LV. These rotors seemed to meander around the posterior LV and promote the spinning off of daughter wavelets that on occasion collide with the dominant wave front and extinguish the rotor. The rotor subsequently reforms in a different area. The dominant wave front also appeared to be driving the VF because there was a gradient of frequencies from the LV to the RV and from the area of the
rotor to the apex of the LV, which was at a lower frequency than where the rotor appears. In addition, the core of the rotor is at a lower frequency, indicating block into this region. Most acute ischemia animals (4 of 5) showed an initial focal mechanism of activation before transitioning to reentry. Subsequent VF episodes were then consistently reentrant as a primary mechanism. As in controls, there was a gradient of frequencies from LV to RV in the ischemia group. It is interesting to note that for the acute ischemic animals, if a rotor extinguished, it would reappear in a region similar to that of its predecessor. However, the wave front might rotate in the opposite direction. This is in contrast to the control group, in which extinguished rotors would later reappear in a different location. For the CHF group, each VF episode was distinctly either focal or reentrant, and all episodes of VF in each animal had the same mechanism (i.e., in each animal with focal VF, all episodes were focal and no reentry was seen; in each animal with reentrant VF, all episodes were reentrant). In the 1 CHF dog with no apparent driver in the LV, the RV had consistently higher DFs, suggesting that the VF driver was in the RV of this dog.

Previous Studies on Mechanisms of VF

Controversy still exists as to the mechanism of VF being either a mother rotor or multiple wavelet reentry, and several studies have claimed support for each mechanism.27–34 Using both RV and LV wedge preparations from swine hearts, Valderrabano et al31 showed that the VF in their study was characterized by transmural reentry in the RV, intramural reentry in the LV, and wave break induced by anatomic structures. Even though the VF had reentrant characteristics, the reentry was short-lived and unstable. Another study by the same group using a similar ventricular wedge preparation showed unstable areas of DFs during VF,32 further supporting wave break as the mechanism for maintaining the VF. Choi et al29,30 showed that VF consists of dynamically changing areas of frequencies in both guinea pigs29 and rabbits,30 which would support the multiple wavelet theory. Rogers et al27 found evidence of sustained reentry in the LV of pig hearts; however, they did not find any evidence that this reentry was driving the VF and would be considered a mother rotor. A study by Wu et al35 showed that 2 types of VF can exist within the same heart. Type I VF, which consisted of fast VF with high DFs, was shown to correspond with a steep action potential duration restitution curve. This type of VF supported the multiple wavelet hypothesis. When the excitation-contraction uncoupler methoxyverapamil (D600) was given, a slower, more organized VF developed that was called type II VF and was associated with a flat action potential duration restitution curve. It was then shown that the mechanism of type II VF was a mother rotor.34 Contrary to these studies, Zaitsev et al33 have shown that during VF in sheep, areas of stable frequencies exist that would remain unchanged during 8 to 10 seconds of VF. Chen et al28 also demonstrated stable, high-frequency areas in rabbit hearts, which would support the mother rotor theory that a stable, high-frequency reentrant source is driving the VF. The present study demonstrated that in control dogs with structurally normal hearts, meandering, reentrant spiral wave activity was the dominant feature of the VF. Because of this meandering rotor, the discrete high-frequency areas shifted in relation to the position of the reentrant activity. Although previous studies claimed that changing frequencies supported multiple wavelets as a mechanism of VF, it was clear from the isopotential movies that the reentrant rotor was driving the VF and that the shifting frequencies result from the meandering of the rotor.

As for other studies with diseased hearts, Huang et al10 demonstrated that VF in a heart failure model was significantly different from the VF found in control dogs. This study analyzed VF electrograms recorded from a plaque electrode on the epicardial surface of the RV and LV. The VF patterns were quantified, and it was shown that VF in the setting of heart failure had a lower peak dV/dt, a slower activation rate, a significantly lower occurrence of reentry, and an increased occurrence of block than that of VF in controls. In a study that induced heart failure in sheep, Moreno et al36 showed that the
heart failure group had lower DFs and higher levels of organization during VF than in normal hearts. When the heart failure dog model also included a healed myocardial infarction, the DFs during VF were similar to those of controls, but the heart failure model had a decreased number of wave fronts as observed with noncontact mapping.\textsuperscript{38,39} The present study shows data that supports the finding by Huang et al and Moreno et al by also showing a slower activation rate in the heart failure animals because, on average, the DFs were lower than in the control or ischemia animals. However, the present study also showed that a stable mechanism can exist in the CHF dogs of either reentry or focal.

In hearts subject to acute ischemia, 2 studies have shown evidence for 2 different mechanisms during VF.\textsuperscript{38,39} The present study shows data that support the findings of Pogwizd et al\textsuperscript{39} and Janse et al\textsuperscript{38} showing that the VF in the setting of acute ischemia has both reentrant and focal mechanisms. In addition, a recent study by Liu et al\textsuperscript{40} showed that the acute ischemic region creates a substrate for the occurrence of 2 different types of VF simultaneously. Our study also shows that the stage of VF in which the analysis takes place plays a key role in which mechanism will be observed. On the basis of the data in the present study, early stages of VF will likely have a focal mechanism and later stages of VF will have a reentrant mechanism.

Clinical Implications
A recent study has brought to the surface the idea that VF might have an excitable gap.\textsuperscript{31} This finding, along with the presence of single reentrant rotors found in this study, raises several possibilities for altering the organization of VF or even VF termination with either pacing or time shocks.\textsuperscript{41}

A recent study has shown that triggered activity causing recurrent VF can be terminated with catheter ablation\textsuperscript{42} and with the aid of noncontact mapping.\textsuperscript{43} The present study also supports this finding because it showed that the rotors of foci driving the VF in CHF and acute ischemia, once initiated, occurred in the same area. If these areas could be mapped and ablated, VF could possibly be ablated in patients with frequent ICD shocks.

Study Limitations
All experiments were performed with canine hearts. It is unknown whether human hearts would behave similarly; however, the models reported in this study are clinically relevant models of VF (heart failure and ischemia). LV activation was determined with noncontact mapping to enable endocardial mapping in the intact, in vivo animal. The technique has been extensively validated. In addition, we performed validation/confirmation in each animal by correlating contact electrograms with the virtual unipolar electrogram from the same site. There was a high degree of correlation in all animals both in sinus rhythm and during VF. We used the noncontact mapping catheter in its “high resolution” mode (within 4 cm), and in the LV of the dog (even those with CHF), the balloon was never >4 cm from any portion of the LV. An additional limitation with any mapping technique is that we mapped the endocardial surface and did not map transmurally. This also poses some limitations in defining the actual mechanism of the focal VF. We used the term “focal” to indicate that the origin of the tachycardia occurred in a small region of the endocardium without apparent macroreentry because the noncontact mapping system may not be sensitive enough to determine whether the observed focal activity was microreentry or endocardial breakthrough of an intramural rotor.

Conclusions
The mechanism of VF varied among the animal models studied. Almost all control dogs demonstrated a meandering single rotor. The CHF group showed evidence of either a stable rotor or a focal source that, when extinguished, would reappear in the same location, and it was not confined to the LV. The acute ischemia group showed evidence for an initial focal mechanism that would transition into reentry. Frequency domain analysis showed that the rotor readily captured most of the ventricle at high rates in control dogs but that most of the LV was dominated by frequencies lower than the highest frequency in the CHF group. Future studies need to study why the rotor appears in the same location in CHF and acute ischemic dogs.

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References

**CLINICAL PERSPECTIVE**

Coronary artery disease and heart failure from any cause predispose to sudden death, commonly because of VF. Despite extensive study, the mechanisms of VF are controversial. During VF, cardiac activation is not random but displays a degree of organization. Meandering reentry waves have long been considered a potential mechanism, but there is also evidence supporting rapid activation from a stable driving focus or rotor of reentry that spawns daughter waves. The later mechanism is intriguing because it suggests the possibility that ablation to prevent VF might be possible. There has been little in vivo, whole-heart analysis of VF in different pathological conditions. This study compared VF induced in healthy canine hearts, during acute myocardial ischemia, or after heart failure induced by rapid pacing. Analysis of cardiac activation during VF demonstrated evidence for >1 mechanism, including a single rotor. The predominant mechanism varied with the underlying cardiac pathophysiological state and was generally the same in each animal during repeated inductions of VF. In heart failure animals, stable rotors tended to occur in the same region in individual animals. Thus, the substrate in which VF occurs plays a key role in its mechanism. These findings support the possibility that identification and ablation of regions supporting driving rotors or foci might prevent VF in some disease states.
Mechanisms of Ventricular Fibrillation in Canine Models of Congestive Heart Failure and Ischemia Assessed by In Vivo Noncontact Mapping
Thomas H. Everett IV, Emily E. Wilson, Scott Foreman and Jeffrey E. Olgin

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