Improvement of Defibrillation Efficacy and Quantification of Activation Patterns During Ventricular Fibrillation in a Canine Heart Failure Model

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Background—Little is known about the effects of heart failure (HF) on the defibrillation threshold (DFT) and the characteristics of activation during ventricular fibrillation (VF).

Methods and Results—HF was induced by rapid right ventricular (RV) pacing for at least 3 weeks in 6 dogs. Another 6 dogs served as controls. Catheter defibrillation electrodes were placed in the RV apex, the superior vena cava, and the great cardiac vein (CV). An active can coupled to the superior vena cava electrode served as the return for the RV and CV electrodes. DFTs were determined before and during HF for a shock through the RV electrode with and without a smaller auxiliary shock through the CV electrode. VF activation patterns were recorded in HF and control animals from 21×24 unipolar electrodes spaced 2 mm apart on the ventricular epicardium. Using these recordings, we computed a number of quantitative VF descriptors. DFT was unchanged in the control dogs. DFT energy was increased 79% and 180% (with and without auxiliary shock, respectively) in HF compared with control dogs. During but not before HF, DFT energy was significantly lowered (21%) by addition of the auxiliary shock. The VF descriptors revealed marked VF differences between HF and control dogs. The differences suggest decreased excitability and an increased refractory period during HF. Most, but not all, descriptors indicate that VF was less complex during HF, suggesting that VF complexity is multifactorial and cannot be expressed by a scalar quantity.

Conclusions—HF increases the DFT. This is partially reversed by an auxiliary shock. HF markedly changes VF activation patterns. (Circulation. 2001;103:1473-1478.)

Key Words: fibrillation ■ heart failure ■ mapping

The incidence and prevalence of heart failure (HF) have increased over the past decade.1,2 Ventricular fibrillation (VF) is common in these patients.3,4 Changes in failing hearts, including ventricular hypertrophy and dilatation, electrophysiological remodeling, sympathetic activation, and electrolyte abnormalities,5 may increase the defibrillation threshold (DFT) for the transvenous shocks delivered by implanted devices, just as has been shown for shocks through epicardial electrodes.6 Similarly, HF is likely to change the organization of activation during VF.

A minimum electrical potential gradient may be needed in all or most of the ventricles for a shock to defibrillate.7 For shocks near the DFT, earliest postshock activations arise predominantly where the shock potential gradient is weakest.8 Because of ventricular dilation and hypertrophy, failing hearts probably have a larger region of weak potential gradient than do normal hearts for a given shock.9 If so, it may be possible to lower the DFT in failing hearts by including an additional shock electrode in the region of low potential gradient.

The present study tested 3 hypotheses: (1) HF increases the DFT for transvenous shocks; (2) a small auxiliary shock given to the region of low potential gradient for a transvenous electrode configuration lowers the DFT in HF; and (3) HF changes the organization of activation during VF.

Methods

All studies were performed in accordance with institutional guidelines.

Animal Preparation

Two groups were studied. Group 1 (HF group) included dogs with rapid pacing–induced HF; group 2 (control) included dogs without rapid pacing. The same methods for preparation, DFT measurement, and mapping were used in both groups. Mongrel dogs (29±3 kg, mean±SD) were anesthetized with 25 mg/kg IV thiopental sodium and maintained with isoflurane in 100% oxygen delivered by mechanical ventilation. Succinylcholine was given at 1 mg/kg initially, followed by 0.25 to 0.5 mg/kg at 20-minute intervals, to decrease movement during defibrillation shocks. Lactated Ringer’s solution was continuously infused (2 to 5 mL/kg per minute). Core
body temperature, arterial blood gas values, and serum electrolytes were maintained within the normal range throughout the experiment.

**Hemodynamic Evaluation, Electrodes, and Shock Waveforms**

Under fluoroscopic guidance, via right external jugular access, a 7F Swan-Ganz thermodilution catheter was advanced into the pulmonary artery for determination of baseline quadruplicate cardiac output, pulmonary arterial wedge pressure, and right ventricular (RV) pressure. The catheter was then withdrawn, and another was placed (0094 Endotak, Guidant) with a 4.7-cm electrode in the RV and a 6.9-cm electrode in the superior vena cava (SVC). Another catheter with a 4-cm electrode was placed in the great cardiac vein via the coronary sinus (Figure 1A). This electrode was generally on the anterior wall of the left ventricle (LV) near the region of weakest potential gradient for shocks between the RV and SVC.10 A bipolar pacemaker lead (Bi 4269, Guidant) was placed in the RV apex. A 55-cm³ titanium can was placed in the left pectoral region. All catheters were left in place after the baseline study.

An external waveform generator was used to deliver biphasic truncated exponential shocks with a 60/40 ratio of first/second shock phases (Figure 1B). Either a single primary shock or a primary shock followed by an auxiliary shock (P₁→A shocks) was delivered. The primary shock was delivered to the RV electrode, and the auxiliary shock was delivered to the LV electrode. The SVC electrode connected to the active can was the first-phase anode for both shocks. For P₁→A shocks, the leading-edge of the auxiliary pulse was set equal (±10 V) to the trailing edge of the primary pulse with a 5-ms delay. The primary and auxiliary shocks each had an overall fixed tilt of 40% from an effective capacitance of 225 μF. Total waveform duration varied with shock impedance.11

After DFT measurement, a pacemaker (model 1230, Guidant) was implanted. Only the HF group was paced at 220 bpm.

**DFT Determination**

VF was induced with 30-V, 60-Hz alternating current through the defibrillation catheter. After 10 seconds of VF, a defibrillation shock was given. The leading-edge current of the first shock was the mean DFT from previous experiments. For the first animal, it was 8 A. Depending on the success or failure of the shock, the leading-edge current was decreased or increased by 1 A. The transition from failure to success or success to failure was recorded as the first data point. The up-down algorithm was continued until the third reversal of success to failure or failure to success. The DFT was determined by averaging 4 shock strengths delivered around the 3 reversals.12 At least 4 minutes elapsed after every fibrillation-defibrillation episode until blood pressure and heart rate returned to normal.

**M-Mode Echocardiographic Measurements**

Echocardiograms were performed before and every week after pacing was started (Model 77020, Hewlett Packard). LV dimension was marked at the chordal level just below the tips of the mitral valve. The right and left septum and the posterior wall endocardium and epicardium were marked at end systole and end diastole for 4 or 5 consecutive cardiac cycles. End systole was identified as the smallest cavity dimension; end diastole was taken as the cavity dimension just before the onset of posterior wall and septal thickening. Average LV end-diastolic dimensions and ejection fractions were calculated.

**Further Study**

Three to 5 weeks after the baseline study, the dogs were anesthetized, intubated, and ventilated as previously described. The pacemaker was removed, and the ends of the catheters were exposed. Hemodynamic variables and DFTs were determined as described previously. The heart was then exposed through a median sternotomy and supported in a pericardial cradle.

A 504-electrode (24×21) plaque covering ≈20% of the epicardium was sutured to the anterolateral RV and adjacent LV epicardium. The unipolar electrodes were 1-mm-diameter silver spheres with 2-mm spacing.

VF was induced as described before. A rescue biphasic shock of 400 to 500 V was given 45 seconds after VF induction. A minimum of 15 minutes elapsed before VF was reinduced. VF was induced 4 to 6 times in each animal. The dogs were euthanized by electrically induced VF. The plaque location was marked, and the heart was excised and weighed.

**Mapping and Data Acquisition**

Unipolar electrograms referenced against a right leg electrode were bandpass-filtered (0.5 to 500 Hz), sampled at 2 kHz, and recorded continuously.13 Data for 1-second intervals beginning 0, 5, 10, 15, and 20 seconds after VF induction and for a 4-second interval beginning 15 seconds after induction were transferred to a computer workstation (Sun Microsystems) for analysis.

**Quantitative Analysis of VF Activation**

Activation patterns during VF were quantified by decomposing VF into individual wave fronts.14 From this decomposition, the following 10 descriptors were computed for each 1-second data set: (1) number of wavefronts,14 (2) fraction of wave fronts that fractionate,14 (3) fraction of wave fronts that collide,14 (4) mean area swept out by wave fronts,14 (5) fraction of wave fronts that block,15 (6) fraction of wave fronts that break through to the epicardium or are foci,16 (7) multiplicity (a measure of the number of distinct activation pathways),16 (8) mean negative peak dV/dt of VF activations, (9) overall activation rate,15 and (10) mean propagation speed of the wave fronts.15

The following 3 descriptors relating to reentry were computed for the 4-second interval beginning 15 seconds after VF induction17: (1) incidence of reentry, (2) mean number of reentrant cycles, and (3) mean core area of reentrant circuits.

**Statistical Analysis**

Results are expressed as mean±SD. In both the control and HF groups, hemodynamic variables at baseline and restudy were compared by paired t tests. DFTs were compared by bivariate repeated-measures ANOVA, in which the dependent variables were DFT voltage and energy. Three orthogonal contrasts were defined to compare DFTs for (1) primary shocks at baseline and restudy, (2) P₁→A shocks at baseline and restudy, and (3) P₁→A at restudy and primary shock at restudy. Baseline data from the control and HF groups were pooled in bivariate repeated-measures ANOVA to compare DFTs of primary and P₁→A shocks for normal hearts. The 10 VF descriptors computed by use of 1-second data intervals were compared by 3-way multivariate ANOVA.
compared by unpaired $t$ tests. For all analyses, a value of $P \leq 0.05$ was considered significant.

### Results

Nine dogs in the HF group survived for restudy. Two could not be rescued after VF induction because of very high DFTs, and another died during the thoracotomy procedure. Thus, complete data were collected from 6 dogs in this group. The control group contained another 6 dogs. Heart weight averaged 276±23 g for HF dogs and 168±16 g for control dogs ($P < 0.01$).

### Hemodynamic Variables

There was evidence of systolic and diastolic myocardial dysfunction in the HF but not control animals (Table 1). Mean cardiac output and ejection fraction for the HF dogs both decreased by >50%, accompanied by significant increases in LV end-diastolic dimension, pulmonary arterial wedge pressure, and RV pressure.

### Defibrillation Threshold

In the HF animals, multivariate ANOVA showed that DFTs in the 4 groups (primary shock at baseline and restudy and P+A shock at baseline and restudy) were not all the same ($P < 0.001$). Further examination of the specific contrasts showed that DFT leading-edge voltage and energy for both primary and P+A shocks were significantly increased for the HF dogs at restudy compared with baseline (Figure 2). The mean pairwise differences were 60±37% and 122±133% for voltage and energy, respectively, for primary shocks and 34±22% and 67±54% for voltage and energy, respectively, for P+A shocks in HF. DFT voltage and energy for P+A shocks were significantly lower than for primary shocks (27±8% and 23±6%, respectively) in HF (Figure 2).

In the control animals, multivariate ANOVA showed that DFTs in the 4 groups were not all the same ($P < 0.01$). However, the specific contrasts that we examined showed that DFTs did not change between baseline and restudy for either shock configuration (Figure 3). In addition, at restudy, DFTs for the P+A shocks were the same (Figure 3).

We compared DFT voltage and energy for primary versus P+A shocks at baseline for all 12 animals. The DFTs again differed ($P < 0.001$ by multivariate ANOVA). Univariate tests showed that voltage was significantly lower for P+A shocks than for primary shocks (mean pairwise difference 10±8%), but energy was not different.

### Quantitative Analysis of VF Activation Patterns

Examples of VF activation sequences are shown in Figure 4. The quantitative descriptors of VF activation are shown in Table 2. In each group of animals, data from all 1-second

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**TABLE 1. Hemodynamic Variables**

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=6)</th>
<th>HF Group (n=6)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before Pacing</td>
<td>After Pacing</td>
</tr>
<tr>
<td>EF, %</td>
<td>69±9</td>
<td>68±7</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>4.1±0.2</td>
<td>4.2±0.2</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>9±3</td>
<td>8±4</td>
</tr>
<tr>
<td>RVP, mm Hg</td>
<td>4±2</td>
<td>3±3</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.8±0.2</td>
<td>4.9±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

EF indicates ejection fraction; LVEDD, LV end-diastolic dimension; PAWP, pulmonary artery wedge pressure; RVP, RV pressure; and CO, cardiac output.

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**Figure 2.** Leading-edge voltage (A) and total delivered energy (B) at DFT for HF group. $P$ indicates primary shock. For overall ANOVA, $P < 0.001$. Probability values for specific comparisons are indicated by brackets. Circle with minus within indicates means.
intervals are pooled in Table 2. There was a significant overall multivariate difference between the HF and control groups ($P<0.001$). The number of wave fronts, incidence of collision and fractionation, mean area swept out by wave fronts, propagation speed, peak negative dV/dt, activation rate, multiplicity, reentry incidence, and number of reentry cycles were all smaller in the HF group than in the control group. The incidence of wave fronts that broke through to the epicardium or blocked within the mapped region and the core area of reentry were larger in the HF group. Univariate tests indicated that all these individual differences were significant.

**Discussion**

The main findings of the present study are as follows: (1) HF significantly increased the DFT. (2) An auxiliary shock to the LV from an electrode in the great cardiac vein significantly decreased the DFT during HF. In normal hearts, DFT voltage was slightly, but significantly, reduced by the auxiliary shock, but energy was not changed. (3) HF significantly changed all quantitative descriptors of activation during VF. VF in HF was slower and by many measures more organized, suggesting a decrease in tissue excitability and lengthened refractory period. By some measures, VF was less organized during HF, indicating that VF organization is not a single scalar quantity.

**Pacing-Induced HF in Dogs**

Incessant atrial or ventricular pacing in animals at rates $>220$ bpm reliably reproduces many of the hemodynamic, structural, and neurohumoral alterations seen in humans with HF. Myocytes isolated from animals with tachycardia-induced dilated cardiomyopathy consistently reveal abnormalities in repolarization similar to those in cells from failing human myocardium. Therefore, we used this animal model to investigate the quantitative changes in activation sequences during VF caused by HF and to determine the effect of HF on the DFT with transvenous electrodes.

**Left-Side Lead for Defibrillation in Failing Hearts**

DFT energy has been reported to be 4 times higher in HF dogs than in control dogs for monophasic shocks with epicardial electrodes, but it was not significantly increased for biphasic shocks with cutaneous electrodes. The present
study using biphasic waveforms and standard transvenous electrodes showed a more than doubling of DFT energy for dogs in HF.

There are at least 3 possible reasons why the DFT for transvenous shocks is elevated in HF: (1) VF activation patterns may have changed in such a way that wave fronts are more difficult to halt with a given strength shock. (2) Electrophysiological and anatomic changes at the myocyte and myofiber bundle level may increase the strength of the shock field needed to alter transmembrane potential sufficiently to defibrillate.9 (3) Geometric changes to the ventricular walls and chambers18,23 may alter the magnitude and distribution of the electric field in the heart. Specifically, the increased size of the heart and the change in shape from ellipsoidal to spherical could decrease the shock field in the lateral-apical LV, where the shock field is weakest in normal hearts for electrode configurations with an RV electrode.10 The first global activation front after shocks near the DFT arises in this region.8 The findings that HF increases the DFT for endocardial electrodes (which create an uneven shock field)10 but not for body surface electrodes22 (which probably create a relatively even shock field)24 suggest that geometric changes are primarily responsible for the elevated DFTs in the present study.

In a previous study, auxiliary shocks to the LV through the posterior cardiac vein in normal hearts reduced DFT energy by 62%.25 In the present study, the auxiliary shock did not change the energy DFT in normal hearts and reduced it by only 21% in failing hearts. The difference may be because the LV electrode in the present study was in the great cardiac vein, which may have been farther from the low gradient region than the LV electrode in the previous study. The difference may also be due to the different shock pulse configuration used in the previous study.

Quantitative Changes in VF Activation Caused by HF
Our quantification of VF activation patterns showed that VF in failing hearts is markedly different from that in normal hearts. All of the VF descriptors that we computed differed significantly between the 2 groups. Inspection of individual descriptors suggests that the electrophysiological substrate for VF is altered by HF, largely by a decrease in excitability. This is indicated by diminished peak dV/dt, activation rate, propagation velocity, and area swept out by wave fronts, by an increased incidence of wave fronts that block, and by the reentrant core area.26 An increased core area is also consistent with the prolonged action potential duration and refractory period that have been reported for failing hearts.19,21 Other disease states have also been shown to alter VF activation patterns. Damle et al27 have shown that subacute and chronic myocardial infarction increases the apparent size of wave fronts, decreases the activation rate, and decreases propagation velocity during VF.

As reported by us and others,17,28 reentry was uncommon in the mapped epicardium, involving 11% of wave fronts in the control group. Reentry was also short-lived, lasting an average of only 2.8 cycles. This paucity of reentry suggests that VF is maintained by only a few reentrant circuits distributed throughout the ventricular myocardium, that reentry is primarily in regions other than anterior RV and LV,29 or that most reentry is transmural, which cannot be detected by epicardial mapping. If the latter is true, our data indicate that in HF the balance between epicardial and transmural reentry is tipped even further toward transmural reentry. We found that in HF, reentry incidence was reduced to only 2% of wave fronts and that the lifetime of these circuits was even shorter than in control (1.8 cycles). Furthermore, the incidence of epicardial breakthrough/foci was increased, suggesting that wave fronts were more likely to travel perpendicular to the epicardium than parallel to it. Intramural recordings will be necessary to test these ideas.

It is intriguing that although most of the differences in VF descriptors are indicative of decreased VF complexity during HF (decreased wave fronts, multiplicity, and incidence of fractionation and collision), other descriptors suggest an increase in complexity (increased incidence of wave fronts

<table>
<thead>
<tr>
<th>TABLE 2. VF Activation Pattern Descriptors</th>
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<tbody>
<tr>
<td>Control</td>
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<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Wave fronts, n</td>
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<tr>
<td>Area swept out, mm²</td>
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<tr>
<td>Fractionation incidence</td>
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<tr>
<td>Collision incidence</td>
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<tr>
<td>Block incidence</td>
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<tr>
<td>Breakthrough/focal incidence</td>
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<tr>
<td>Multiplicity</td>
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<tr>
<td>Peak dV/dt, V/s</td>
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<tr>
<td>Activation rate, s⁻¹</td>
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<tr>
<td>Speed, m/s</td>
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<tr>
<td>Reentry incidence</td>
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<tr>
<td>Reentry cycles, n</td>
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<tr>
<td>Core area, mm²</td>
</tr>
</tbody>
</table>

Values are mean±SD.
that block and reduced area swept out by wave fronts). This emphasizes our previous finding\(^{15}\) that contrary to the implicit assumption of many previous investigations, the complexity of VF is not a simple scalar variable; rather, VF can exhibit complexity simultaneously in multiple ways that do not necessarily change concordantly.

**Study Limitations**

Many of the limitations of the present study are common to extracellular electrical mapping studies from epicardial arrays: (1) The array covered only 20% of the epicardium, so complete activation pathways could not be determined. (2) Because mapping was confined to the surface of the heart, intramural reentry could not be detected. (3) The clinical syndrome of HF may not always be well represented by 3 to 5 weeks of rapid pacing.

**Acknowledgments**

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**References**

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