

Stability of the Defibrillation Probability Curve with the Development of Ventricular Dysfunction in the Canine Rapid Paced Model

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FRIEDMAN, P.A., ET AL.: Stability of the Defibrillation Probability Curve with the Development of Ventricular Dysfunction in the Canine Rapid Paced Model. Most patients with implantable defibrillators have diminished cardiac function. Progressive heart failure might impair defibrillation efficacy, leading to interpreted device failure. This study sought to determine the effect of ventricular dysfunction on defibrillation energy using a biphasic endocardial system. Eleven dogs were ventricularly paced at 225 pulses/min for 2 weeks to induce ventricular dysfunction, and five control dogs remained unpaced. Dose response defibrillation probability curves were generated for each animal at baseline, after 2 weeks (at which time the pacemakers were turned off in the paced group), and then 1 week later. The defibrillation thresholds, ED_{20} , ED_{50} , and ED_{80} (the 20%, 50%, and 80% effective defibrillation energies, respectively) were determined for each dog at each study. In the paced dogs, the mean ejection fraction fell from 55% to 25% after pacing ($P < 0.0001$), and rose to 46% after its discontinuation ($P = 0.0002$). The defibrillation threshold, ED_{20} , ED_{50} , and ED_{80} remained unchanged in both the control and paced groups for all three studies, even after adjustment for dog weight or left ventricular mass. Rapid pacing produced no change in left ventricular mass. It induced ventricular cavity dilatation and wall thinning, which had opposing effects on defibrillation energy requirements, resulting in no net change of the ED_{50} in heart failure. In conclusion, the defibrillation efficacy of a biphasic transvenous system is not changed by the development of heart failure using the rapid paced canine model. (PACE 1998; 21:339-351)

ventricular fibrillation, electrical countershock, heart failure, canine model, defibrillation threshold, cardiomyopathy

Introduction

Since their first use in 1980, over 25,000 automatic implantable defibrillators have been placed in patients at high risk for sudden cardiac death.¹ National estimates indicate that up to 21,000 new patients per year may benefit from the devices under current implant guidelines.² Because a low ejection fraction is the single most significant risk factor for sudden death,³ it is not surprising that most patients who receive devices

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have poor cardiac function.⁴ Many of these patients experience a continuing decline in cardiac function after device implantation.⁴ The effect of heart failure on defibrillation efficacy, however, has not been well studied. Increases in the energy requirements of defibrillation due to progressive cardiac dysfunction could lead to interpreted device failure.⁵

Heart failure induced increases in the defibrillation threshold have been reported recently in a canine model using monophasic shocks and epicardial leads.⁵ However, newer systems utilize biphasic waveforms with endocardial leads because of their greater efficiency and decreased associated morbidity, respectively.⁶⁻⁸ Thus, the purpose of this study was to determine whether ventricular dysfunction would affect the energy requirements for defibrillation in a transvenous biphasic system. Because the

relative influence of cardiac geometry, function, and electrophysiological properties on defibrillation energy remains unsettled, these factors were analyzed. We chose the canine pacing induced heart failure model to study this question because it has been well characterized⁹⁻¹⁴ and it produces cardiac dysfunction in a predictable manner.

Methods

Twenty adult mongrel dogs weighing 21.5 ± 3.0 kg (mean \pm SD) were studied. Experimental dogs ($n = 13$) served as their own control in a crossover design, with experimental data obtained at baseline (study #1), after 2 weeks of rapid pacing (study #2), and 1 week after the discontinuation of pacing (study #3). To study the effects of the thoracotomy, the baseline studies were further divided into two groups (in a two by two factorial design)—an immediate group of dogs, that underwent defibrillation testing immediately postoperatively after pacemaker implantation (during the same anesthetic), and a delayed group allowed 48–72 hours recovery before defibrillation testing. The results of the immediate versus delayed testing are reported elsewhere.¹⁵ Although there was a transient increase in postoperative defibrillation energy requirements, the present findings were found to be valid regardless of whether the entire population or only the delayed baseline group was included in the analysis. Therefore, the data for the entire population are presented, except where explicitly stated.

For each study, left ventricular functional assessments, pacing thresholds, effective refractory period determinations, defibrillation threshold, and defibrillation dose response curve measurements were obtained. All dogs were allowed to eat and take water ad libidum throughout the study. Measurements of weight and respiratory rate were made at least 3 times per week; heart rate was checked daily in the paced dogs to ensure pacemaker capture.

Control dogs ($n = 7$) underwent all aspects of the protocol except rapid pacing (their pacemakers were programmed to VVI 30 pulses/min to inactivate them). This study was approved by the Institutional Animal Care and Use Committee at Mayo Clinic.

Surgical Preparation

The dogs were anesthetized with pentobarbital (30 mg/kg),¹⁶ intubated, and ventilated with oxygen enriched room air via a Harvard respirator (Harvard Apparatus, South Natick, MA, USA); for follow-up studies, paced dogs were anesthetized using 15 mg/kg to prevent excess hypotension. A subcutaneous arterial vascular access port for pressure monitoring during studies was placed in the left femoral artery via a cut-down approach.

A left anterolateral thoracotomy was performed at the fifth intercostal space and a single screw-in epicardial electrode (model #6917, Medtronic Inc., Minneapolis, MN, USA) was placed in the left ventricular free wall near the apical septum using care to avoid the coronary arteries. The end of this lead was tunneled subcutaneously to a pocket made in the high posterior thorax and attached to a specially modified single chamber, programmable unipolar pacemaker pulse generator capable of rapid pacing (Medtronic Inc.). A chest tube was inserted at the sixth intercostal space and connected to wall suction. The pleura and overlying fascial layers were then closed in succession using absorbable sutures, and the chest tube removed at the end of the closure.

After completion of the surgery, an active fixation lead containing distal tip and ring electrodes, capable of pacing and sensing and a defibrillation coil (Medtronic model #6966), was placed in the right ventricular apex under fluoroscopic guidance, via a right external jugular cutdown. The ends of the lead were tunneled subcutaneously to a pocket made in the low posterior cervical region. Subsequently, defibrillation testing was performed, as described below. At the end of each procedure the leads were capped and the pocket closed. All paced dogs were given 72 hours recovery before commencing pacing.

Defibrillation Threshold and Defibrillation Dose Response Measurements

Defibrillation testing was performed at the completion of the initial surgical procedure, after 2 weeks of rapid pacing at 220–225 pulses/min (depending on the specific pacemaker model), and 1 week following the discontinuation of pacing. In the rapid paced dogs, pacing was discon-

tinued just prior to induction of anesthesia at the 2-week session. The ends of the right ventricular defibrillation electrode were exteriorized and connected to an external defibrillation system (Medtronic model #2394) capable of delivering a programmable stored voltage. A printer module (Medtronic model #2394013) displayed the stored and delivered energy, voltage, and current, and the calculated impedance for each shock. The right ventricular defibrillation coil was the cathode (of the first phase) and a rectangular cutaneous patch (Cardiotronics, Carlsbad, CA, USA) placed on the left lateral chest wall was the anode for defibrillation. The patch was aligned with the thoracotomy scar to assure its identical placement during the three defibrillation testing sessions. Surface electrocardiographic leads and femoral arterial pressure were monitored on a portable oscilloscope (VMS-1, Physiocontrol, Redmond, WA, USA) and multichannel recorder (VR-16, Electronics for Medicine, Lenexa, KS, USA).

Fibrillation was induced via a 5-second burst of 60-Hz alternating current delivered through the distal tip and ring electrodes of the right ventricular catheter. All shocks were biphasic with equal leading edge voltages and with a fixed tilt of 65% for each phase. Shocks were delivered 10 seconds after the onset of alternating current. If a shock failed, a rescue shock was delivered from a precharged transthoracic defibrillator within 5 seconds; rescue shocks were not considered in the analysis. A minimum of 3 minutes was allowed between each episode of fibrillation.

The defibrillation threshold was determined using a modified step-down/step-up method.¹⁷ Starting at 400 V (12.4 J), successive shocks in 50-V decrements were delivered until failure to defibrillate occurred. The lowest successful energy was considered the step-down threshold. To find the starting point for the step-up threshold, the defibrillation voltage was decreased in additional 50-V steps, starting at 50 V below the last test shock delivered, until a second failure occurred. Fifty-volt increments were then tested; the first successful voltage while stepping upwards was the step-up defibrillation threshold. The step-down/step-up threshold was calculated by averaging the step-down and the step-up thresholds, and was used as the starting point for dose response measurements, described below. If the

first 400-V shock failed, the step-up threshold was found first. Then, additional 50-V increments were tested, starting at 50 V above the last test shock delivered, until a second success occurred, which defined the starting point for the step-down defibrillation threshold. This was then determined as described above.

For each dog the defibrillation dose response relationship was determined by testing defibrillation voltages at the: threshold -40%; threshold -20%; threshold; threshold + 20%; and threshold +40%, each five times (for a total of 25 additional episodes of fibrillation), in a balanced, random order. These were then analyzed, in conjunction with the shocks used in the defibrillation threshold determinations, to find the 20%, 50%, and 80% effective energy doses (the ED₂₀, ED₅₀, and ED₈₀, respectively), for each dog as described in the analysis section below. Figure 1 depicts a defibrillation dose response curve for one animal, illustrating an increasing probability of successful defibrillation with increasing energy.

Sodium, potassium, and arterial blood gas measurements were made at the initiation of anesthesia and serially every 30–45 minutes thereafter during defibrillation testing. All metabolic and electrolyte abnormalities were corrected by adjustment of respiratory parameters or via supplemental intravenous crystalloid, as needed.

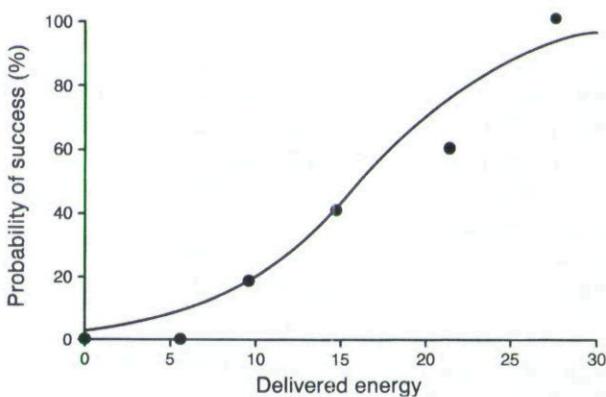


Figure 1. Actual dose response curve from a test animal, with defibrillation threshold equal to 15 J. The black circles represent the actual percentage of successful shocks at the energies shown.

Radionuclide Ventriculography

Using 0.5-cc pyrophosphate and 15 mCi Tc 99 to label erythrocytes in vivo, ECG gated radionuclide ventriculograms were obtained to measure ejection fraction prior to defibrillation testing. In paced animals, pacing was discontinued immediately prior to acquiring data. All studies were performed with the animals lightly sedated with 0.5- to 1.0-cc Torbugesic.

Echocardiography

From dog #7 onwards, all dogs (10 paced and 4 control animals) underwent echocardiography to assess their left ventricular size and function. After induction of general anesthesia, two-dimensional and M mode short-axis images were recorded on videotape. Using a Cardiology Workstation (Freeland, Broomfield, CO, USA) the endocardial contours were traced in systole and diastole to calculate the ejection fraction. Also, the left ventricular mass was calculated using the method of Devereux and associates,¹⁸ and the ejection fraction was calculated using the method described by Quinones et al.^{19,20} The average of the two-dimensional and M-mode ejection fraction was used in the analysis, to improve precision (unpublished analysis). All measurements were reviewed by a cardiologist blinded to the animal's group and status.

Hemodynamic Measurements

Heart rate, arterial blood pressure, right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output were recorded. Cardiac output measurements were obtained after the pacemakers were inhibited by triplicate injection of 5-mL saline, with plotting of the thermodilution decay curves to ensure adequate mixing.

Measurements of Excitability and Refractoriness

The pacing threshold (measure of excitability) and impedance at pulse width 0.5 ms using the tip (cathode) and ring (anode) of the right ventricular intracardiac lead was measured prior to each defibrillation threshold testing study, with the dog anesthetized. The effective refractory period of the ventricle at pacing cycle length 300 ms

with an eight-beat drive train at twice late diastolic threshold was measured before and after defibrillation testing.

Statistical Analysis

Best fit sigmoidal defibrillation probability curves were generated using the logistic regression, where the probability of success is given by:

$$\text{Success} = \frac{1}{1 + e^{-(ax + b)}}$$

where e is the base of the natural logarithm (2.718); x is the shock energy; a is the slope; and b the intercept of the logistic equation that is unique for each animal; and

$$ED_n = \frac{-\ln(1 - n)}{a}$$

where $n = 0.2, 0.5$, or 0.8 to give an expression for the energy that has a likelihood of successful defibrillation 20%, 50%, or 80% of the time, respectively.

A two-way ANOVA, with repeated measures in one factor was used to analyze the effects of pacing (vs control) on the effective refractory period, ejection fraction, left ventricular dimensions, defibrillation energy, pacing threshold, and impedance determinations. Posthoc pairwise comparisons using the Student's *t*-test were performed only when the ANOVA demonstrated a significant difference among the means. A multiple regression model was used to explore the relationship between ED_{50} and ejection fraction, left ventricular cavity size, wall thickness, mass, effective refractory period, and right ventricular pacing threshold and impedance. Results are presented as mean \pm SD; error bars in graphs represent SD. Results with a $P < 0.05$ were considered significant; a Bonferroni's inequality adjustment was used when multiple comparisons were made to determine significance. The SAS program (SAS Institute Inc., Cary, NC, USA) was used to determine the logistic coefficients. All other analyses were performed using the Statview 4.0 statistical software (Abacus, Berkeley, CA, USA).

Results

Data from two dogs in the control group were not available for analysis: one due to equipment

failure (dog #1) and the other due to postoperative complications resulting in death (dog #9). Complete defibrillation data from two dogs in the paced group were not available: one dog died during induction of anesthesia for study #2 (dog #4); and the other died of a spontaneous ventricular arrhythmia during testing at study #2 (dog #5). Dog #14 suffered cerebral ischemia after the 2-week study and was subsequently euthanized, so provides no data for study #3. Therefore, data from 11 paced (including dog #14) and 5 control dogs were available for analysis. Due to technical difficulties, radionuclide ventriculograms were not consistently available after dog #9; therefore, the echocardiographic data were used in these cases. In all dogs, complete data were available from either the echocardiograms or the ventriculograms, and in no case was ventriculographic data compared to echocardiographic data in an analysis.

Cardiac Function

Rapid pacing led to a marked decrease in ejection fraction, that was not seen in the control group (Fig. 2). At baseline, the paced and control group's ejection fractions were not different. The ejection fraction of the control group did not significantly change throughout the protocol. In contrast, the paced group's ejection fraction fell from the baseline value of $52.3\% \pm 7.2\%$ to $26.3\% \pm 10.4\%$ in study #2 ($P < 0.001$). After discontinuation of pacing, the mean ejection fraction rose to $44.3\% \pm 11.0\%$, which was higher than the heart failure ejection fraction ($P = 0.005$), and lower than the baseline ejection fraction ($P = 0.01$).

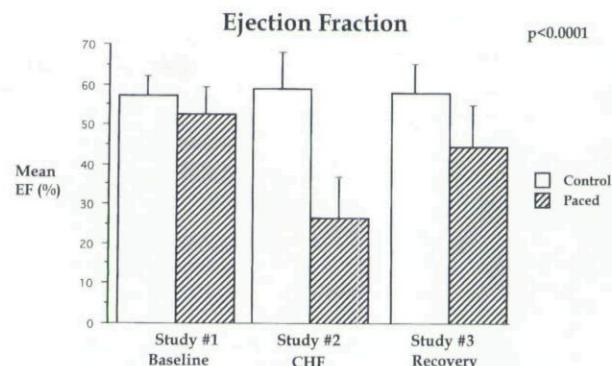


Figure 2. Ejection fraction found in the paced and control dogs at each of the three studies. There was no difference between groups at baseline, and the control group's ejection fraction remained unchanged throughout the study. Rapid pacing led to a significant decrease in ejection fraction, which partially recovered after discontinuation of pacing. P value is for overall ANOVA. See text for details.

The effects of rapid pacing on left ventricular wall thickness, cavity dimensions, and mass are summarized in Table I. Rapid pacing led to significant left ventricular dilatation. This cardiac dilatation was associated with thinning of the posterior and septal ventricular walls in both systole and diastole. Both the enlargement and wall thinning partially recovered after pacing was discontinued, as shown in Table I. Although the left ventricle enlarged, due to the concomitant thinning of the chamber walls, there was no net change in the echocardiographically determined mass. There were no significant changes in ventricular size, wall thickness, or mass in the control group.

Table I.
Left Ventricular Cavity Size, Wall Thickness, and Mass in the Paced Group

Paced Group	Baseline Study #1	CHF Study #2	Recovery Study #3	Study #1 vs Study #2 P Value
VS (mm)	8.9 ± 1.4	6.7 ± 1.3	7.5 ± 0.5	0.008
PW (mm)	9.1 ± 1.4	6.6 ± 1.6	8.1 ± 1.3	0.006
LVEDD (mm)	40 ± 4.3	46 ± 5.5	41 ± 4.6	0.015
LV Mass (g)	113.8 ± 31.4	94.4 ± 20.0	95.8 ± 25.5	0.33

LV mass = left ventricular mass; LVEDD = left ventricular end diastolic volume; PW = posterior wall; VS = ventricular septum.

Table II.
Hemodynamic Changes in the Paced Group

Paced Group	Baseline Study #1	CHF Study #2	Recovery Study #3
SBP (mmHg)	150.9 ± 19.3	130.9 ± 12.7	157.6 ± 15.5 ⁺⁺
DBP (mmHg)	103.3 ± 13.5	81.0 ± 7.2 ⁺	97.9 ± 14.7 ⁺
HR (bpm)	129.4 ± 32.1	90.7 ± 16.4 ⁺⁺	75.7 ± 22.0

⁺ P < 0.01 compared to the preceding study; ⁺⁺ P < 0.001 compared to the preceding study; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Heart failure led to decreases in systolic, diastolic, and mean blood pressures, and to a decrease in heart rate (measured during anesthesia), as summarized in Table II. These changes were not seen in the control group. There were no significant changes in cardiac output, and pulmonary artery systolic or wedge pressures for either the paced or the control groups, although the heart rate at the time of these measurements varied from 53–194 beats/min. Additionally, there was no difference in dog weight or serum sodium levels in either the paced or control groups throughout the study.

Electrophysiological Function

Defibrillation Energy

Heart failure did not affect the energy required for defibrillation as measured by the defibrillation threshold (Table IIIA). This was found to

be true regardless of whether the step-down/step-up method was used (P = 0.88 for the overall ANOVA) or whether the step-down method alone (substituting the step-up method alone for those dogs in which the first shock failed) was used (P = 0.73). For the paced dogs, the mean defibrillation threshold using the step-down method was 16.0 ± 1.2 J at baseline, 14.8 ± 0.6 J after 2 weeks of rapid pacing, and 14.4 ± 2.4 J at study #3. Similarly, there was no significant change in any measure of defibrillation energy in the control dogs (Tables IIIB and IIIC).

For each dog, the dose response curve was plotted by fitting the data to the logistic regression, and the ED₂₀, the ED₅₀, and the ED₈₀ were calculated. A representative curve is shown in Figure 1. As with the defibrillation threshold, there was no significant change in ED₅₀ between any of the studies in either group, and there was no difference between groups at any study (P =

Table IIIA.
Measures of Defibrillation Energy in the Paced Group at All Three Studies

Paced Group	Baseline Study #1	CHF Study #2	Recovery Study #3
ED ₂₀ (J)	9.9 ± 6.8	8.7 ± 3.8	10.9 ± 10.2
ED ₅₀ (J)	17.6 ± 8.5	15.5 ± 6.8	19.5 ± 14.5
ED ₈₀ (J)	26.1 ± 10.3	22.6 ± 10.6	28.8 ± 20.2
ED ₅₀ /LV _{Mass} (J/g)	.14 ± .06	.17 ± .07	.22 ± .12
DFT _{SDTF} (J)	16.0 ± 1.2	14.8 ± 0.6	14.4 ± 2.4

P = NS for each measure of energy; ED₂₀ = energy dose with 20% defibrillation success rate; ED₅₀ = energy dose with 50% defibrillation success rate; ED₈₀ = energy dose with 80% defibrillation success rate; ED₅₀/LV_{Mass} = ED₅₀ ÷ left ventricular mass; DFT_{SDTF} = step-down to failure DFT.

Table IIIB.

Measures of Defibrillation Energy in the Control Group at All Three Studies

Control Group	Baseline Study #1	CHF Study #2	Recovery Study #3
ED ₂₀ (J)	17.9 ± 13.9	10.3 ± 6.9	8.0 ± 3.9
ED ₅₀ (J)	24.5 ± 18.0	16.6 ± 8.0	17.9 ± 9.3
ED ₈₀ (J)	31.1 ± 22.1	23.1 ± 9.0	27.8 ± 15.6
ED _{50/LV_{Mass}} (J/g)	.38 ± .11	.25 ± .08	.25 ± .06
DFT _{SDTF} (J)	18.1 ± 4.3	13.2 ± 1.2	12.5 ± 1.4

P = NS for each measure of energy; ED₂₀ = energy dose with 20% defibrillation success rate; ED₅₀ = energy dose with 50% defibrillation success rate; ED₈₀ = energy dose with 80% defibrillation success rate; ED_{50/LV_{Mass}} = ED₅₀ ÷ left ventricular mass; DFT_{SDTF} = step-down to failure DFT.

0.3 for the overall ANOVA). In Figure 3, the mean delivered ED₅₀ is plotted for both groups over the three studies, illustrating this point. Similarly, an analysis of ED₅₀/kg dog weight and the ED₅₀/left ventricular mass showed no difference between the paced and control groups across any of the studies. Because it is possible that heart failure might cause a change in the slope of the defibrillation probability curve without shifting its mid-point (that is, the ED₅₀ might remain the same, but the distance from the ED₂₀ to the ED₈₀ could change), the ED₂₀ and ED₈₀ were also analyzed. As with the case for the ED₅₀, there was no significant change in ED₂₀ or ED₈₀ in any

study for both the paced and control groups. These data are summarized in Tables IIIA and IIIB.

A power calculation was done to determine the significance of the negative result found. The power (1-β) to detect a four-fold increase in defibrillation energy (as has been reported in epicardial, monophasic systems⁵) was > 99% (using alpha = 0.05), even when limiting the analysis to the delayed baseline defibrillation group (n = 6). Using a power of 90% (1-β = 0.90, alpha = 0.05), differences in the ED₅₀ of 5 J or greater (or a 29% change from the baseline ED₅₀ of 17 J) could have been detected, had they existed.

Table IIIC.

Measures of Defibrillation Energy in the Control Group at All Three Studies (as in Table IIIB), but Limited to Only Those Animals in the Delayed Baseline Group. Note that the Apparent Elevation in the Baseline Values is No Longer Present when the Animals Tested Immediately Post-thoracotomy are Excluded

Control Group	Baseline Study #1	CHF Study #2	Recovery Study #3
ED ₂₀ (J)	9.9 ± 9.0	8.5 ± 7.8	6.9 ± 3.5
ED ₅₀ (J)	13.9 ± 10.9	14.2 ± 8.5	16.6 ± 12.2
ED ₈₀ (J)	18.0 ± 12.9	20.3 ± 9.0	26.2 ± 21.3
ED _{50/LV_{Mass}} (J/g)	.26	.22	.23
DFT _{SDTF} (J)	11.8 ± 1.4	12.5 ± 0.9	11.8 ± 0.6

P = NS for each measure of energy; ED₂₀ = energy dose with 20% defibrillation success rate; ED₅₀ = energy dose with 50% defibrillation success rate; ED₈₀ = energy dose with 80% defibrillation success rate; ED_{50/LV_{Mass}} = ED₅₀ ÷ left ventricular mass; DFT_{SDTF} = step-down to failure DFT.

Defibrillation Impedance

The impedance measured across the defibrillation electrodes while delivering shocks was calculated. Comparing the impedance measured with the first shock in a defibrillation experiment to the impedance of the last shock in the same experiment revealed a $4.5 \pm 4.4 \Omega$ drop from $78.9 \pm 10.3 \Omega$ to $74.4 \pm 11.0 \Omega$ ($P < 0.0001$). This difference was found for both the paced and control groups. Since there was a change in the impedance after repeated shocks, a comparison between groups using only the impedance of the first shock in an experiment was done.^{21,22} For the paced group, the mean impedance measured $76.5 \pm 9.5 \Omega$, $74.6 \pm 6.2 \Omega$, and $78.2 \pm 7.1 \Omega$ at baseline, after pacing, and after recovery, respectively. Similarly, in the control group, the impedances measured $79.3 \pm 15.5 \Omega$, $80.2 \pm 9.1 \Omega$, and $85.0 \pm 11.0 \Omega$ for study #1, study #2, and study #3, respectively. There was no significant difference across repeated studies or between groups (overall ANOVA $P = 0.7$).

Refractoriness and Excitability

There was a significant prolongation in the effective refractory period in the paced dogs (from 152.4 ± 23.7 ms to 170.3 ± 12.7 ms, $P < 0.003$) that was not found in the control dogs. In both control and paced groups there was no significant difference in the mean effective refractory period done before and after the same study, suggesting intraexperimental stability.

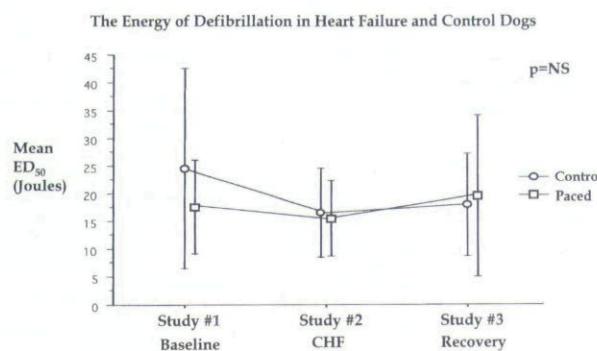


Figure 3. The mean delivered ED_{50} is plotted for each separate study. There is no change in the ED_{50} in either the paced or the control groups over any of the three studies.

The pacing threshold measured from the right ventricular lead increased significantly in both paced and control dogs from 0.9 ± 0.6 V to 3.4 ± 1.4 V ($P < 0.001$) for both groups combined. There was no significant difference in right ventricular threshold between the paced and control groups for any study. Similarly, the pacing impedance measured between the tip and the ring of the right ventricular lead significantly decreased in both paced and control dogs from a mean of $781 \pm 242 \Omega$ at study #1 to $588 \pm 44 \Omega$ at study #2 ($P = 0.002$). There was no significant difference in mean pacing impedance between the paced and control groups for the baseline or for the follow-up studies.

Predictors of Defibrillation Energy Requirement

In order to explore the relationship between the energy required for defibrillation and the ejection fraction, left ventricular geometry and cardiac electrophysiological properties, a multiple regression model was developed using ED_{50} as the dependent variable (overall significance $P < 0.0001$, $r = 0.88$). The results of the regression analysis are shown in Table IV.

The regression models predicted that defibrillation energy should decrease with decreasing posterior wall thickness, increase with increasing cavity size, and increase with mass. The mean left

Table IV.
Determinants of Defibrillation Energy Requirements:
Multiple Regression Analysis
(with ED_{50} as Dependent Variable)

Independent Variable	Coefficient	P Value
RV Impedance	$0.014 \text{ J}/\Omega$	<0.05
PW _{thickness}	$1.96 \text{ J}/\text{mm}$	<0.05
LVEDD	$-2.52 \text{ J}/\text{mm}$	<0.01
LVESD	$+1.62 \text{ J}/\text{mm}$	0.01
LV Mass	$0.215 \text{ J}/\text{g}$	<0.05
Pacing Threshold		NS
Ejection Fraction		NS
ERP		NS
Shock Impedance		NS

ERP = effective refractory period; LVEDD = left ventricular end diastolic dimension; LVESD = left ventricular end systolic dimension; NS = not significant; PW_{thickness} = posterior wall thickness; RV impedance = right ventricular pacing impedance.

ventricular mass did not change in this experiment. The mean thinning of the ventricular walls found after rapid pacing predicted a decrease in ED₅₀ of 4.9 J. However, the mean increase in ventricular cavity size induced by rapid pacing predicted an increase in ED₅₀ of 4.3 J. The two morphological changes produced by rapid pacing, left ventricular cavity dilatation and wall thinning, had opposing effects on defibrillation energy, so that there was no significant net change in the ED₅₀ in heart failure predicted by this model.

Last, as shown in Table IV, the ejection fraction, effective refractory period, pacing threshold, and shock impedance were not associated with the ED₅₀.

Discussion

Major Findings

The energy needed to defibrillate with a biphasic nonthoracotomy system was unchanged in a canine pacing induced dilated cardiomyopathy model. Rapid ventricular pacing led to left ventricular cavity enlargement, which by itself, increased the energy needed to defibrillate, according to a multiple regression analysis. The effect of this structural change was opposed by the concomitant thinning of the left ventricular walls, which, by an equal amount, reduced the energy needed to defibrillate. Consequently, no net change was observed in the energy needed to defibrillate in this dilated cardiomyopathy model compared to baseline or to controls, using biphasic endocardial shocks. Left ventricular mass did not change with rapid pacing, but was found that to be directly associated with the energy needed to defibrillate, so that dogs with an initially greater left ventricular mass had a higher predicted ED₅₀, other factors being equal. Ejection fraction was not associated with defibrillation energy in this heart failure model.

Defibrillation Energy Requirements in Heart Failure

Quantifying the effect of heart failure on defibrillation energy has been limited by the complexity of the structural, geometric, and neurohormonal derangements of heart failure, and by the difficulty in determining the impact that each of

these may have upon defibrillation. Numerous authors have investigated the effects of left ventricular cavity dimension on the energy requirements of defibrillation with contradictory results.²³⁻²⁶ Similarly, the relationships between ejection fraction and defibrillation energy,^{8,24,27} and between increasing left ventricular mass and defibrillation energy^{23,24,27,28} have been explored with conflicting findings.

In a study designed to specifically assess whether heart failure affects defibrillation energy, Lucy et al.⁵ used a canine rapid paced model similar to that used in the present study, but with a monophasic epicardial defibrillation system. Six paced dogs (240 pulses/min) had significant reductions in cardiac output and increases in plasma norepinephrine levels after 17 days, compared to seven control dogs. As in the present study, moderate heart failure was induced, with depression of cardiac function to approximately 50% of baseline, and no change in mean animal weight or sodium levels. The mean defibrillation threshold of the paced group, however, at the end of the 17 days, was four times greater than that of the control group. The postmortem weight of the paced left ventricles was significantly greater than that of the control ventricles.

As in the present study, Lucy et al.⁵ found a significant correlation between left ventricular mass and defibrillation energy. However, unlike the present and other studies,^{10,12,29-34} which have reported ventricular dilatation and wall thinning with no change in mass after rapid pacing, Lucy et al.⁵ found an increased left ventricular mass in the paced group compared to the control group. This increase in mass may be critical in explaining the elevation in defibrillation threshold found by Lucy et al.⁵ in the paced group, that was not found in the present study. Of note, Lucy et al.⁵ did not record the baseline left ventricular mass, and the paced group had a significantly greater mean body weight than the control group ($P < 0.05$). Thus, some of the difference in ventricular mass may have existed before rapid pacing commenced, although the authors note that the ventricular weight-to-body weight ratio was elevated in the paced dogs above that of the control dogs. Similarly, as baseline defibrillation thresholds were not measured, it is possible that some of the difference in threshold between the

two groups of dogs may have existed at baseline, especially in light of the groups' different mean body weights.

Differential Effect on Waveform/Lead System

Differences in shock waveform and lead system may have, in part, accounted for the difference in the findings of the study by Lucy et al.⁵ and the present report. Biphasic waveforms have been demonstrated to require 35%–45% less energy to defibrillate than monophasic waveforms,^{6,35,36} and consequently may be less affected by the pathophysiological changes of heart failure. This may result since a decrease in the potential gradient across a segment myocardium as a consequence of ventricular cavity enlargement might cause failure to defibrillate with the less effective monophasic waveform, whereas the diminished gradient is still adequate with the more efficient biphasic waveform. Alternatively, a given monophasic gradient may cease to be effective due to cellular aberrations that occur in heart failure, even though the gradient itself is not diminished; this may simply not hold true for biphasic waveforms.

Epicardial and endocardial lead systems may be differentially affected by heart failure. Epicardial lead systems, such as those used by Lucy et al.,⁵ have been shown to distribute the defibrillating electric field more homogeneously over the myocardium, and thus require less energy, than endocardial-based systems.^{36,37} Based on available data, one would predict that these more efficient systems would be less susceptible to the geometric changes induced by heart failure than endocardial systems, such as the system used in the present study. Thus, it seems unlikely that the increased energy of defibrillation reported by Lucy et al.⁵ and not found in the present study resulted from the lead system used, though only a direct comparison of lead systems would determine whether this holds true.

Rapid Paced Canine Cardiomyopathy Model

The finding that rapid ventricular pacing led to diminished cardiac function, ventricular enlargement, and wall thinning with no change in ventricular mass agrees with previous descriptions of this model.^{10,12,29–34} Recovery of systolic

function within 48 hours of discontinuing rapid pacing, with persistence of diastolic dysfunction has also been reported.^{11,31} We found marked but incomplete recovery of ejection fraction 1 week after discontinuing pacing. The approximately 15 mmHg decrease in mean arterial pressure we found is similar to that previously reported for this model¹⁰; the decrease in heart rate we found has been reported by some,^{10,32} but not other³¹ investigators, and may in part have been due to the measurement of hemodynamic variables during general anesthesia. The absence of statistically significant changes in cardiac output and pulmonary capillary wedge pressure we reported may have been due to large variances in these values due to the marked differences in heart rate at the time of their measurement; other investigators have recorded these values while pacing in order to control for this. In the present study there was no change in dog body weight or sodium levels. This may have reflected the moderate degree heart failure induced, or may have been due the anorexia associated with this heart failure model.^{11,32} In the study by Armstrong et al.¹⁰ a group of dogs paced at 250 pulses/min for 3 weeks developed significant cardiac dysfunction, cardiac enlargement, and elevated plasma norepinephrine levels, but no change in body weight; a second group paced for a mean of 5.3 weeks developed clinical ascites and increased body weight, in addition to the other abnormalities.

The electrophysiological characteristics of the rapid paced canine heart failure model have not been previously reported. We found that heart failure produced no change in defibrillation energy requirements or in defibrillation impedance. The effective refractory period significantly prolonged after rapid pacing (from 152.4 ± 23.7 ms to 170.3 ± 12.7 ms, $P < 0.003$), and did not significantly recover 1 week after the discontinuation of pacing (164 ± 14.4 ms). This raises the question of whether the persistence of a prolonged effective refractory period after the discontinuation of pacing is associated with diastolic dysfunction, which also persists postpacing. Acute and chronic pacing thresholds and impedances were not influenced by the development of heart failure, and were similar in the paced and control dogs.

Limitations

Some dogs in the study received echocardiograms while others received radionuclide ventriculograms. However, a close correlation ($r = 0.80$, $P < 0.0001$) was found between the two methods of assessing left ventricular function, and for any given dog, the same modality was used for all three experiments.

Paced dogs received a lower dose of pentobarbital at follow-up studies, possibly affecting defibrillation thresholds. However, although the dose differed, the same level of anesthesia was used in all studies; after 2 weeks of rapid pacing, the animals were exquisitely sensitive to pentobarbital. The initial use of 30 mg/kg (baseline dose) at a follow-up study resulted in extreme hypotension and death at induction, prompting the change in dosage. Additionally, Babbs has demonstrated in awake and anesthetized dogs that pentobarbital does not alter the defibrillation threshold, acutely or chronically.¹⁶ The results found may have been influenced by the lead system used, a configuration not frequently used in clinical practice today. Nonetheless, basic insights into defibrillation mechanisms can be gleaned from the experimental system.

In order to limit the animal mortality associated with multiple ventricular fibrillation episodes, only moderate congestive heart failure was induced. It is possible that different results would have been obtained had a greater degree of heart failure been present. As stated above, however, the degree of heart failure induced was similar to that in the study by Lucy et al.⁵ which had markedly different results. We used a dilated cardiomyopathy model; these results may not be applicable to patients whose ventricular dysfunction

is due to coronary artery disease. There may also be important differences between the canine paced model of cardiomyopathy and human cardiomyopathies. Pressure overload cardiomyopathies are characterized by concentric hypertrophy, with increased wall thickness and little change in cavity size^{38,39}; ischemic cardiomyopathies may have reactive hypertrophy with remodeling^{40,41}; and dilated cardiomyopathies may have eccentric hypertrophy with both left ventricular cavity enlargement and increased wall thickness (and thus, a greater ventricular mass).^{39,42-44}

Conclusion

The energy required for defibrillation using a biphasic shock waveform is unchanged by congestive heart failure in this rapid paced canine dilated cardiomyopathy model. This was found regardless of whether the defibrillation threshold or the dose response curve was utilized to assess defibrillation energy. The direct relationship between ventricular mass and defibrillation energy that was found corroborates anecdotal observations of higher defibrillation thresholds in patients with hypertrophic cardiomyopathies. Further studies to assess the impact on defibrillation energy of other forms of heart failure, especially those characterized by ischemic injury and increased mass, are needed. An understanding of the factors that affect defibrillation energy requirements is essential to successfully treating patients at high risk for VF, and may lead, in the near future, to universally successful defibrillator implantation.

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