Adrenergically mediated variations in the energy required to defibrillate the heart: observations in closed-chest, nonanesthetized dogs*

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ABSTRACT The day-to-day variations in epicardial defibrillation threshold (DFT) were examined in closed-chest, unanesthetized dogs. In 11 animals, DFT decreased from 15.8 ± 2.1 J (mean ± SE) at the beginning of the study (day 1), to 7.4 ± 1.7 J on day 2 (p < .0001). DFT measured daily for 5 consecutive days in seven dogs decreased from 22.1 ± 3.1 J on day 1 to 9.3 ± 2.3 J on day 2 (p < .01) and remained stable from day 2 to day 5. Transcardiac impedance, measured in six dogs, decreased from 112 ± 6 Ω on day 1 to 100 ± 6 Ω on day 2 (p = NS). Propranolol given on day 2 in 14 dogs increased DFT from 12.0 ± 2.2 to 18.0 ± 3.1 J (p < .05). The effects on DFT of sequential administration of isoproterenol and propranolol were examined in 10 dogs. Isoproterenol decreased DFT from 10.0 ± 1.9 to 5.5 ± 1.5 J when given before propranolol (p < .001, n = 10), and from 11.7 ± 3.0 to 9.7 ± 3.1 J when given after propranolol (p < .05, n = 9). Propranolol increased DFT from 10.6 ± 3.0 to 14.6 ± 3.9 J when given before isoproterenol (p < .02, n = 9), and from 10.7 ± 1.4 to 14.4 ± 1.5 J when given after isoproterenol (p < .01, n = 10). These experiments demonstrate a sustained cardiac effect of epicardial defibrillation reflected by a decrease in DFT that is partially reversible by propranolol. A similar decrease was produced by β-adrenergic stimulation, an effect that was partially blocked by propranolol. Thus, variations in the autonomic state of the heart may be an important modulator of cardiac DFT. These findings, however, are experimental, and do not support the use of isoproterenol alone in traditional clinical defibrillation.


THE DEVELOPMENT of an implantable device for automatic defibrillation of the human heart has spurred research efforts to identify factors that may facilitate or hamper direct ventricular defibrillation. The effects of some antiarrhythmic drugs,1 as well as those of myocardi al ischemia, metabolic abnormalities, acid base disorders, and ventricular hypertrophy, on defibrillation threshold (DFT) have been studied.2–4 Recently, we reported the effects of β-adrenergic stimulation and blockade on the energy required to defibrillate the hearts of open-chest anesthetized dogs.5 This study extends these initial observations to a closed-chest, nonanesthetized preparation, and examines the pattern of DFT measurements repeated daily over several days.

Material and methods

Dogs weighing between 11 and 19 kg were anesthetized with 22.5 mg/kg pentobarbital and ventilated with a Harvard respirator using room air. A left thoracotomy was performed on each, and the left ventricular free wall was exposed. A 2.5 cm diameter cupped electrode (Parsonnet Porous Epicardial Electrode) was sutured on the anteroseptal surface of the left ventricle, and its cable was extended through the rib cage and tunneled under the skin onto the left infrascapular area. The thoracotomy was closed in layers, the skin was sutured, and the dogs were taken back to their cages. Several days after thoracotomy, and after the dogs’ complete recovery from the operation, experiments were begun. Each animal was sedated with 2.25 mg/kg subcutaneous morphine sulfate and placed on a rubber thermal blanket to prevent current leakage. This amount of morphine sulfate produced enough sedation to allow placement of the dogs on their sides, loosely restrained, for the duration of the experiment. The animals, however, were awake, responsive, and did not require respiratory support. Standard electrodes were placed for continuous monitoring of the surface electrocardiogram. The electrocardiographic signals were displayed and recorded on a VR-12 Electronics For Medicine instrument.
After each animal was given local anesthesia (1% lidocaine), a jugular vein was isolated and a No. 10F catheter electrode designed for cardioversion and defibrillation (Medtronic No. 6880) was introduced into the central venous circulation. The catheter has two pairs of stainless steel electrodes that have a surface area of 2.5 cm² per pair. One pair of electrodes is situated near the tip of the catheter (distal pair), and the other pair is located 150 mm proximally (proximal pair). The electrodes of each pair are separated by 5 mm. The distal pair of electrodes was connected to a Medtronic 323L programmable stimulator, programmed to overdrive the dog's spontaneous rhythm.

The entire length of the catheter, except for its most distal 2 to 3 cm, was kept rigid with a stylus, and the electrode was advanced into the right ventricle with the help of continuous electrocardiographic monitoring. Proper placement of the electrode was accomplished when consistent 1:1 ventricular pacing with left bundle branch block morphology was achieved with a pulse current delivery of less than 10 mA. The stylus was then removed, the catheter was sutured in place at the jugular level, and the proximal pair of defibrillating electrodes, situated in the superior vena cava, was connected to the defibrillating unit to constitute the anode. Next, a 30 cm, 16 gauge cannula was inserted in the jugular vein, alongside the electrode catheter, and sutured in place for injection of pharmacologic agents. Finally, with the animal given local anesthesia (1% lidocaine), an incision was made in the left infrasacral area, and the proximal end of the epicardial electrode was isolated and connected to the defibrillator to constitute the cathode.

Ventricular fibrillation was induced by high-rate stimulation of the right ventricular apex with 20 mA bipolar stimuli delivered by the programmable stimulator.

**Determination of DFT.** Twenty seconds after the onset of ventricular fibrillation, attempts to defibrillate were begun. This 20 sec period of ventricular fibrillation resulted in the dogs' complete loss of consciousness, thereby preventing their perception of the shocks. Each attempt consisted of up to three shocks delivered by the epicardial-intravascular system and, if defibrillation was not accomplished, by a transthoracic direct-current shock, of an energy between 10 and 50 J. The first shock of the very first attempt had an arbitrarily chosen energy of 15 J which was increased in increments of 5 J if ventricular fibrillation persisted. The energy of the shocks delivered on subsequent attempts at defibrillation was chosen according to the results of the previous attempt. When ventricular fibrillation had been successfully terminated by the implanted system, the energy of the first shock of the next attempt was set at a value 3 J below that of the successful shock. Each attempt was followed by 5 min of recovery. By repeating the attempts systematically, a threshold for defibrillation was determined to the nearest joule. Only the first shock of each attempt was considered for threshold determination and, in each case, the lowest effective value was confirmed by a subsequent attempt. Table 1 illustrates the typical steps followed for the determination of DFT.

**Measurement of transcardiac impedance.** The output of the defibrillator was connected with the two defibrillating electrodes in series with a 1 Ω precision resistor. The voltages across the animal's heart and the 1 Ω resistor (Vout), and across the 1 Ω resistor alone (VR) were measured by displaying the waveforms on a storage oscilloscope. The defibrillator and the oscilloscope were both isolated from ground through an isolator-transformer. The impedance of the animal's heart was calculated as:

\[
\frac{\text{Vout}}{\text{VR}} = 1, \text{since } I = \frac{\text{Vout}}{\text{VR}}
\]

**Study protocols.** The three following groups of experiments were performed.

**Group I.** Group IA consisted of 11 dogs in which DFT was determined on 2 consecutive days, and seven in which determinations were made daily for 5 consecutive days. Group IB consisted of six additional dogs in which DFT and transcatheter impedance were measured on 2 consecutive days. In addition, the possible influence on DFT of the lidocaine used for local anesthesia was examined by the measurement of the serum lidocaine levels in four of these dogs at the time of baseline DFT determination on day 1.

**Group II.** In 14 dogs, DFT was measured on 2 consecutive days and, on day 2, after determination of DFT at baseline, 0.2 to 0.6 mg/kg propranolol was administered intravenously over 2 min; the determinations were then repeated, starting 5 min after the end of the injection.

**Group III.** In 10 dogs DFT was measured before and during sequential intravenous administration of isoproterenol and propranolol hydrochloride. In group IIIA, after baseline determination of DFT, a continuous drip of isoproterenol (4 to 8 μg/min) was begun, and a 50 to 100 μg intravenous bolus was administered. Adequate β-adrenergic stimulation was considered present when the heart rate had increased by at least 50% above the predrug value. Ventricular fibrillation was reinduced at the time of peak effect, and further attempts to determine DFT were made. When the effect of isoproterenol on heart rate was dissipating, additional 50 to 100 μg boluses were given before the attempts. After the new DFT was determined, the isoproterenol drip was discontinued. Shock attempts were repeated thereafter every 10 to 15 min until return of the DFT to or toward control values. Propranolol, 0.2 to 0.6 mg/kg, was then administered as an intravenous bolus over 2 min. The DFT determinations were repeated, starting 5 min after the end of the injection.

In group IIIB 0.2 to 0.6 mg/kg propranolol was given before isoproterenol. The procedure was otherwise similar to that followed in group IIIA.

Six dogs in group III underwent more than one sequential drug experiment on separate days, and in these dogs the order of drug administration was inverted from one experiment to the next.

**Statistical methods.** The data were analyzed with the use of the statistical analysis system (SAS) and the Washington University mainframe IBM computer system. After giving appro-

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Values represent energy in joules.

TP = transthoracic paddles. Circled number represents confirmed DFT.
Results

**Group I.** The mean energy required to defibrillate the heart in group I A was 15.8 ± 2.1 J on the first day, and decreased to 7.4 ± 1.7 J on day 2 (p < .0001). DFT decreased from day 1 to day 2 in all 11 dogs (figure 1). In the seven dogs from this group that underwent daily measurements for 5 consecutive days, mean DFT remained stable from the second to the fifth day, while heart rate, measured just before determination of DFT, showed small, nonsignificant changes between day 1 and day 5 (figure 2).

In group IB DFT decreased from 10.3 ± 2.5 J on the first day to 2.3 ± 0.7 J on the second day (p < .05), while impedance decreased from 112 ± 6 Ω on day 1 to 100 ± 6 Ω on day 2 (p = NS). Figure 3 illustrates the changes in DFT and in impedance measured from day 1 to day 2 in each of the six dogs. The serum lidocaine concentration measured on day 1, at the time of determination of DFT, was less than 2 mg/liter in each of four dogs in which it was measured.

**Group II.** In this group of dogs, the mean energy required to defibrillate the heart also decreased significantly from 20.7 ± 3.1 J on day 1 to 12.0 ± 2.2 J on day 2 (p < .01). When, on day 2, propranolol was given after the baseline determination of DFT, the energy required to defibrillate rose significantly from a mean value of 12.0 ± 2.2 to 18.0 ± 3.1 J (p < .05, figure 4).

**Group III.** The mean DFT before drug intervention was 10.0 ± 1.9 J in group IIIA and 10.6 ± 3.0 J in group IIIB; these values were not statistically different. Figure 5, A illustrates the results of the experiments in group IIIA: isoproterenol decreased DFT from a mean of 10.0 ± 1.9 to 5.5 ± 1.5 J (p < .001). At a mean of 89 min after the end of isoproterenol infusion, the DFT returned to the control value. After propranolol DFT increased from a mean of 10.7 ± 1.4 to 14.4 ± 1.5 J (p < .01). Figure 5, B illustrates the results of the experiments with group IIIB: propranolol increased DFT from a mean of 10.6 ± 3.0 to 14.6 ± 3.9 J (p < .02). At a mean of 69 min after injection of propranolol, DFT had returned toward the control value. Isoproterenol then decreased DFT from a mean of 11.7 ± 3.0 to 9.7 ± 3.1 J (p < .05).

Table 2 summarizes the measurements of DFT, along with the Δ EN, the measurements of heart rate just before induction of ventricular fibrillation at the

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**FIGURE 1.** Decrease in DFT measured between first and second day of experimentation in 11 closed-chest, unanesthetized dogs. Individual results are shown, along with mean ± SE.

**FIGURE 2.** DFT and heart rate measurements obtained over 5 consecutive days in seven closed-chest, unanesthetized dogs. The decrease in DFT measured between day 1 and day 2 is the only statistically significant change (p < .01).
FIGURE 3. Changes in DFT and transcardiac impedance (IMP) measured between first and second day of experimentation in six closed-chest, unanesthetized dogs.

Time of each DFT determination, and the number of shocks, number of attempts, and experimental time required to define each DFT in each group of experiments. In group IIIA, heart rate increased significantly (p < .001) during administration of isoproterenol and then returned toward baseline (Control I vs Control II, p = NS). In group IIIB, heart rate also increased significantly with isoproterenol (p < .05), but the magnitude of increase was considerably less than that in group IIIA (p = .01).

The importance of the order of drug administration was examined by comparing Δ EN1 before and after propranolol, and Δ EN2 before and after isoproterenol. When isoproterenol preceded propranolol, Δ EN1 was 0.8 ± 0.9 J, and when propranolol preceded isoproterenol, Δ EN2 was 2.0 ± 0.8 J (p = .055). When propranolol preceded isoproterenol Δ ENp was 3.7 ± 0.8 J and when isoproterenol preceded propranolol, Δ ENp was 4.0 ± 1.2 J (p > .8).

Discussion

The day 1–day 2 phenomenon. Several studies designed to measure the energy required to defibrillate the ventricles have demonstrated temporal stability of the DFT.3,4,6,7 Most of these experiments, however, were performed in open-chest, anesthetized animals and lasted only a few hours. Limited data are available regarding the stability of DFT in closed-chest animals instrumented over a long term8,9; our observation of a marked decrease in energy required for defibrillation occurring between the first and second day of testing has not been reported previously. This phenomenon is important from an experimental point of view since, unless accounted for, it could be interpreted as the result of an intervention in studies of DFT in dogs instrumented over a long term. Moreover, exploring the mechanisms of this decrease in DFT may provide a better understanding of ventricular fibrillation and suggest more effective forms of electrical treatment.

One of our first hypotheses was that, as a result of the first testing period, changes in the autonomic nervous control of the heart took place, specifically intramyocardial release of neurotransmitters, resulting in facilitation of the defibrillation process. Changes in the autonomic activity of the heart after transthoracic defibrillation in anesthetized dogs were described by Panseran, Abboud and their co-workers10,11 who observed a strong cardiac autonomic response with both cholinergic and adrenergic components. The cholinergic effect produced transient sinus node depression and atrioventricular block, whereas the adrenergic compo-
stimulation\textsuperscript{12} and by field stimulation\textsuperscript{13} has also been demonstrated, and both have been found to produce sympathetic as well as parasympathetic cardiac effects. The lack of a significant increase in sinus rate between day 1 and day 2 in our study militates against a heightened sympathetic cardiac activity. However, the autonomic responses produced by cardiac defibrillation may be different in the atrium than they are at the ventricular level, as suggested by the studies of Pansegrau and Abboud and their colleagues.\textsuperscript{10, 11}

The reversal of the decrease in DFT by propranolol given on the second day supports, but does not prove, the premise that enhanced myocardial sympathetic activity is responsible for the day 1–day 2 phenomenon. Instead of reflecting an antiadrenergic effect of propranolol, the rise in DFT measured on day 2 may be due to the membrane-stabilizing effect of the drug. Indeed, an increase in DFT produced by quinidine and other sodium-channel blockers was demonstrated by Babbs et al.\textsuperscript{1}

Transcatheter impedance is known to decrease as a result of repeated transcatheter shocks.\textsuperscript{14, 15} In our experiments, a decrease in transcardiac impedance was measured in four of six dogs between day 1 and day 2. Although this change may have contributed to the day 1–day 2 phenomenon in some of the dogs, it cannot be its only explanation, since two dogs who had a marked decrease in DFT had a rise in impedance between day 1 and day 2.

\textbf{\textit{\textbeta}}-\textit{Adrenergic activity and DFT.} An important finding of our studies was a marked decrease in energy requirements for defibrillation produced by \textit{\textbeta}-adrenergic stimulation. Confirmation of this initial observation in nonanesthetized dogs, originally made in the open-chest preparation,\textsuperscript{5} is important since it disallows a possible interactive effect on the DFT of surgical stress, anesthesia, and \textit{\textbeta}-adrenergic stimulation. The

\begin{table}[h]
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\caption{Summary of results}
\begin{tabular}{lcccc}
\hline
 & \textbf{Group III A (n = 10)} & & \textbf{Group III B (n = 9)} & \\
 & \textbf{Control I} & \textbf{ISO} & \textbf{Control II} & \textbf{PRO} & \textbf{Control I} & \textbf{PRO} & \textbf{Control II} & \textbf{ISO} \\
\hline
\textbf{Heart rate (bpm)} & 83 \pm 8 & 179 \pm 13 & 93 \pm 8 & 98 \pm 11 & 79 \pm 7 & 75 \pm 11 & 83 \pm 11 & 124 \pm 15 \\
\textbf{No. of shocks (cumulative)} & 13 \pm 2 & 20 \pm 2 & 37 \pm 4 & 46 \pm 5 & 13 \pm 2 & 21 \pm 3 & 31 \pm 5 & 43 \pm 11 \\
\textbf{No. of attempts (cumulative)} & 8 \pm 1 & 13 \pm 1 & 20 \pm 2 & 25 \pm 2 & 8 \pm 1 & 12 \pm 1 & 19 \pm 2 & 23 \pm 2 \\
\textbf{Time (cumulative min)} & 34 \pm 4 & 56 \pm 5 & 145 \pm 22 & 172 \pm 26 & 34 \pm 4 & 57 \pm 4 & 128 \pm 27 & 147 \pm 29 \\
\textbf{Energy (J)} & 10.0 \pm 1.9 & 5.5 \pm 1.5 & 10.7 \pm 1.4 & 14.4 \pm 1.5 & 10.6 \pm 3.0 & 14.6 \pm 3.9 & 11.7 \pm 3.0 & 9.7 \pm 3.1 \\
\hline
\textbf{\Delta EN} & -4.5 \pm 0.9 & 3.7 \pm 0.8 & & & 4.0 \pm 1.2 & & & -2.0 \pm 0.8 \\
\textbf{Values are mean } \pm \textbf{ SEM.}
\end{tabular}
\end{table}

ISO = isoproterenol; PRO = propranolol.
\textsuperscript{a}p < .001; \textsuperscript{b}p < .01; \textsuperscript{c}p < .02; \textsuperscript{d}p < .05.
experiments presented here simulated more closely in a canine preparation the conditions of a cardiac arrest resulting from ventricular fibrillation as it may occur in humans. Studies performed many years ago in animals demonstrated a beneficial effect of catecholamines in resuscitation from cardiopulmonary arrest with and without ventricular fibrillation.16-24 These observations constituted the basis for the clinical use of epinephrine in resistant ventricular fibrillation, treatment recommended by the current guidelines of the American Heart Association. It should be emphasized, however, that in some of these experiments of transthoracic defibrillation, stimulation alone (with isoproterenol) resulted in a distressingly low survival rate of the animals.25 Thus, if the results of our study have any clinical relevance, they may be more applicable to the situation of internal cardiac defibrillation than to that of traditional cardiopulmonary resuscitation assisted by damped sinusoidal, transthoracic shocks.

As in our previous series of experiments,5 propranolol increased the DFT when given as a first as well as a second drug. This increase in the energy requirement for defibrillation may not be due solely to the drug's beta-adrenergic-blocking properties, but may represent, as discussed above, a membrane-stabilizing effect. This possibility is supported by the return of the DFT to control value at a time when beta-blockade was still present as indicated by: (1) a lesser increase in heart rate when isoproterenol was given as a second than when it was given as a first drug, and (2) the smaller \( \Delta EN \) when isoproterenol was given as a second drug than when it was given first, a difference that was of borderline statistical significance. Conversely, \( \Delta EN_p \) was similar whether propranolol was given first or second, in keeping with the short biological half-life of isoproterenol.

**Limitations of the study.** Our experiments demonstrated conclusively in the closed-chest unanesthetized dog (1) a sustained cardiac effect of epicardiac defibrillation reflected in a decrease in DFT lasting as long as 24 hr, and (2) the effects of beta-stimulation and beta-blockade on the energy required to defibrillate the heart. However, these experiments did not clarify the mechanisms by which these changes were mediated. It is likely that the understanding of such mechanisms will require detailed analysis of the characteristics of ventricular fibrillation before and after beta-adrenergic stimulation and blockade. Furthermore, besides changes in the autonomic control of the heart, other changes at the myocardial level may result from repeated defibrillation and these may explain the durable decrease in DFT noted in the first groups of experiments. These changes may be taking place at the cellular level, or in the interstitial space, enhancing the ability of a direct-current shock to depolarize a large amount of myocardium. A decrease in DFT was measured by Babbs et al.26 when extracellular potassium concentration was increased in the anesthetized dog. In addition, one could hypothesize that, as a result of beta-adrenergic stimulation or blockade, changes in cardiac physical properties, particularly size, may have been produced that could have mediated some of the changes in measured DFT.

Since the electrode catheter was placed without the use of fluoroscopy, its subsequent dislodgement may have been a source of error in the determination of DFT. In each animal, however, the pacing threshold and surface electrocardiographic pattern remained stable from one day to the next. Furthermore, since the electrode was sutured securely at the jugular level, migration of the proximal pair of electrodes used for defibrillation was virtually impossible. Finally, one would expect the result of dislodgement of a defibrillating electrode to be random variations in DFT, and not a systematic decrease from day 1 to day 2, followed by stabilization from day 2 to day 5.

The effects of lidocaine on DFT in the dog have been studied and published in a preliminary report.27 A progressive rise in DFT has been measured with concentrations of lidocaine of 3 mg/liter or higher. The doses used for local anesthesia in our experiments produced serum concentrations below 2 mg/liter, and therefore the use of this drug does not explain the day 1-day 2 phenomenon.

Since the dogs were sedated with morphine sulfate they were under predominantly vagal influence from the beginning of the experiments. This vagal predominance was reflected in the absence of a significant decrease in heart rate after the administration of propranolol in the dogs from groups IIIA and IIIIB. This baseline autonomic imbalance may in itself have influenced our results, and conceivably accentuated the effects of beta-adrenergic stimulation. Further studies of the effects of cholinergic activity on DFT are evidently needed to determine its importance.

Despite the spectacular reduction in DFT produced by beta-stimulation, we do not wish to propose the clinical use of isoproterenol alone for treating cardiac arrest resulting from ventricular fibrillation. Although in our experiments we did not find that isoproterenol hampered reanimation of the dogs, other investigators found alpha-stimulation to be of distinctly greater benefit than beta-stimulation in this context.25, 28 Thus, the relevance of our experimental observations to the
clinical scene remains to be defined, particularly since most cardiac arrests from ventricular fibrillation in humans occur in the presence of severe organic heart disease, an element that was missing from our animal preparation.

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Adrenergically mediated variations in the energy required to defibrillate the heart: observations in closed-chest, nonanesthetized dogs.
R Ruffy, K Schechtman, E Monje and J Sandza

Circulation. 1986;73:374-380
doi: 10.1161/01.CIR.73.2.374

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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