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THERAPEUTIC INDICES FOR TRANSCHEST DEFIBRILLATOR SHOCKS: EFFECTIVE, DAMAGING, AND LETHAL ELECTRICAL DOSES

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Abstract

Although prospective studies of defibrillator shock overdose cannot be performed in man, the therapeutic indices of various defibrillating current waveforms can be measured in animals. We determined the ratios TD_{50}/ED_{50} and LD_{50}/ED_{50} (where TD_{50} = median "toxic" or damage-inducing dose, ED_{50} = median effective or defibrillating dose, and LD_{50} = median lethal dose) as measures of the therapeutic index for damped sine wave defibrillator shocks in dogs. Death of an animal and/or any degree of cardiac damage found by gross or microscopic examination were defined as harmful effects of shock, analogous to drug toxicity. In terms of peak current, the ED_{50} , TD_{50} , and LD_{50} were 1.1, 5.8, and 24 amperes/kg; the therapeutic indices were $TD_{50}/ED_{50} = 5$ for morphologic damage and $LD_{50}/ED_{50} = 22$ for death. In terms of delivered energy the ED_{50} , TD_{50} , and LD_{50} were 1.5, 30, and 470 joules/kg; the therapeutic indices were $TD_{50}/ED_{50} = 20$ for damage and $LD_{50}/ED_{50} = 320$ for death. These data indicate a reasonable margin of safety for damped sine wave defibrillator shocks in dogs, and are consistent with reported incidences of suspected shock-induced damage in humans.

Key words: defibrillation, myocardial damage, toxicity, ventricular fibrillation, waveform

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Introduction

Ventricular defibrillation by an electric shock applied across the chest is a lifesaving, but not necessarily innocuous, clinical procedure. Animal studies have demonstrated both morphologic damage and functional impairment of the heart following defibrillator shocks. Indirect evidence for shock-induced myocardial damage in man includes ECG changes, elevated cardiac isoenzyme levels in plasma, and positive scintigrams. In order to prescribe the safest and most effective electrical dose for defibrillation, knowledge of the margin of safety for defibrillator shocks is required. The classical pharmacologic measure of the margin of safety of a drug is the therapeutic index, which may be defined as the ratio of either the median toxic or the median lethal dose to the median effective dose. Because harmful effects cannot be intentionally induced in human subjects, it is necessary to consider this relationship between effective and damaging electrical doses in experimental animals. The present study establishes therapeutic indices for single damped sine wave defibrillator shocks in anesthetized dogs.

Methods

The experimental defibrillator

Investigations of the therapeutic and damaging effects of single, damped sine wave shocks were conducted with our experimental, high energy defibrillator [1]. The energy storage capacitor of this device could be varied from 0 to 100 microfarads; the series inductance could be varied from 0 to 100 millihenries; and the initial voltage of the capacitors could be varied continuously from 0 to 10,000 volts. For the study of effective shock strengths the operating mode of the experimental defibrillator was selected to simulate a typical clinical unit (16 or 32 microfarads, 50 or 100 millihenries, 0 to 400 joules stored energy). In this mode of operation the output pulse duration (time between pulse onset and first zero crossing of the underdamped sine wave), which is somewhat dependent upon subject resistance, averaged 5.1 msec. For the study of "toxic" shock strengths greater defibrillator capacitance (50 microfarads) charged to higher initial voltages (5,000 to 10,000 volts) was required in order to deliver sufficient energy to produce myocardial damage. In this mode of operation shock durations averaged 7.4 msec. To achieve the highest electrical dose tested, corresponding roughly to the LD50, a capacitance of 100 microfarads charged to 10,000 volts was necessary in 6 of 11 animals in one group. With 100 microfarad capacitance the output waveform was an overdamped sine wave, as described in reference [10], and in this case the pulse duration was taken as the time required for the pulse to decay to 10 percent of its peak value.

In both studies the current waveforms were similar to those delivered by conventional damped sine wave defibrillators. The delivered pulse durations were within the 2 to 10 msec range described for clinical defibrillators by Finlay [11] and within the 4 to 8 msec range we calculated for typical commercially available, damped sine wave defibrillators using published values for output circuit components [12] and for the range of human thoracic resistances (25 to 105 ohms) encountered clinically [13].

Animal experiments

In the first study, reported in detail elsewhere [14], shocks of a strength near the defibrillation threshold were tested for their efficacy in defibrillating the ventricles of 36 dogs, average weight $14 \pm 7^*$ kg, in which fibrillation was produced by electrical stimulation of the right ventricular endocardium. Transchest ventricular defibrillation threshold was determined in each animal by repeated trials with successive shocks of diminishing peak current amplitude, each shock being 10% less than that of the preceding shock. The shocks were administered via 8 cm. electrodes in 12 dogs weighing less than 10 kg and via 10 cm electrodes in the larger dogs. The ventricles were never permitted to fibrillate for longer than 30 seconds, and another fibrillation-defibrillation episode was never conducted until systemic blood pressure had returned to a stable level.

In the second study of damaging and lethal effects, a single high intensity damped sine wave shock was given to each of 65 dogs, average weight 8 ± 2 (SD) kg, via 10 cm. diameter transchest electrodes. Details of this protocol have been reported previously [15]. In brief, each dog was assigned either to a control group which received no shock or to one of six experimental groups which received an unsynchronized shock of approximately 1, 3, 6, 9, 12, 15, or 20 amperes peak current per kilogram body weight (90 to 4,700 joules total delivered energy). To calculate the voltage setting required to deliver the desired current, the apparent chest impedance to 50 KHz, non-stimulating, sinusoidal current was measured as described by Geddes and associates [16]. Delivered energy was calculated as previously described [12] from current and voltage waveforms registered on a storage oscilloscope. Mean delivered energy doses for the groups of animals ranged from 1 to 512 joules per kilogram body weight. The hearts were in normal sinus rhythm, rather than fibrillation, when the unsynchronized shocks were applied to ensure that any observed damage was due to the shock and not to pre-existing circulatory arrest.

Hearts of animals that died immediately after shock, as well as hearts of animals that survived and were later killed, were removed from the thorax promptly after death. Gross cardiac lesions were observed carefully and were graded according to predetermined criteria [15]. Entire hearts were then fixed in 10% neutral buffered formalin. Blocks of myocardial tissue from 22 standardized sites were collected, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Microscopic lesions were identified and graded according to previously established criteria [15].

Determination of efficacy, damage, and lethality curves

The criterion for efficacy of transchest shocks was ventricular defibrillation. For each of 36 dogs in the efficacy study, five to 20 threshold energy values were obtained and averaged. Histograms were constructed using these mean values to illustrate animal-to-animal variations in threshold within this population. Percent successful defibrillation vs. electrical dose curves were constructed for the 36 dogs according to the method of Goldstein and colleagues [17] by integrating the threshold energy histograms. Using this technique, it was possible in particular to establish the 50% effective dose or ED₅₀ for the population, since one half of the dogs had

defibrillation thresholds below this value and the other half of the dogs had defibrillation thresholds above this value.

The criterion for "toxicity" of transchest shocks was any degree of morphologically detectable myocardial damage. According to this criterion, a heart was scored as damaged if there were any gross lesions present or if any of the 22 blocks taken for histologic study showed defibrillator-induced necrosis of muscle fibers, epicardial reaction, or both. In addition, the hearts of dogs that died within 15 minutes after shock were scored as damaged, although gross and microscopic lesions were often subtle at this early time after injury. The percentage of animals defibrillated, damaged, or killed by shock in each dose group were plotted as functions of the current or energy dose per kilogram body weight. Normalization of dose by body weight is classically employed in experimental pharmacology and has proved of value in earlier defibrillation studies [18]. For such plots, smooth curves were fitted to experimental data by probit transformation and linear regression, using the method of Litchfield and Wilcoxon [19] and interpolated values were identified for the ED₅₀, TD₅₀, and LD₅₀ -- the median effective, toxic, and lethal electrical doses.

Results

Figure 1 shows the incidence of defibrillation, morphologic damage, and death as functions of delivered peak current in amperes/kg. In terms of peak current the ED₅₀, TD₅₀, and LD₅₀ were 1.1, 5.8, and 24 amperes/kg, respectively. These values represent the median current doses which were capable of defibrillating, damaging, and killing 50% of the animals studied. The corresponding therapeutic indices are TD₅₀/ED₅₀ = 5 for morphologically detectable damage and LD₅₀/ED₅₀ = 22 for death. Thus, it took five times as much peak current to produce detectable damage in a typical dog, and 22 times as much peak current to kill a typical dog, than it did to defibrillate.

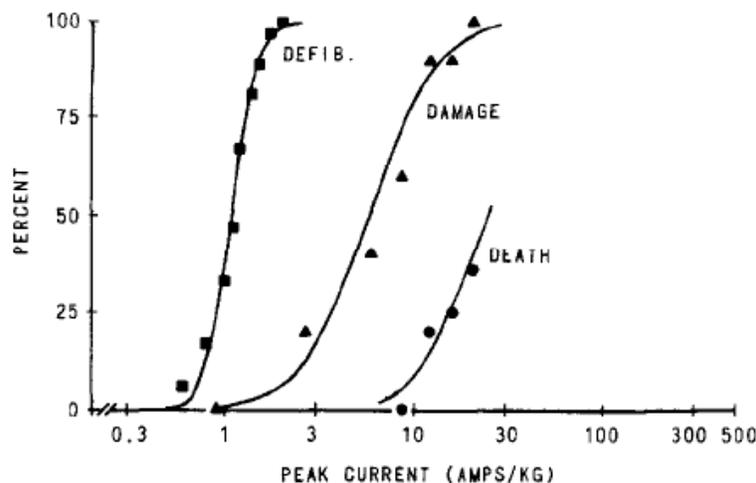


Figure 1. Current dose-response curves for defibrillation, morphologic damage, and death. The peak current has been normalized to body weight.

Figure 2 shows the incidences of defibrillation, morphologic damage, and death as functions of delivered energy in joules/kg. The ED_{50} , TD_{50} , and LD_{50} were 1.5, 30, and 470 joules/kg. The corresponding therapeutic indices were $TD_{50}/ED_{50} = 20$ for damage and $LD_{50}/ED_{50} = 320$ for death. Hence, it took 20 times as much energy to produce detectable damage in a typical dog and 320 times as much energy to kill a typical dog than it did to defibrillate. The larger numerical dose range and the larger therapeutic indices may be expected when energy is used to describe shock strength, because delivered energy varies as the square of the current [12].

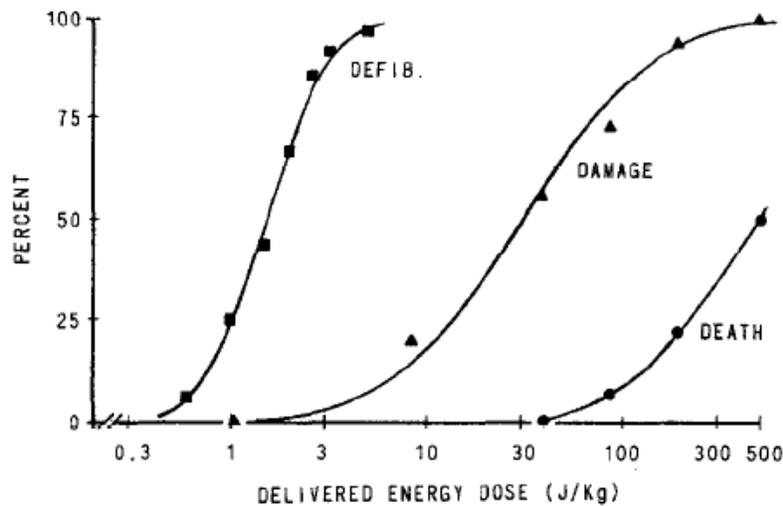


Figure 2. Energy dose-response curves for defibrillation, morphologic damage, and death. The delivered energy has been normalized to body weight.

The slopes of the curves of Figures 1 and 2 indicate considerable biologic variability among dogs in their susceptibility to defibrillation, damage, or death. Variability in susceptibility to the harmful effects of shock was remarkable. For example, an electrical dose of 120 joules/kg was sufficient to kill 10% of the animals; however, this same dose produced no detectable damage in 12% of the animals, while the remaining 78% showed varying degrees of damage. Despite this biologic variability, the therapeutic indices were sufficiently large so that there was no overlap between the death and the defibrillation curves and only slight overlap between the morphologic damage and the defibrillation curves. The calculated curves indicate that the risk of detectable damage was 2 to 4% for 90% successful shocks and 5 to 10% for 99% successful shocks. This degree of overlap between the efficacy and toxicity curves is similar regardless of whether current or energy is used to measure the electrical dose.

Discussion

The studies described in the present paper indicate that therapeutic indices may be calculated for defibrillator shocks on the basis of reasonable criteria for effectiveness and "toxicity." The resultant values may be interpreted in a manner analogous to therapeutic indices of drugs. Although similar, studies of intentional shock overdose cannot be performed in man; the therapeutic indices of various defibrillating current waveforms can be measured in animals in order to design defibrillators with the greatest margin of safety.

The relatively large therapeutic indices reported here for animals indicate a reasonable safety margin for damped sine wave defibrillator shocks. Extrapolation of this conclusion to the clinical arena, however, must be done with caution. The present studies were conducted in healthy animals with normal rather than diseased hearts. Moreover, in the efficacy study the time of circulatory arrest due to fibrillation was less than 30 seconds, and in the damage study shocks were administered to beating hearts. In general the hearts of animals in both studies were relatively well oxygenated. Human hearts in clinical situations are typically diseased and may be poorly oxygenated at the time of defibrillation. Under these less favorable conditions the therapeutic indices for defibrillation may be significantly different from those reported here.

Nonetheless, the available clinical data seem to confirm the relatively low incidence and extent of shock-induced damage we have observed at therapeutic shock strengths in dogs. Ehsani and colleagues [8] and Werner and associates [20] have shown 7 and 8% incidence, respectively, of indirect evidence for damage in humans after high cumulative energy doses from defibrillators. Accordingly, in view of both the animal and the human data available at this writing, we believe that fear of inducing damage should not be a dominant factor in determining defibrillation dose. Instead, effectiveness should be the major criterion.

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