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THE EFFECTS OF NORMOTHERMIC AND HYPOTHERMIC CARDIOPULMONARY BYPASS UPON DEFIBRILLATION ENERGY REQUIREMENTS AND TRANSMYOCARDIAL IMPEDANCE

BY

D. MARTIN, J. GARCIA, C. LIM, M. DOURSOUNIAN,
C.R. VALERI, AND S.F. KHURI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

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Difficulties in the defibrillation of hypothermic patients may be caused by increased defibrillation threshold, increased tissue impedance or by refibrillation. To evaluate these questions we studied the effect of controlled hypothermia upon defibrillation energy requirements and transcardiac impedance in a canine model of cardiopulmonary bypass in which 26 animals underwent right atrial and femoral arterial cannulation as well

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as continuous hemodynamic and intramyocardial temperature monitoring. The defibrillation energy requirements were evaluated at 60 minute intervals using an epicardial patch system, and transcardiac impedance was measured before and after the multiple inductions and terminations of ventricular fibrillation. In Group 1 defibrillation energy requirements were evaluated immediately after initiation of cardiopulmonary bypass at 37 C (T_o), after gradual cooling to 28 C (T_1), and after rewarming to 37 C (T_2). Group 2 comprised time controls that were identically instrumented and studied, but maintained at 37 C throughout. Percent successful defibrillation was plotted against stored energy, and the raw data fit by logistic regression. The derived energy at which 50% of shocks were successful (E_{50}) was 3.23±89J at T_o, 5.12±85J at T_1, and 4.42± 1.22J at T_2 in group 1; this was not significantly different from the corresponding group 2 E_{50} values which were 3.11±1.39J, 4.95 ±2.47J, and 5.59±3.18J respectively. Both groups demonstrated a significant increase in E_{50} during the first hour of cardiopulmonary bypass ($p < 0.05$). Transmyocardial impedance fell progressively during the group 2 experiments from 73.6±12.9 at T_o to 61.4±8.9 at T_2. A similar reduction was observed in the group 1 experiments except at T_1 where impedance was significantly elevated to 77.4±12.3 ($p < 0.05$). There was no relationship between defibrillation energy requirements and transcardiac impedance; there was also no correlation between either of these parameters and intramyocardial extracellular pH or left ventricular and diastolic pressure. We conclude that defibrillation energy requirements significantly and persistently increase during the first hour of cardiopulmonary bypass and the effect is temperature dependent. Systemic hypothermia significantly and reversibly elevates transmyocardial impedance but multiple shocks reduce this effect at 28 C as they do at 37 C.

Abstract:
Difficulties in the defibrillation of hypothermic patients may be caused by increased defibrillation threshold, increased tissue impedance or by refibrillation. To evaluate these questions we studied the effect of controlled hypothermia upon defibrillation energy requirements and transcardiac impedance in a canine model of cardiopulmonary bypass in which 26 animals underwent right atrial and femoral arterial cannulation as well as continuous hemodynamic and intramyocardial temperature monitoring. The defibrillation energy requirements were evaluated at 60 minute intervals using an epicardial patch system, and transcardiac impedance was measured before and after the multiple inductions and terminations of ventricular fibrillation. In Group 1 defibrillation energy requirements were evaluated immediately after initiation of cardiopulmonary bypass at 37°C (T_0), after gradual cooling to 28°C (T_1), and after rewarming to 37°C (T_2). Group 2 comprised time controls that were identically instrumented and studied, but maintained at 37°C throughout. Percent successful defibrillation was plotted against stored energy, and the raw data fit by logistic regression. The derived energy at which 50% of shocks were successful (E_{50}) was 3.23±0.89J at T_0, 5.12±1.85J at T_1, and 4.42±1.22J at T_2 in group 1; this was not significantly different from the corresponding group 2 E_{50} values which were 3.11±1.39J, 4.95±2.47J, and 5.59±3.18J respectively. Both groups demonstrated a significant increase in E_{50} during the first hour of cardiopulmonary bypass ($p<0.05$). Transmyocardial impedance fell progressively during the group 2 experiments from 73.6±12.9Ω at T_0 to 61.4±8.9Ω at T_2. A similar reduction was observed in the group 1 experiments except at T_1 where impedance was significantly elevated to 77.4±12.3Ω ($p<0.05$). There was no relationship between defibrillation energy requirements and transcardiac impedance; there was also no correlation between either of these parameters and intramyocardial extracellular pH or left ventricular end diastolic pressure. We conclude that defibrillation energy requirements significantly and persistently increase during the first hour of cardiopulmonary bypass and the effect is temperature independent. Systemic hypothermia significantly and reversibly elevates transmyocardial impedance but multiple shocks reduce this effect at 28°C as they do at 37°C.

Ventricular fibrillation in hypothermic patients is both common and highly refractory to resuscitative efforts until substantial rewarming has occurred[1-4]. Clinical difficulties in the defibrillation of hypothermic patients may be caused by an elevation in defibrillation energy requirements but there is suggestive evidence from previous studies that this is not the case[5,6]. Alternative hypotheses accounting for the difficulty in defibrillation of hypothermic patients include increased tissue impedance reducing energy delivery to myocardium, and a proarrhythmic effect of defibrillatory shocks leading to refibrillation[7].

The implantation of cardioverter/defibrillators (ICDs) requires determination of defibrillation energy requirements (or "threshold", DFT) in order that an adequate safety margin for device efficacy can be demonstrated[8-11]. At least 10% of ICD implants are performed concomitantly with cardiac surgery requiring cardiopulmonary bypass, and DFT testing is routinely performed after such surgery is substantially complete[12]. Recent work has demonstrated the significant metabolic and hemodynamic sequelae of prolonged hypothermic and normothermic bypass as well as the effects of hypothermia in lowering the ventricular fibrillation threshold[7,13-16]. However, no rigorous assessment of the effect, if any, of normothermic and hypothermic cardiopulmonary bypass upon the energy requirement for defibrillation has been performed.

We used an established canine model of cardiopulmonary bypass to evaluate the influence of hypothermic and normothermic cardiopulmonary bypass upon defibrillation energy requirements and transmyocardial impedance to defibrillatory shocks. This experimental model is the first to permit accurate and stable control of myocardial temperature in an intact canine preparation. It was also our objective to define the relationships between intramyocardial pH, transmyocardial impedance and defibrillation energy requirements.

Methods:

Animal preparation:

All experimentation conformed with the requirements of the American Physiologic Society, and the Animal Care Subcommittee of the Institutional Review Board of the Brockton/West Roxbury VA Medical Center. Adult male

mongrel dogs weighing 30-35 lbs were anesthetized with sodium thiamylal (20mg/Kg iv), paralyzed with succinylcholine (20 mg iv) and maintained on a ventilator throughout the experiment. Further anesthesia was established with halothane as needed. Arterial and venous access and pressure monitoring were performed using the carotid and jugular vessels. The heart was exposed via a left thoracotomy and suspended in a pericardial cradle. A high fidelity micromanometer (Konigsberg Instruments) was placed in the left ventricular cavity for measurement of developed, and end diastolic, pressure, as well as the first time derivative of LV pressure (dP/dt). Extracellular myocardial Ph and myocardial temperature were continuously monitored in the anterior wall of the left ventricle using previously described techniques[17-19]. Defibrillating patches with a surface area of $14cm^2$ (Cardiac Pacemakers Inc) were sutured to the epicardium over right and left ventricles, and a closely spaced dipole established using screw-in epicardial electrodes (Cardiac Pacemakers Inc) on the lateral wall of the left ventricle. Hemodynamic data (arterial and left ventricular pressure, and dP/dt) were recorded continuously on a multichannel physiologic recorder, as were temperature and pH values. The defibrillating and rate-sensing leads were connected to an external defibrillator (ECD2, Cardiac Pacemakers Inc) to which was also attached a 60Hz alternating current source for induction of ventricular fibrillation. The defibrillator utilized a single phase truncated exponential waveform of 60% tilt and variable pulse width, thus ensuring that stored and delivered energies were almost identical and unaffected by changes in transmyocardial impedance.

After instrumentation the animal was heparinized (400 units/Kg) and placed on full cardiopulmonary bypass by passage of right atrial (34F) and femoral arterial (16F) cannulae. A Sarnes membrane oxygenator with a centrifugal pump primed with 500 ml of Ringer's lactate solution formed the core of the cardiopulmonary bypass circuit and flow was maintained at 2-2.5 l/min. No cardioplegia was administered, and the heart was allowed to continue beating in the partially unloaded state. Arterial blood gases, hematocrit, and serum electrolytes including calcium and magnesium were periodically measured and corrected as necessary during the experiment. Arterial pH was maintained between 7.35 and 7.45 at all times.

Experimental procedure:

The defibrillation energy requirements were estimated in this study by the generation of dose-response curves from which the energy for 50% successful defibrillation (the E_{50}) was derived[11,20,21]. For each animal three dose-response curves of defibrillation efficacy were defined commencing at three consistent time points: T_0, immediately after establishment of cardiopulmonary bypass at 37°C; T_1, one hour after the beginning of the T_0 dose-response curve; T_2, two hours after the beginning of the T_0 dose-response curve. In group 1 animals the T_1 measurements were made after gradual cooling over a 20 minute period to 28°C, and the T_2 data were generated after gradual rewarming to 37°C. Group 2 animals acted as time controls: all dose-response curves were generated at 37°C.

After stabilization at 37°C, the transcardiac impedance was measured by delivery of a 2J shock during sinus rhythm; the impedance was measured by the external defibrillator 50μsec into the pulse. This measurement was repeated after multiple shocks necessary for generation of the defibrillation efficacy data, and such measurements were duplicated at each time point. Ventricular fibrillation was induced by delivery of 2 seconds of alternating current, and, after a 10 second delay, a shock was delivered to attempt defibrillation. The initial energy selected was 15J, with energies for subsequent episodes of ventricular fibrillation decrementing through 10, 8, 5, 4, 3, 2, and 1J until failure to defibrillate occurred. After the first failure to defibrillate, subsequent energies were randomly selected from the two higher and two lower settings available on the defibrillator and multiple shocks at these energy settings were delivered in order to develop the dose-response curve. For each episode of ventricular fibrillation only the response to the initial shock was studied. Following successful defibrillation, hemodynamic parameters and pH were allowed to return to baseline before reinduction of ventricular fibrillation. There was a minimum 2 minute delay between defibrillation and reinduction of ventricular fibrillation.

Data Analysis:

For each experiment at each time point a logistic curve was generated relating percent successful defibrillation to stored energy. Using nonlinear regression the best fit to the following function was derived: $y=e^x/(1+e^x)$. The energy at which 50% of shocks successfully terminated ventricular fibrillation (the E_{50}) was derived from these curves[22]. Because the animals used in this study were all of closely similar weight, and because there is no strong correlation between total body or excised heart weight and E_{50}, the defibrillation energy requirements were not normalized for weight[23]. A repeated measures analysis of variance was performed to determine if E_{50}, transmyocardial impedance, or intramyocardial Ph changed with time or temperature. Pairwise differences were tested using paired t-tests when the overall F-test rejected the null hypothesis (Fisher's Least Significant Difference procedure). Equality of variance in the normothermic and hypothermic groups was evaluated by pooling the log transformed E_{50} data for each animal and comparing variances using an F-test. Linear regression was used to explore the relationship between E_{50} and transmyocardial impedance. All results are expressed as mean±SD. A p value <0.05 was considered significant for all analyses.

Results:

Of 35 dogs surgically prepared for this experimental protocol, nine became hemodynamically or metabolically unstable (N=7), or were unable to be cannulated for cardiopulmonary bypass (N=2). Results for the remaining 26 animals are presented; there were 10 group 1 (hypothermic) and 16 group 2 (normothermic) experiments.

Table 1 depicts the effect of bypass duration upon defibrillation energy requirements (E_{50}), transmyocardial impedance, and intramyocardial pH in both groups. Heart rate (mean 136-140 beats per minute) remained stable throughout the experiment when the temperature was kept constant at 37°C. However, heart rate fell significantly (from 131 to 93 beats per minute) in group 1 animals after cooling to 28°C during the second hour of cardiopulmonary bypass.

The logistic model used in the derivation of the defibrillation dose-response curves satisfactorily fitted the data derived from each individual animal and

there was no difference in variance of the data between the two groups. A sample family of dose-response curves from a single experiment is shown graphically in figure 1. In both groups the E_{50} immediately after establishment of cardiopulmonary bypass (T_0) was comparable (3.23J and 3.11J, p=NS). There was a significant increase in E_{50} in both groups after the first hour of cardiopulmonary bypass (T_1) to 5.12J (group 1) and 4.95J (group 2), p=0.0001. However, there remained no difference between the groups indicating no separate effect of hypothermia upon the energy requirement for defibrillation. This elevation in E_{50} was sustained after the second hour of cardiopulmonary bypass (T_1) at 4.42J in group 1 and 5.59J in group 2 (p=NS for both the between-group comparison and the within-group time effect).

Transmyocardial impedance measured across the defibrillating patches ranged from 40Ω to 98Ω throughout the experiment in both groups. Impedance was significantly lower after the multiple shocks necessary for the generation of a dose-response curve compared with the pre-curve measurement in each group at each time point; this is shown graphically in figure 2. Transmyocardial impedance increased significantly after cooling, rising from 74.2Ω at 37°C to 77.4Ω at 28°C; after rewarming to 37°C impedance fell significantly to 62Ω, comparable with the impedance of 64Ω in the group 2 animals at the same time point. This elevation in impedance at 28°C is in marked contrast to the changes in transmyocardial impedance observed in the group 2 animals over the same time course but at a constant 37°C: in these latter experiments the impedance fell progressively during the period of cardiopulmonary bypass as illustrated in figure 2.

Extracellular intramyocardial acid-base balance remained stable throughout the experiments while the preparation was maintained at 37°C. However, there was a significant acidosis at 28°C, even after correcting for the effect of temperature upon the measurement[24,25] with a fall in mean pH from 7.48 at baseline to 7.27 after cooling ($p<0.05$). Mean pH at 37°C ranged from 7.29 to 7.49 and no significant differences emerged when paired data from groups 1 and 2 were compared at similar time points provided the temperature was 37°C. In addition, no changes were noted in paired pH values measured before and immediately after the multiple shocks necessary for the generation of the defibrillation efficacy dose-response curves.

Left ventricular end diastolic pressure remained low in all normothermic experiments with no significant change over the two hours of cardiopulmonary bypass. However, in the hypothermic experiments the LVEDP rose significantly from 2.5mmHg at 37°C to 11.8mmHg at 28°C; after rewarming the LVEDP in these preparations returned to 3.6mmHg.

Linear regression analysis disclosed no relationship between defibrillation energy requirements and the transmyocardial impedance at any temperature or time point. In addition, there was no correlation between these parameters and intramyocardial pH or left ventricular end-diastolic pressure.

Discussion:

This is the first study to describe the effects of non-cardioplegic cardiopulmonary bypass upon defibrillation energy requirements as measured by the dose-response method. We have shown that the E_{50} increases significantly during the first hour of cardiopulmonary bypass, and that hypothermia neither ameliorates nor exacerbates this effect. Our results differ from a study of Klein and co-workers in which they report no effect of cardiopulmonary bypass upon defibrillation energy requirements[26]. Their study included 10 patients undergoing cardiac surgery who underwent DFT measurement using a combined transvenous/epicardial system immediately after cannulation and 10 minutes after the establishment of full-flow bypass. Our experimental protocol attempted to parallel clinical practice in the measurement of defibrillation energy requirements by allowing a much longer duration of bypass prior to defibrillation threshold testing.

That hypothermia to 28°C has no effect upon E_{50} is unexpected in the context of frequent clinical difficulties in the defibrillation of hypothermic patients[1,3]. Previous studies that have examined this question in animals have also concluded that hypothermia does not increase defibrillation energy requirements[5,6,27]. Two of these earlier reports conclude the opposite, namely that cooling reduces defibrillation energy requirements[5,27]. However, these studies neither documented the method of measurement of defibrillation energy requirements nor used enough subjects to permit robust conclusions. In addition, these studies used cooling methodologies that could not measure or

ensure constant myocardial temperature. The current study ensured accurate control of myocardial temperature, and used a validated methodology of evaluating defibrillation energy requirements[22].

The progressive reduction in transmyocardial impedance observed in our study during 2 hours of normothermic cardiopulmonary bypass confirms earlier observations on the effect of multiple shocks in which transthoracic defibrillation was used[28-30]. After the generation of the defibrillation dose-response curve at 28°C the impedance in our study remained elevated albeit to a lesser degree, demonstrating that this multiple shock effect occurs under hypothermic conditions.

The statistically significant increase in transmyocardial impedance both before and after multiple shocks at 28°C is an important finding which may have clinical importance. Using a different method of impedance measurement, Garrido and co-workers reported similar, though more dramatic, increases in tissue resistance after 30 minutes of hypothermic bypass that were prevented by application of cardioplegia[31]. They related elevated myocardial impedance to increased extracellular water consequent upon ischemia and argued that measurement of resistance gives data reflective of myocardial viability. The mean impedance increase at 28°C in our study was only 4%, but 50% of the animals demonstrated an increase in excess of 20%. Elevations in impedance proportionally reduce energy delivery to myocardium when fixed pulse width defibrillators are used: therefore this phenomenon may be at least partly responsible for impaired resuscitation in hypothermia as well as in other patients after prolonged ventricular fibrillation[32].

The relative degree of intramyocardial acidosis (manifested by a significant reduction in temperature-corrected pH) observed at 28°C may reflect ischemia, as is usually imputed from such values recorded clinically[14,19,33]. However, it may be that the low pH reflected reduced washout rather than increased production of H^+ ions and that therefore there was no true intracellular acidosis. It is noteworthy that no animals in our study developed spontaneous ventricular fibrillation during cooling, and that this degree of "acidosis" manifestly had no effect upon defibrillation energy requirements. Our findings

with regard to intramyocardial pH contrast with earlier clinical studies of acid-base status during hypothermic cardiopulmonary bypass, and particularly with the work of Swain and co-workers[34-36]. They reported that cardiac electrical stability (as evidenced by the ventricular fibrillation threshold) was improved by maintaining alkaline pH (7.58) during hypothermia, thereby reproducing the metabolic adjustments made by ectothermic species. Our findings also differ from those of Echt and co-workers who found that the elevating effect of lidocaine upon defibrillation threshold was pH-dependent and could be enhanced and reversed by acidosis and alkalosis respectively[20]. This variance in our data from previously published reports can be explained by the fact that we directly measured extracellular myocardial pH in contrast to most work which has relied solely upon arterial blood gas data[20,36].

The elevation in LVEDP observed at 28°C reflects reduced myocardial compliance, possibly due to the edema associated with hypothermia; because of previous work from our laboratory elucidating the time course of ischemic damage under hypothermic conditions we do not believe the elevation in LVEDP is due to ischemia[14]. Although acute increases in ventricular volume and pressure have been shown in other models to be arrhythmogenic[37], it is noteworthy that in our study these significant elevations in LVEDP were not associated with increased spontaneous arrhythmia or increased energy requirements for defibrillation.

This study is limited by the inability to achieve "true" normothermia on cardiopulmonary bypass because of the open chested nature of the model. Initial myocardial temperatures after the establishment of cardiopulmonary bypass were typically 35°C and all preparations were warmed to 37°C prior to initiation of ventricular fibrillation; however, the normal canine core temperature is 39°C and we were unable to achieve this for the normothermic testing protocol because of heat loss through the wound despite our use of a radiant heat source above the operating field. Other potential limitations of this study relate to the true electrophysiologic comparability of groups 1 and 2 during the T_1 testing period (at 28°C in group 1, and 37°C in group 2). The temperature difference between preparations in the two groups was responsible for the difference in heart rates and the significant bradycardia in the

hypothermic group may account for the elevation in transmyocardial impedance. Since the ionic mechanism underlying the dynamics of myocardial electrical impedance are unknown, it remains unclear whether heart rate or temperature (alone or in combination) are responsible for this observation. Atrial pacing in the group 1 preparations during the T_1 testing (in order to maintain constancy of heart rate) may have clarified this question, but would have deleteriously affected myocardial metabolism and the hemodynamic stability of the experimental preparation.

In conclusion, our data suggest that the difficulty in resuscitation of hypothermic patients is not due to an elevation in defibrillation energy requirement. It is possible that part of the resuscitative difficulty is related to elevated tissue impedance reducing delivery of shock energy to myocardium, but this effect would seem to be modest at the usual shock energies used clinically. Our results are also consistent with the view that resuscitation of hypothermic individuals is difficult because of reinitiation of ventricular fibrillation by the delivered shock[38,39]. Refibrillation after shock application may be facilitated by the lowered ventricular fibrillation threshold present at low myocardial temperature[7].

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Legend Table 1:

HR denotes heart rate in beats per minute; Imp_1 denotes transmyocardial impedance prior to defibrillation dose-response curve generation; Imp_2 denotes impedance immediately after completion of multiple shocks for curve generation; pH_1 and pH_2 are similarly defined. T_0, T_1, T_2, refer to measurements made during the first, second, and third hours respectively of cardiopulmonary bypass. $^*P<0.05$ compared with T_0. Note that pH measurements at 28°C are corrected for temperature assuming $\Delta pH/°C=-0.015$[24,25].

Legend Figure 1:

Sample family of dose-response curves derived from a single hypothermic experiment. Circles denote measurements made immediately after the establishment of cardiopulmonary bypass; Triangles and squares denote the repeated dose-response measurements made after one and two hours of cardiopulmonary bypass respectively.

Legend Figure 2:

Graph of pooled impedance data expressed as a percentage of impedance at the beginning of T_0 defibrillation dose-response curve generation plotted for the beginning and end of each series of inductions of ventricular fibrillation. Open circles denote normothermic group, closed circles denote hypothermic group. $^*P<0.05$ compared both with T_0 and with the normothermic group.

Table 1A: Effects of hypothermic cardiopulmonary bypass.

	T_0 (37°C)	T_1 (28°C)	T_2 (37°C)
E_{50} (J)	3.23±0.89	5.12±1.85*	4.42±1.22*
HR (BPM)	131±13	93±20*	141±19
Imp_1 (Ω)	74.2±4.1	77.4±12.3*	62.7±6.5
Imp_2 (Ω)	72.6±8.7	75.7±8.3*	61.4±9.6
pH_1	7.48±0.20	7.27±0.15*	7.37±0.15
pH_2	7.41±0.18	7.25±0.17*	7.29±0.12
LVEDP (mmHg)	1.9±2.1	11.8±9.4*	3.6±5.5

Table 1B: Effects of duration of normothermic cardiopulmonary bypass.

	T_0 (37°C)	T_1 (37°C)	T_2 (37°C)
E_{50} (J)	3.11±1.39	4.95±2.47*	5.59±3.18*
HR (BPM)	138±18	136±24	140±24
Imp_1 (Ω)	73.6±12.9	71.7±10.9	64.3±6.8
Imp_2 (Ω)	73.9±12.4	67.6±7.6	61.4±8.9
pH_1	7.48±0.13	7.49±0.14	7.42±0.12
pH_2	7.49±0.14	7.44±0.13	7.40±0.11
LVEDP (mmHg)	2.5±1.7	2.6±2.1	4.4±4.2

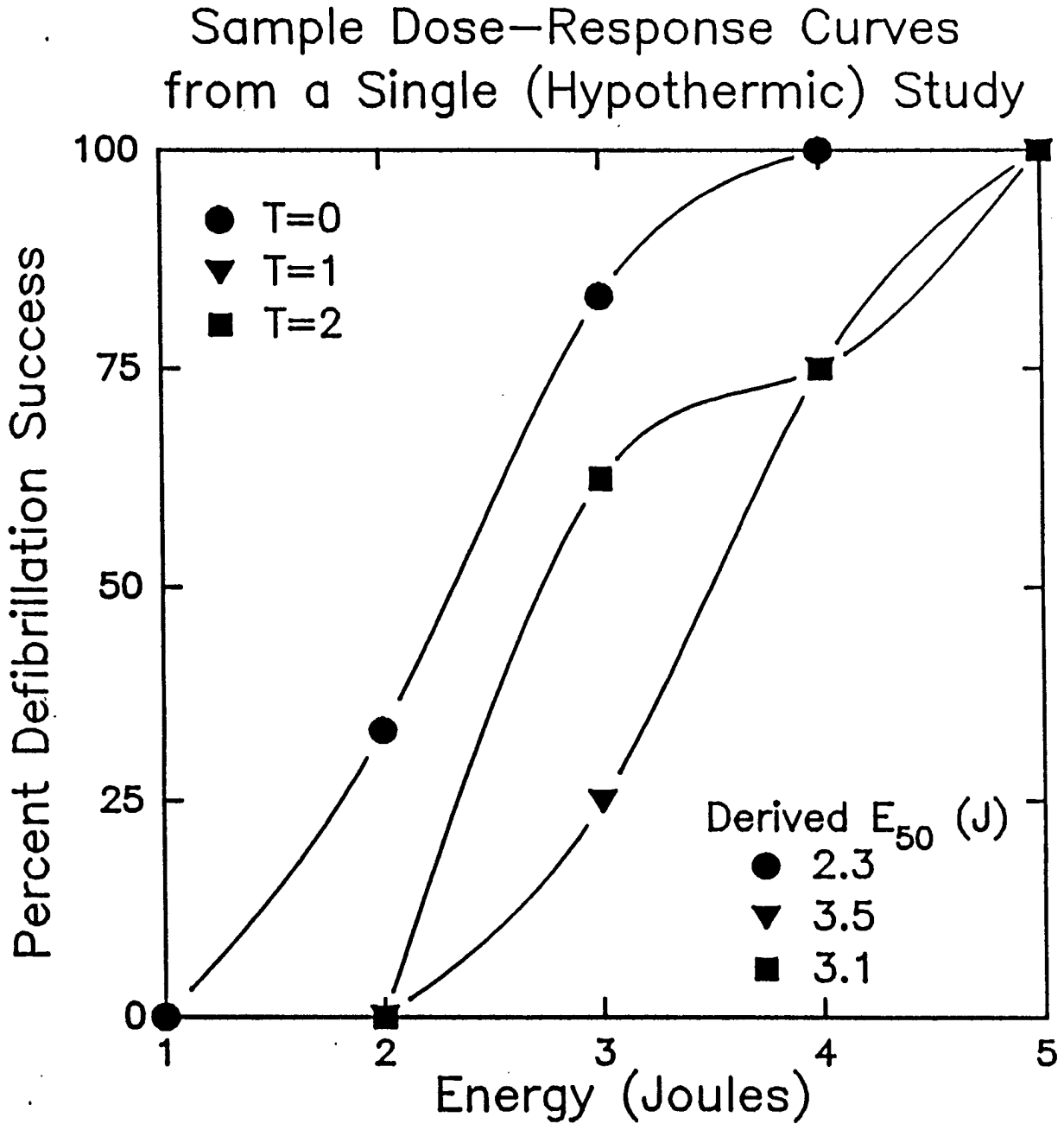
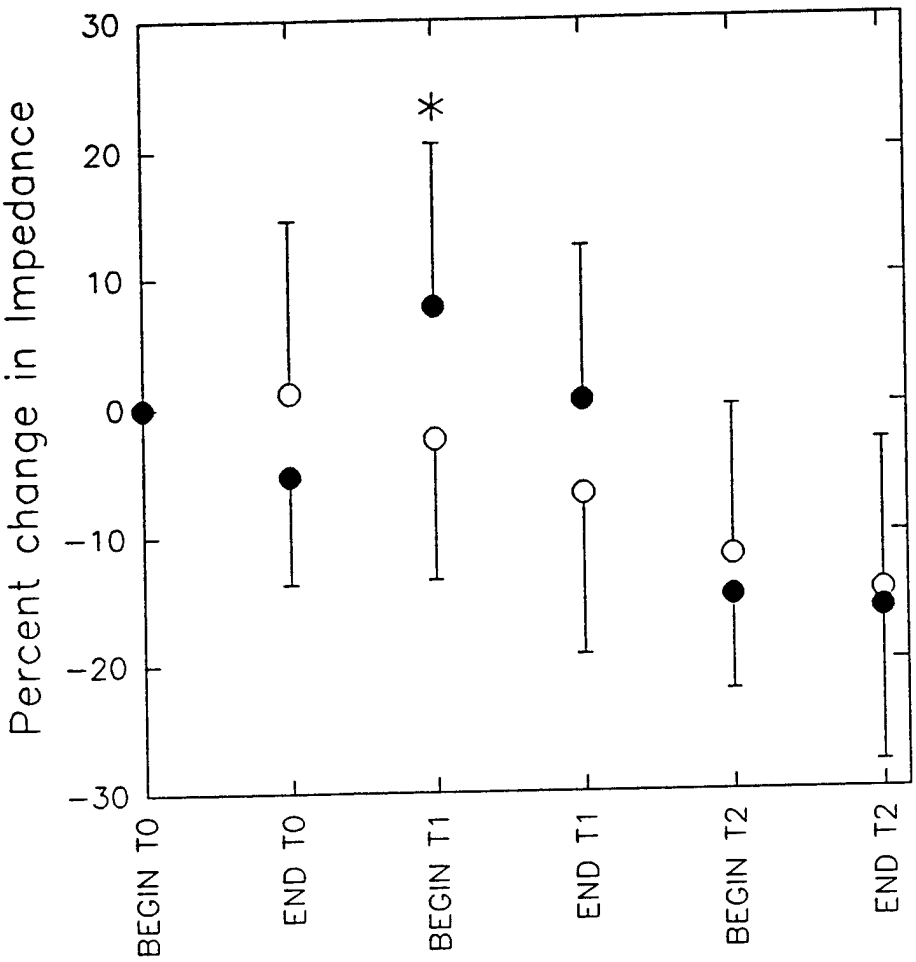

Sample Dose–Response Curves
from a Single (Hypothermic) Study
Percent Defibrillation Success
100
75
50
25
0
1
2
3
4
5
Energy (Joules)
T=0
T=1
T=2
Derived E_{50} (J)
2.3
3.5
3.1

Figure 2


Percent change in Impedance
30
20
10
0
−10
−20
−30
*
BEGIN T0
END T0
BEGIN T1
END T1
BEGIN T2
END T2