Relation Between Shock-Related Myocardial Injury and Defibrillation Efficacy of Monophasic and Biphasic Shocks in a Canine Model

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Background Certain biphasic waveforms with specific time ratios of positive and negative components require less energy for successful defibrillation of the fibrillating ventricles than monophasic waveforms. However, if more efficient waveforms were also to be associated with more injurious effects on myocardial function, they might not provide a true biological advantage. This study investigates the relation between defibrillation efficacy and potential toxicity of monophasic and asymmetric, single capacitor, biphasic waveforms with equal durations of positive and negative components.

Methods and Results The myocardial lactate extraction rate (LER) was used to measure the injurious effects on myocardial oxidative metabolism of two synchronized 35-J shocks in sinus rhythm. LER, mean arterial pressure (MAP) and, in a subset of experiments, cardiac output (CO) and coronary blood flow (CBF) were measured at baseline, 30 seconds, 60 seconds, 90 seconds, 150 seconds, 300 seconds, and 600 seconds after the shocks. In 12 dogs, three different waveforms (M 10: monophasic 10 milliseconds; BI 10: biphasic 10 milliseconds; BI 20: biphasic 20 milliseconds) were tested as series of two consecutive shocks (60 seconds apart) resulting in a total of 36 sets of data. At baseline, LER was 25±11%. After monophasic shocks, LER decreased significantly more than after biphasic shocks (LER at 150 seconds: M 10: -6±31% versus BI 10: 21±15% versus BI 20: 21±16%; M 10 versus BI 10 and M 10 versus BI 20, P<.05) and showed also a slower recovery (LER at 300 seconds: M 10: 1±24% versus BI 10: 20±11% versus BI 20: 20±15%; M 10 versus BI 10 and M 10 versus BI 20, P<.05).

With the introduction of nonthoracotomy lead (NTL) systems and the decrease in morbidity and mortality of device implantation,1,2 the implantable cardioverter-defibrillator (ICD) has increasingly been used in patients with severe left ventricular dysfunction. Generally, NTL configurations require higher energy for defibrillation than epicardial lead systems.3-6 Defibrillation energy requirements, however, have been shown to decrease by using specific biphasic shocks with equal duration of positive followed by negative components (5- and 5-millisecond biphasic shocks) in experimental models, whereas other ratios may result in even more superior or actually less efficient shocks.7 Recent clinical availability of biphasic shock capability with its higher defibrillation efficacy allows the successful implantation of NTL systems in more than 90% of patients.8,9 Clinically, the higher defibrillation efficacy of certain biphasic waveforms has been reported in several studies.5-16 Extensive studies performed in cultured chick embryo myocardial cells have shown that not only defibrillation efficacy but also adverse effects such as postcountershock mechanical dysfunction and arrhythmias depend largely on the waveforms used.14,16-19 This relation between defibrillation efficacy and potential toxicity is less well studied in vivo models and clinically, and it remains to be shown whether the potential advantage of the higher efficacy of currently clinically used biphasic waveforms may be outweighed by more injurious effects on myocardial function and therefore provide no true biological benefit. This might become an important safety issue in patients with critical left ventricular dysfunction.

Electrical myocardial injury, ranging from reversible myocardial depression with arterial hypotension and intermittent heart block to irreversible myocardial necrosis, is a well-recognized complication of high-energy transventricular defibrillation.20-23 Experimental studies have identified impaired mitochondrial function with transient suppression of oxidative metabolism and the generation of free intracellular radicals as possible mechanisms underlying high-energy transventricular defibrillation injury.24-26 These injurious effects on cell...
metabolism, together with their indirect effects on intracellular ion homeostasis, lead to cell membrane disruption and disintegration of normal cell structures. It is not known whether such injurious effects may also result from repetitive internal ICD countershocks, and only limited data about shock-induced deterioration in cardiac function have been reported in the literature. Using hemodynamic and metabolic monitoring techniques, the present study investigates the relation between electrical shock–related myocardial injury and defibrillation efficacy of monophasic and biphasic shocks delivered during sinus rhythm.

**Methods**

**Experimental Preparation**

The protocol was approved by the Massachusetts General Hospital Committee on Research and the Subcommittee on Research Animal Care, and all procedures were conducted in compliance with the guidelines from the NIH Guide for Care and Use of Laboratory Animals.

Twelve mongrel dogs (weight, 35 ± 6.7 kg; range, 27 to 46 kg) were anesthetized with methohexital (15 mg/kg) and pentobarbital (20 mg/kg) and ventilated with oxygen (2 L/min) and room air. Deeper anesthesia for operative procedures was achieved with additional halothane (1.0% to 2.0%), which was later discontinued to avoid anesthesia-related myocardial depression during the study protocol. To reduce shock-induced skeletal muscle contractions with uncontrolled lactate release into the systemic circulation, muscle relaxation was induced by intravenous administration of metocurine iodide (0.05 to 0.10 mg/kg). Under general anesthesia, the heart was exposed via a left lateral thoracotomy through the fourth intercostal space. After the pericardium was opened, two defibrillation patch electrodes (Ventritex Inc) with a surface area of 8 cm² were positioned over the right ventricular outflow tract and the left ventricular inferior wall and sutured to the epicardial surface to ensure proper contact of the patch electrodes with the myocardium. Then the pericardium was closed. At the end of the implantation procedure, a single synchronized 10-millisecond monophasic test shock of 500 V was delivered for determination of the lead resistance, which was later used for estimation of the first shock energy. After externalization of the leads, the chest was closed in layered fashion, and intrathoracic air was evacuated via suction over a chest tube.

Under fluoroscopy, a coronary sinus NIH 7F catheter with two side holes (USCI) was placed in the coronary sinus via the right external jugular vein. A standard quadripolar 7F EP catheter (Webster Laboratories Inc) was inserted through the right femoral vein and positioned at the right ventricular apex (RVA) for later pacing and sensing purposes. Heart rate (HR), intracardiac electrograms (IECG), surface ECG, and the mean arterial pressure (MAP) were monitored continuously. Arterial blood samples were analyzed at regular intervals to keep the arterial blood gas values in the physiological range (SaO₂ > 95%; PCO₂, 38 to 44 mm Hg; pH, 7.36 to 7.44).

**Defibrillation Protocol**

The externalized defibrillation electrodes (RV-patch=positive polarity, LV-patch=negative polarity) and the right ventricular pacing and sensing electrode catheter were connected to an HVS-02 pulse generator (Ventritex), which has the capability to deliver synchronized monophasic and single capacitor (150-μF) biphasic high-energy shocks with truncated exponential waveforms of programmable voltage (50 to 990 V) and pulse duration (0.5 to 20 milliseconds). The study protocol required the delivery of two synchronized 35-J shocks during sinus rhythm with an interpulse duration of 60 seconds. The stored voltage for the first 35-J shock was estimated based on the resistance and measured energy of the test shock at the end of the implantation procedure. If the delivered first shock energy differed by more than ±1.5 J from the estimated energy (35 J), adjustments were made for the second shock based on the actual measurements of the first shock. Lead impedance (R), delivered energy (E), and stored voltage (V) were recorded for each shock.

Two different biphasic waveforms (Fig 1) with a 50:50 phase duration (BI 10: 5- to 5-millisecond biphasic pulse, total pulse duration 10 milliseconds, first component positive, and BI 20: 10- to 10-millisecond biphasic pulse, total pulse duration 20 milliseconds, first component positive) were compared with a single monophasic pulse wave (M 10: monophasic pulse wave, 10-millisecond pulse duration). In random order, each waveform (M 10, BI 10, BI 20) was tested as two consecutive 35-J shocks delivered during sinus rhythm, which allowed us to study metabolic and hemodynamic changes unrelated to myocardial ischemia superimposed by the induction of ventricular fibrillation (VF). Since the 50:50 ratio was never altered throughout the study, “biphasic” will mean biphasic with a 50:50 phase ratio (5 and 5 milliseconds biphasic or 10 and 10 milliseconds biphasic) for the rest of this study.

**Metabolic and Hemodynamic Monitoring**

The lactate concentration was simultaneously measured in the arterial and the coronary sinus (CS) blood at baseline (t 0), 30 seconds (t 30), 60 seconds (t 60), 90 seconds (t 90), 150 seconds (t 150), 300 seconds (t 300), and 600 seconds (t 600) after delivery of the first synchronized shock. The first shock was delivered immediately after baseline measurements (L<sub>Ebaseline</sub>, MAP<sub>baseline</sub>) and the second in a similar fashion immediately after the measurements at elapsed time 60 seconds (L<sub>Epostshock</sub>, MAP<sub>postshock</sub>).

Immediate deproteinization of the blood with 0.6N perchloric acid (incubated tubes) and storage on ice ensured that the blood lactate was not further metabolized in vitro and that the measured lactate concentration was accurate. The lactate-pyruvate-dehydrogenase method (enzymatic assay with spectrophotometric measurement of NADH production) was used for lactate measurements. For standardization of the assay, a standard curve using a Sigma 735-11 standard series was obtained. The lactate extraction rate (LER) was derived from the arteriovenous difference of the lactate concentration in the arterial (art) and CS blood and expressed as a percentage (LER = ([lactate]<sub>art</sub> - [lactate]<sub>CS</sub>)/[lactate]<sub>art</sub> × 100). The minimal LER (LER<sub>min</sub>) was defined as the lowest LER measured at any point after delivery of the first shock, and the maximal decrease in LER was derived by comparing LER<sub>min</sub> with LER<sub>baseline</sub>. Similarly, the lowest MAP (MAP<sub>min</sub>) after shocks was used to calculate the maximal decrease in MAP. To enable the metabolic and hemodynamic changes to return to baseline,
a recovery period of at least 15 minutes was provided after completion of each shock series.

Continuous hemodynamic monitoring (HR, MAP) was obtained in all experiments (36 of 36). Metabolic monitoring (LER) was obtained in only 34 of 36 experiments; in one experiment (BI 10), the coronary sinus catheter was displaced and could not be repositioned. In another experiment (BI 20), the catheter was occluded and did not allow further blood sampling after the shocks. Serial cardiac outputs (CO) measured by the thermodilution technique (7F Swan Ganz catheter, 2095A Cardiac Output Computer, Edwards Laboratories), continuous pulmonary artery (PA) and right atrial (RA) pressures, as well as continuous coronary blood flow (CBF) measurements using a Doppler flow probe (2R probe, HT 101D, Transonic Systems Inc) over the exposed left anterior descending artery were additionally obtained in 8 of 36 experiments. Vascular resistance in response to high-energy shocks was calculated for the systemic arterial and coronary arterial circulation \( R = [P1 - P2]/flow \).

### Defibrillation Threshold Measurements

After acquisition of hemodynamic and metabolic data for the three different shock wave series, the defibrillation efficacy was assessed for each waveform (M 10, BI 10, and BI 20) by determining the defibrillation threshold (DFT) using the same electrode configuration and polarity as before. For DFT estimation, VF was repeatedly induced by burst pacing (output, 10 V; pulse duration, 1.5 milliseconds; cycle length, 20 to 50 milliseconds) at the RVA. After a 10-second period of VF, a high-energy shock at a selected energy was delivered for VF termination, followed by a first rescue shock of 25 J and a second of 40 J if VF was not successfully terminated. A 3-minute recovery period was allowed between each VF induction. A “up-and-down” algorithm was used for determination of the DFT.31 With this algorithm, the actually tested shock energy is determined by the success of the preceding shock. Starting at 15 J, the energy was decreased by 1.0-J steps after each successful shock until failure to defibrillate was encountered. After a nonsuccessful shock, a rescue shock was delivered, and the energy was increased by 1.0 J for the subsequent defibrillation attempt. Depending on the result of this latter defibrillation attempt, we either further increased the energy for the subsequent shock or decreased it again. This algorithm was carried out until a triplicate confirmation of the lowest successful shock energy was found, which was defined as the DFT. This DFT estimation is comparable to the ED50 derived from sigmoidal dose-response curves.30,31 If a rescue shock was required, a recovery of 5 minutes was allowed to let the hemodynamic parameters return to baseline and ensure stability of the preparation throughout the study. Leading-edge voltage, delivered energy, and measured resistance were recorded for each single defibrillation shock.

### Statistical Analysis

All values are given as mean±1 SD. Continuous variables were compared (baseline versus values at specific time intervals) using two-sided paired Student’s t test (Figs 2 and 3). ANOVA with repeated measures was used to compare serial measurements between different groups to detect global differences among the different shock waves. Because it was also desirable to determine at which time interval a significant difference from baseline occurred, the ANOVA was performed with factorial analysis using a Scheffe’s F test (Figs 4 through 7). A value of \( P < .05 \) was considered to indicate a significant difference.

### Results

A total of 36 series consisting of two synchronized 35-J shocks during sinus rhythm were given in 12 animals. In random order, a series of two monophasic shocks of 10-millisecond duration (M 10) separated by a 60-second period was compared with a series of two similarly spaced biphasic shocks of 10-millisecond duration (BI 10) and another series of two biphasic shocks of 20-millisecond duration (BI 20) in each animal. All 72 shocks were confirmed to be synchronized to the IECG signal recorded at the RVA, and none of them induced VF. However, in some experiments the shocks induced brief runs of accelerated junctional or idioventricular rhythm, which uniformly terminated spontaneously within a few seconds. Thirty-four of 36 series of lactate sampling (M 10: \( n=12 \); BI 10: \( n=11 \); BI 20: \( n=11 \) ) were successfully completed and therefore included in this analysis. The DFT for each waveform was determined after completion of the lactate sampling protocol in all 36 experiments.

### Metabolic and Hemodynamic Response to High-Energy Shocks in Sinus Rhythm

The mean delivered energy, resistance, and leading-edge voltage are listed separately for each waveform in the Table. Biphasic waveforms of 10-millisecond duration (BI 10) required a significantly higher voltage for delivery of a 35-J shock than monophasic shocks of 10 milliseconds (M 10), whereas biphasic shocks of 20 milliseconds (BI 20) were characterized by the lowest voltage of all tested waveforms \( (P < .001 \) by ANOVA).

The mean LER at baseline was 25±11% (range, 5% to 48%) for all configurations tested, indicating that lactate was extracted and metabolized by the myocardium (positive values). Fig 2 depicts the overall changes of LER in response to two consecutive 35-J shocks during sinus rhythm (\( n=34 \) experiments). LER decreased significantly from 25±11% \( (\text{LER}_{\text{baseline}}) \) to 17±19% after the first shock \( (\text{LER}_{1}) \) and to 11±25% after the second shock \( (\text{LER}_{2}) \). After 10 minutes of
recovery, LER was still significantly depressed compared with baseline (24.8±11.1% versus 20.2±14.5%; LERbaseline versus LERmin; P<.05 by paired t test).

The MAP showed a parallel decrease after shocks (Fig 2, bottom). Although the recovery of MAP was faster than that of LER, it was incomplete, with the pressures remaining slightly depressed after 10 minutes compared with baseline (94±16 versus 90±17 mm Hg, MAPbaseline versus MAPmin; P=.05 by paired t test).

Since the time course of decrease in LER manifested marked individual variations, the lowest LER measurement (LERmin) at any point after the shocks was compared with the corresponding baseline value (LERbaseline). By this analysis, a maximal decrease in LER was observed (LERmax = [LERbaseline - |LERmin|] of 25±22% was observed (P<.0001 by paired t test). Fig 3 compares LER at baseline with the lowest values for each experiment individually. Myocardial lactate production, as indicated by negative LER values, occurred in 13 of 34 experiments (38%). Similarly, there was a comparable maximal decrease in MAP of 22±15 mm Hg, if the lowest MAP (MAPmin) was compared with the corresponding baseline value (MAPbaseline) in each series (Fig 3, right). For the following analysis, both the maximal decrease in LER (LERmax) and MAP (MAPmax) as well as their absolute changes over time were used for quantitative comparison of defibrillation injury caused by the three different shock waves (M 10, BI 10, BI 20).

**Fig 2.** Bar graphs show metabolic and hemodynamic changes after two consecutive 35-J shocks in sinus rhythm for all experiments (n=36). The first shock was delivered immediately after completion of the baseline measurements and the second was delivered 60 seconds apart (dashed lines). Top, Overall response of the lactate extraction rate in 34 of 36 experiments (M 10: 12 of 12 series of monophasic shocks of 10 milliseconds; BI 10: 11 of 12 series of biphasic shocks of 10 milliseconds; BI 20: 11 of 12 series of biphasic shocks of 20 milliseconds of pulse duration). Bottom, Changes in mean arterial pressure are shown at the same time intervals after shocks. Values are given as mean±SD. Changes after shocks are compared with baseline using a two-sided paired t test.

**Fig 3.** Plots show maximal changes in lactate extraction and mean arterial pressure compared with their baseline values for all experiments (two-sided paired t test). The minimal lactate extraction rate (LERmin) and the minimal arterial blood pressure (MAPmin) were defined as the lowest values observed at any time after the shocks. Mean values ±1 SD are depicted.

**Shock-Related Myocardial Injury of Monophasic and Biphasic Shocks**

Fig 4 depicts the serial changes in LER after delivery of monophasic and biphasic shock waves. During late recovery, LER150 and LER300 were markedly lower after two monophasic shocks than after two biphasic shocks (M 10 versus BI 10 and M 10 versus BI 20, both P<.05 by ANOVA with factorial analysis), whereas no significant difference between the two biphasic shock waves was found. In 7 of 12 series (58%) of monophasic shocks, lactate production occurred immediately after the shocks, accounting for a negative mean LER for the whole group at 150 seconds of elapsed time (LER150 =6±31%). In contrast, lactate production was observed in only 6 of 22 series (27%) with biphasic shocks (P=.15). There was also a greater decrease in MAP after monophasic shocks, but statistically the difference between M 10 and BI 20 was only borderline significant (Fig 5).
When the maximal decrease in LER and MAP were compared (Fig 6), the differences between monophasic and biphasic shocks became even more evident, with the monophasic group showing a decrease in LER by 41±27% compared with 18±15% (BI 10) and 15±11% (BI 20) in the groups with biphasic shocks (P<.05). The difference between the two biphasic shocks did not reach statistical significance. Similarly, the maximal decrease in MAP (MAP_{max}) was greater after monophasic shocks (28±15 mm Hg versus 21±15 mm Hg versus 14±11 mm Hg; M 10 versus BI 10 versus BI 20), but this difference was only significant between the groups with monophasic shocks of 10-millisecond and biphasic shocks of 20-millisecond duration (P<.05). Neither voltage nor pulse duration showed a significant correlation with the maximal decrease in LER or MAP, although there was a trend toward a greater maximal decrease in LER with higher leading-edge voltages after monophasic shocks ($r^2 = .35$). However, since the delivered energy was kept constant (35 J), our protocol did not generate sufficient data to define a dose-response curve.

Fig 5. Similar to Fig 4, plot shows the mean arterial blood pressure response to two consecutive 35-J shocks in sinus rhythm depicted for each shock waveform. Although there was a trend toward a more marked hypotension after monophasic compared with biphasic shocks, statistically the difference was only borderline significant between M 10 and B 20 at 90 seconds (P=.10). Abbreviations as in Fig 4.

Fig 6. Similar to Fig 3, bar graphs show maximal decrease in the lactate extraction rate (LER) (left) and mean arterial pressure (right) used for quantitative comparison of the three different shock waveforms (statistical comparison by ANOVA by factorial analysis). The maximal decrease in LER was significantly greater after monophasic shocks than after biphasic shocks. The maximal decrease in MAP, however, was only significantly different between M 10 and BI 20. Abbreviations as in Fig 4. Values are given as mean±1 SD.

Fig 7. Graphs show changes in cardiac output (CO) and systemic vascular resistance as well as coronary blood flow (CBF) and coronary vascular resistance measured over the left anterior descending artery in a subset of eight experiments. A significant decrease in cardiac output compared with baseline (P<.001 by two-sided paired t test) was observed after the second shock (t 60), followed by a prolonged recovery. CBF was intermittently increased after the first shock (P=NS compared with baseline) but stabilized within a narrow range of its baseline value during late recovery when the CO was still reduced. Moreover, at the time when the greatest decrease in LER (t 150 and t 300) was observed, coronary perfusion was normal, suggesting that the changes in LER were not CBF-related but reflected a direct depression of myocardial oxidative metabolism.

Influence of High-Energy Shocks on Coronary Flow and Cardiac Output

In the present study, a decreased LER (or a reduced arteriovenous difference between the arterial and coronary sinus lactate concentration) was used as an indicator of depressed myocardial oxidative metabolism. However, to confirm that the increased lactate concentration after shocks measured in the coronary sinus blood was related to a depressed myocardial lactate extraction and did not result from ischemia or an increased lactate supply to the heart as a consequence of elevated coronary perfusion, CO and continuous CBF were additionally measured in eight experiments.

The blood pressure response in this subset was comparable to that of the whole study group (Fig 2). In all eight experiments, MAP and CO decreased significantly after the shocks with a prolonged and incomplete recovery after 10 minutes in all measured parameters (Fig 7). After an initial decrease, the peripheral vascular resistance increased in response to the markedly depressed CO and MAP after the second shock and returned to baseline after 10 minutes despite persistently reduced CO (Fig 7). In three of eight experiments, an early increase in CBF up to 230% was observed after the first shock, whereas in the remaining five of eight experiments, only minimal changes within a 10% to 20% range were found. However, 90 seconds after the first shock, CBF was only mildly decreased and
remained within a 5% to 10% range of the baseline value beyond 90 seconds of recovery in eight of eight experiments. Moreover, at the time when the maximal decrease in LER was documented (LER<sub>1150</sub>, LER<sub>99</sub>), CBF had returned to baseline. Maintenance of CBF during markedly reduced CO and arterial hypotension after the shocks (t 60, t 90) was related to a decrease in coronary resistance with selective coronary vasodilatation at a time when systemic vascular resistance was increased. Pulmonary vascular resistance increased only moderately, and the PA pressures remained stable despite a significant reduction in CO after the shocks. Thus, the decrease in LER found in our study appears to be related to a suppression of the myocardial oxidative metabolism and is not related to changes in coronary perfusion.

**Defibrillation Efficacy of Monophasic and Biphasic Shocks**

For each waveform, the DFT was assessed after completion of the study protocol. As shown in Fig 8 (left), the energy requirements for reliable defibrillation were significantly higher for monophasic 10-millisecond shock waves compared with biphasic 10-millisecond waveforms (18.6±8.6 J versus 11.5±4.0 J; M 10 versus BI 10; P<.05). The DFT for biphasic 20-millisecond waveforms (BI 20: 15.0±6.1 J) did not significantly differ from the other two waveforms. If the lowest voltage required for successful defibrillation was compared (Fig 8, right), there was no significant difference among the three groups, although there was a trend toward a lower leading-edge voltage for biphasic shock waves (540±117 V versus 475±79 V versus 470±97 V; M 10 versus BI 10 versus BI 20, respectively; P=NS).

**Discussion**

Although serious adverse effects including death have been observed after high-energy transthoracic defibrillation shocks. In the present study, we have demonstrated that internal defibrillation suppresses myocardial oxidative metabolism and cardiac function for at least several minutes after shock delivery. After two 35-J shocks in sinus rhythm, myocardial lactate extraction and hemodynamic performance assessed by CO and arterial blood pressure were substantially impaired and did not fully recover after 10 minutes of recovery. Biphasic shocks were less injurious on myocardial oxidative metabolism compared with monophasic shocks of the same energy and were also associated with less systemic hypotension. In terms of defibrillation efficacy, biphasic shocks required less energy for defibrillation as reflected in lower DFTs. Given the higher defibrillation efficacy and the less injurious effects on myocardial oxidative metabolism and hemodynamic function, the safety margin between efficacy and toxicity, or the “therapeutic range” of biphasic is better than monophasic shock waves, which might provide an important long-term benefit in patients with frequent ICD discharges.

**Mechanisms of Myocardial Defibrillation Injury by High-Energy Shocks**

Since the clinical introduction of direct-current transthoracic defibrillation by Lown et al., serious doubts about adverse outcome after repeated transthoracic countershocks with high-energy direct current have been raised. Complete heart block, severe hypotension resulting in death, as well as myocardial necrosis have previously been reported as complications of high-energy transthoracic defibrillation. However, despite the widespread clinical use of ICDs, there are only a few reports in the literature that suggest that repetitive defibrillation shocks may have serious adverse effects on myocardial function in patients with preexisting left ventricular dysfunction.

Experimental studies have documented myocardial necrosis and acute death after high-energy transthoracic shocks. Severe depression of myocardial lactate and free fatty acid extraction as well as an increase in coronary sinus oxygen saturation after defibrillation offer strong evidence for a shock-induced dysfunction of cell respiration and oxidative metabolism. Membrane breakdown, in addition to functional and morphological mitochondrial changes after high-energy shocks, suggests that an uncoupling effect on the electron transport chain of the mitochondrial membrane may be the primary mechanism of defibrillation injury. However, a recent study in which isolated mitochondria were exposed to high-energy shocks did not find such an uncoupling effect, and the measured lactate extraction in this cell-free mitochondria preparation remained unaffected. Therefore, it was speculated that the in vivo documented suppression of oxidative metabolism might be related to an increased transmembrane permeability and intracellular accumulation of toxic mediators (eg, free intracellular calcium overload or formation of free radicals). This theory is supported by the finding that defibrillation-related myocardial necrosis is reduced by pretreatment with calcium channel blockers but not with β-adrenoceptor blocking agents.
Quantitative Assessment of Myocardial Defibrillation Injury

For the purposes of our study, myocardial LER was chosen as a quantitative marker of defibrillation injury. Although the LER after shocks manifests great interindividual variability, no significant increase in LER was observed after shocks in any of our experiments (Fig 3). The finding that LER recovered more slowly after monophasic shocks than after biphasic shocks suggests that biphasic shocks are less injurious on myocardial oxidative metabolism than monophasic shocks of the same energy. Similar to the metabolic changes was also a trend toward greater systemic hypotension after monophasic shocks (Fig 5). On the basis of our results it appears that metabolic and, to a lesser degree, hemodynamic monitoring are valuable tools for the quantitative comparison of defibrillation injury caused by different shock waves.

In a previous study using a similar defibrillation protocol with two damped cine wave 30-J shocks delivered during sinus rhythm, the investigators reported a maximal decrease in LER from 37% to -20% (lactate production) 2.5 minutes after the first shock. This more marked decrease in LER compared with our study may be related in part to the use of paddles with a greater contact area (19.6 cm² compared with our 8-cm² patches) and also to differences between the shock waves used. However, the shock-related decrease in MAP was comparable with our findings. In that study, relative myocardial ischemia as a potential source of lactate production was excluded by 99mTc pyrophosphate perfusion scintigraphy. In our study, continuous CBF measurements over the left anterior descending coronary artery were used for monitoring coronary perfusion. In fact, by this technique an early increase in CBF immediately after the shocks with return to baseline by 90 seconds was observed. Our results and findings from other studies suggest that this early coronary vasodilation (when the CO is still unchanged) might be directly induced by electrical shocks, whereas the decrease in coronary vascular resistance during late recovery probably occurs as an autoregulatory response to the depressed CO. However, at the time when the maximal decrease in LER (LER150 and LER300) was documented, CBF was constant compared with its baseline value. This finding suggests that the rise in CS lactate concentration seen in this study represents a true suppression of myocardial oxidative metabolism rather than an ischemia-related increase in lactate production or an increased lactate supply due to increased coronary flow.

Currently, there are no data in the literature comparing the adverse effects of monophasic and biphasic internal high-energy defibrillation shocks by other quantitative techniques. Indirect evidence that biphasic shocks may be less injurious compared with monophasic shocks can be found in the work of Zhou et al, who documented less prolongation of the stimulated postshock action potential (MAP) duration after biphasic shocks. This direct effect on repolarization may result in a decreased inhomogeneity of myocardial refractoriness, which in turn may explain the lower propensity for postshock arrhythmias of biphasic waveforms. Although it is difficult to explain metabolic changes by invoking such a mechanism, the two phenomena may share common features such as an intracellular electrolyte imbalance due to a changed membrane and ion-channel permeability. Tovar and Tung demonstrated that both monophasic and biphasic shock waves of the same voltage have the potential to induce cell membrane leakage to a variable degree. Although there was a trend toward a faster recovery after biphasic shocks, the difference between monophasic and biphasic shocks was not significant. This shock-induced membrane leakage with alterations in the intracellular ionic composition with the secondary potential to arrhythmias and dysfunction of the contractile apparatus was documented over a time course of seconds to minutes after the shocks and was even irreversible in some preparations.

Therapeutic Range of Monophasic and Biphasic Defibrillation Shocks

On the basis of the above observations, it appears that monophasic and biphasic shock waves have different effects on cellular membranes, resulting in a differing potential to cause intracellular electrolyte changes that secondarily affect cellular metabolism and electrophysiological properties. These effects may account in part for the differences in defibrillation energy requirements between monophasic and biphasic shocks, but at the same time, they may also be responsible for a different susceptibility to electrical myocardial injury. The concept of a waveform specific safety ratio dates back to the work of Jones and Jones. These investigators used cultured chick embryo myocardial cells to investigate in vitro postcoustershock myocardial dysfunction and arrhythmias and demonstrated that biphasic waveforms had larger safety factors than truncated or rectified waveforms. Recent work from the same investigators demonstrated less injurious effects on myocardial function with triphasic waveforms as measured by postshock contractility of cultured myocardial cells.

In our study, biphasic shocks of 10-millisecond duration were characterized by significantly lower DFTs than monophasic shocks, whereas biphasic shocks of 20-millisecond duration did not differ significantly from either form (Fig 8). If the DFT was defined as the lowest voltage required for successful defibrillation, biphasic waveforms provided only a marginal advantage, which did not reach statistical significance. However, if the less injurious effects of biphasic waveforms are taken into account, the safety margin, or “therapeutic range,” appears to be better for biphasic waveforms.

Limitations

A major limitation of our study is the lack of a “gold standard” for the quantitative assessment of defibrillation injury in vivo. Hemodynamic changes are not accurate enough to detect subtle differences between different shock waves, whereas metabolic monitoring with the method of LER is limited by a considerable interindividual variability. Although compared with histopathological studies, LER monitoring provides the important advantage that different shock waves can be compared in the same animal, it introduces another limitation, namely, that irreversible changes incurred from a preceding series of shocks may influence the
results of the subsequent series. To attempt to overcome this problem, our protocol provided a long recovery period of at least 15 minutes between the shock series. For the same reason, only two shocks per series were delivered, and to avoid irreversible injury incurred from extensive DFT testing, the DFTs were obtained after completion of the study protocol. Therefore, the shock waves had to be compared at fixed rather than individualized energy levels (eg, twice DFT energy for a given heart), which biologically might have been more relevant.

Although relatively large animals were used for this study, and the average heart size was comparable to that of a human heart, energy requirements and resulting voltage gradients across the myocardium are likely to be different in humans. Furthermore, in our experiments, the patch electrode size was relatively small compared with those commonly used for clinical epicardial implantation. Therefore, the results of our study should be extrapolated to the clinical setting with appropriate caution.

Clinical Implications and Conclusions

The results of the present study suggest that biphasic shocks are more efficient at defibrillation and are also associated with less injurious effects on myocardial oxidative metabolism and cardiac function. Therefore, the use of biphasic waveforms should not necessarily be limited to patients with high DFTs, since the better therapeutic range may provide an important long-term benefit in patients with frequent ICD discharges and patients with severe left ventricular dysfunction. Future research should focus not only on defibrillation efficacy but also on defibrillation injury and ways of minimizing it.

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