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Direct Current Shocks to the Heart Generate Free Radicals: An Electron Paramagnetic Resonance Study

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Objectives. **We sought to demonstrate that direct current (DC) shocks to the heart generate free radicals.**

Background. **Although it is a lifesaving maneuver, defibrillation is known to have myocardial toxicity. The mechanism of this toxicity is unknown. If DC shocks generate free radicals, free radicals could be a mechanism of myocardial injury.**

Methods. **In a canine model, DC shocks of 10 to 100 J were delivered to the epicardium of both beating and fibrillating hearts, and 200-J transthoracic shocks were administered in dogs with beating hearts. Ascorbate free radical (AFR) concentration was measured in arterial blood and blood continuously withdrawn from the coronary sinus. In some dogs, the antioxidant enzymes superoxide dismutase (15,000 U/kg) and catalase (55,000 U/kg) (SOD/Cat) were administered before shocks.**

Results. **Ascorbate free radicals were generated by DC shocks. A peak AFR increase of 14 ± 2% (mean ± SEM) was seen 5 to 6 min after 100-J epicardial shocks. A peak AFR increase of 7 ± 5% occurred after transthoracic shocks. There was a significant linear relation between the shock energy and peak percent AFR increase: %AFR increase = 0.18 (Shock energy) + 2.9 ($r = 0.73$, $p < 0.0001$). Shocks delivered to hearts in ventricular fibrillation (30 s) resulted in generation of AFR equal to but not greater than that observed during similar shocks delivered to beating hearts in sinus rhythm. Multiple successive shocks (100 J delivered twice or five times) did not result in a greater AFR increase than single 100-J shocks, indicating that peak, not cumulative, energy is the principal determinant of AFR increase. Animals receiving SOD/Cat before shock administration showed significant attenuation of the AFR increase.**

Conclusions. **Direct current epicardial and transthoracic shocks generate free radicals; antioxidant enzymes reduce the free radical generation by shocks.**

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Electrical defibrillation is the critical maneuver in cardiac arrest due to ventricular fibrillation (VF). Nevertheless, defibrillation can result in myocardial injury, with morphologic and functional evidence of damage (1–5).

The mechanism of defibrillation injury has not been established. Myocardial necrosis and contraction abnormalities may be related to the ischemic period of arrested circulation during VF or to the toxicity of the direct current (DC) shock itself. Both may play a significant role.

Oxygen free radicals are formed when molecular oxygen is reintroduced into ischemic myocardium on reperfusion (6–8), such as occurs in the setting of ventricular fibrillation followed by defibrillation. A recent study (9) suggests that free radicals are generated by DC countershocks alone, delivered to beating hearts not in VF. This finding is consistent with a study (10) that showed that free radicals could be generated solely by an electrical current passing through a physiologic buffer solution. Because oxygen free radicals have known toxicity (11,12), the generation of oxygen free radicals by DC shocks may be a mechanism of defibrillation injury.

The purpose of our study was to evaluate the magnitude and determinants of free radical generation after DC shocks delivered to both fibrillating and nonfibrillating hearts. In an open chest canine model, we utilized a newly developed and validated technique, electron paramagnetic resonance (EPR) measurements of ascorbate free radicals (AFRs), a real-time quantitative marker of free radical generation (13). Six sets of experiments were performed to 1) determine the effect of epicardial shock energy on the magnitude of AFR generation; 2) compare the AFR generation of shocks delivered to fibrillating versus nonbeating hearts; 3) determine whether multiple shocks generate more AFRs than a single shock at the same energy level; 4) determine the effect of the free radical scavenging enzymes superoxide dismutase (SOD) and catalase (Cat), given before shock delivery, on the magnitude of AFR generation; 5) demonstrate that direct contact between the metal electrodes and the epicardial surface of the heart is not required for DC shocks to generate AFRs; and 6) determine whether transthoracic shocks generate AFRs.

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Abbreviations and Acronyms

AFR = ascorbate free radical
Cat = catylase
DBP = diastolic blood pressure
DC = direct current
ECG = electrocardiographic
EPR = electron paramagnetic resonance
NSR = normal sinus rhythm
SBP = systolic blood pressure
SOD = superoxide dismutase
VF = ventricular fibrillation

Methods

Animal preparation. An open chest canine model was used; 38 dogs were studied in total. General anesthesia was achieved with a combination of fentanyl–droperidal (0.13 ml/kg), followed by intravenous pentobarbital (20 mg/kg body weight), supplemented as needed during the course of the experiment. Respiratory support was provided with a volume-cycled respirator after endotracheal intubation. Tidal volume, rate and fraction of inspired oxygen were adjusted according to arterial blood gases to maintain physiologic arterial pH and partial pressure of oxygen.

Femoral arteries and veins were cannulated in both limbs. The left femoral artery was used to monitor blood pressure and the left femoral vein for infusions. Through a left lateral thoracotomy, the pericardial sac was opened and the heart suspended in a cradle. A catheter was passed through the jugular vein into the distal portion of the coronary sinus. A venous–venous shunt was fashioned between the coronary sinus and right femoral vein. Surface electrocardiographic (ECG) recordings were obtained for rhythm and heart rate monitoring before and after administration of shocks.

Electron paramagnetic resonance methods. Measurement of AFR has been previously validated (13,14) as a measure of total oxidative stress and has been described in detail. Ascorbate is the terminal, small-molecule antioxidant; it repairs more oxidizing radicals, such as hydroxyl, superoxide and lipid peroxyl radicals (14,15). Because it donates an electron (hydrogen atom) to repair these oxidizing radicals, ascorbate itself is converted to a free radical, the AFR. This relatively stable pi-radical can be detected and quantitated by the EPR technique. The steady state AFR concentration is proportional to the *total* ongoing oxidative stress of the interventions evaluated.

Electron paramagnetic resonance spectra were obtained using a Varian E-4 spectrometer, with a TM_{110} cavity and an aqueous flat cell. Scans were collected serially on blood being continuously withdrawn from either the great cardiac vein or the femoral artery. Consecutive EPR scans of the coronary venous or femoral artery AFR blood were initiated every 90 to 120 s. A single scan requires 90 s. Because the AFR yields a doublet EPR spectrum, each scan yields two data points, ~45 s apart. An infusion pump was used to circulate the sample through the spectrometer and return it to the dog. In this way, blood could be scanned for AFR concentrations within several seconds of leaving the animal. The following instrument settings were used for all studies because they provide the largest AFR signal (16): nominal power 40 mW, modulation amplitude 0.63 G, time constant 1 s and scan rate 1 G/24 s. A 40-mW nominal microwave power was used because it gives the greatest peak to peak AFR EPR signal height. The AFR EPR signal is partially saturated at this power level (16). Appropriate corrections were made to determine steady state AFR concentrations. The power from the microwave bridge of the Varian instrument is calibrated. The power saturation curve of AFRs in the region of 40 mW has very little gradient; thus, a small error in the nominal power setting produces very little change in AFR signal height.

The concentration of AFR was determined from the signal height of its EPR spectra after calibration using double-integration techniques and 3-carboxy proxyl as the standard. We found that for our experimental conditions, 1 mm of signal height corresponded to 0.0734 nmol/liter AFR, after saturation effects were accounted for. All signal heights were normalized to full gain of the instrument, 1×10^5.

Without ascorbic acid supplementation, the AFR concentration in whole canine blood is too low for detection by EPR. Therefore, to amplify the endogenous AFR signal, 1 g of ascorbic acid was infused intravenously as a bolus, followed by a slow infusion. The AFR concentration varied from dog to dog; the arterial AFR signal was usually ~14 nmol/liter, and the venous AFR signal was usually ~8 nmol/liter. A steady state level of arterial AFR was maintained by adjusting the rate of ascorbic acid infusion, usually ranging between 3.8 and 15.2 mg/min; the arterial AFR level was rechecked after each DC shock, and the infusion rate was adjusted if necessary. The fourfold variation in ascorbic acid infusion rate required to maintain a steady state arterial AFR level may explain in part the substantial variability in absolute AFR levels measured.

Direct current shocks. Direct current shocks were delivered by a Datascope MD2J damped sinusoidal waveform defibrillator. Epicardial shocks were delivered by hand-held electrode paddles cradling the exposed heart. The paddles were coated with a conductive gel (Redux paste, Hewlett-Packard), except for experiment 5 (see later). The range of selected energies varied from 10 to 100 J, which was the maximal possible energy setting allowed on this defibrillator using epicardial electrode paddles. Ventricular fibrillation was accomplished, when required by the protocols, by touching the terminals of a 9-V battery to the exposed epicardial surface of the heart. This simple maneuver reliably induces VF in an open chest canine model.

Transthoracic shocks of 200 J were delivered using hand-held paddle electrodes pressed against the closed, shaved chest in a lateral–lateral orientation (experiment 6).

Measurements of AFR. Baseline measurements of coronary venous and arterial AFR concentrations were obtained using previously discussed methods; baseline ECG and arterial blood pressures were also recorded. After each shock, 16 min

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Table 1. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Shocks

	Coronary Venous AFR Concentration (nmol/liter)									
	10-J NSR Group (n = 6)		40-J NSR Group (n = 6)		75-J NSR Group (n = 14)		100-J NSR Group (n = 20)		Sham Group (n = 4)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Before shock	7.24	0.42	7.16	0.24	7.14	0.34	6.85	0.19	8.32	0.44
Minutes after shock										
3	7.10	0.68	7.26	0.26	7.55	0.38	7.50	0.25	7.99	0.63
4	7.18	0.53	7.15	0.37	7.69	0.27	7.80	0.25	8.35	0.41
5	7.18	0.44	7.37	0.37	8.09	0.35	7.78	0.27	8.06	0.39
6	7.10	0.46	7.06	0.27	7.87	0.36	7.86	0.26	7.78	0.51
7	7.54	0.40	7.66	0.27	7.82	0.45	7.86	0.29	8.21	0.28
8	7.30	0.35	7.03	0.26	7.71	0.35	7.70	0.28	8.21	0.64
9	7.27	0.43	7.40	0.27	7.93	0.38	7.78	0.26	8.42	0.56
10	7.39	0.39	7.58	0.29	8.00	0.41	7.61	0.18	8.10	0.33
11	7.30	0.41	7.25	0.14	7.57	0.42	7.68	0.26	8.21	0.56
12	7.30	0.40	7.30	0.29	7.86	0.41	7.55	0.24	8.14	0.38
13	7.34	0.42	7.27	0.25	7.22	0.38	7.51	0.22	8.21	0.34
14	7.13	0.40	7.39	0.19	7.34	0.38	7.48	0.28	8.28	0.56
15	7.22	0.49	7.30	0.25	7.29	0.30	7.52	0.25	8.39	0.28
16	7.22	0.49	7.10	0.21	6.86	0.20	7.31	0.24	7.68	0.22

	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)*									
	10-J NSR Group (n = 6)		40-J NSR Group (n = 6)		75-J NSR Group (n = 14)		100-J NSR Group (n = 20)		Sham Group (n = 4)	
Minutes After Shock	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
3–4	−2	3	1	2	7	3	12	2	−2	3
5–6	−1	2	1	3	12	2	14	2	−5	2
7–8	3	3	3	3	9	2	14	2	−1	2
9–10	1	2	5	3	12	2	13	2	−1	4
11–12	1	2	2	2	8	3	11	2	−2	2
13–14	0	3	3	2	2	2	10	2	−1	2
15–16	0	2	1	1	2	2	8	2	0	3
Integrated area under AFR conc vs. time curve	2	8	13	6	51†	7	77‡	8	−13	7

*For ascorbate free radical (AFR) percent change comparisons, see Figure 1. †$p < 0.01$ versus 10 J. ‡$p < 0.01$ versus 40 and 10 J. conc = concentration; NSR = normal sinus rhythm.

were allowed for stabilization and recording of coronary venous and systemic arterial AFR levels, the ECG and arterial pressure. The order of shock energies was randomly varied to avoid experimental bias. An adequate coronary sinus blood withdrawal rate was difficult to maintain during the first 2 min of the postshock period because of shock-induced bradycardia and hypotension (17). Therefore, we report coronary venous AFR concentrations at baseline (before shock) and at each minute beginning at 3 min after each shock.

Protocols. *Experiment 1.* In 25 open chest dogs, we studied the effect of DC epicardial shocks on AFR generation, without inducing VF, so that the effect of shocks alone could be studied. Selected energies of shocks administered were varied (10, 40, 75 or 100 J) and delivered in random order to determine the effect of shock energy on the amount of AFR generated. In four of the dogs, "sham" shocks were delivered, whereby the heart was briefly cradled in the epicardial paddle electrodes, but no shocks were delivered. The usual AFR recordings were then obtained. These four "sham" shock dogs were subsequently used for the coronary occlusion portion of experiment 2.

Experiment 2. In 10 open chest dogs, we studied the effect of VF plus DC shocks on AFR generation. Eight of these dogs were also used in experiment 1. Ventricular fibrillation was initiated electrically and allowed to persist for 30 s, after which 40- and 100-J DC shocks were delivered to terminate the VF. In addition, to determine whether the ischemia associated with a 30-s period of fibrillation was sufficiently long to cause an increase in AFR levels, in four dogs we performed a separate experiment: The left anterior descending coronary artery was occluded for 30 s with a snare, followed by snare release and

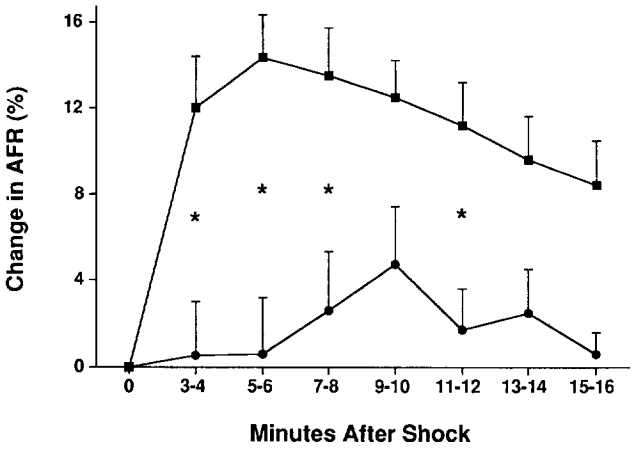


Figure 1. Effect of DC shock energy on AFR generation. There was significantly more AFR generation after 100-J than 40-J shocks, and the peak AFR increase occurred earlier. **Circles** = 40-J NSR group (n = 6); **squares** = 100-J NSR group (n = 20); **vertical lines** = SEM. *p < 0.01.

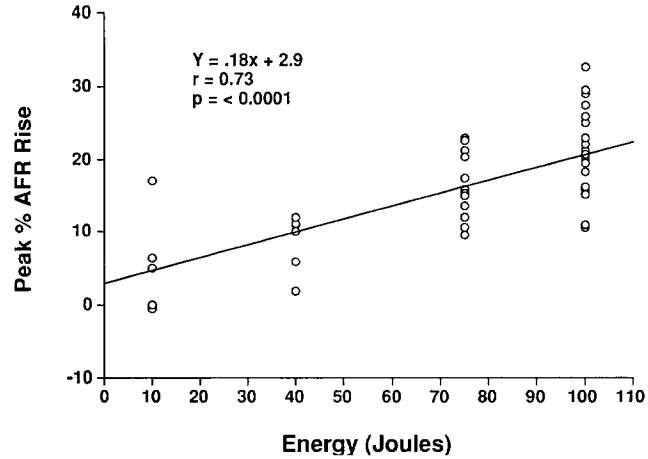
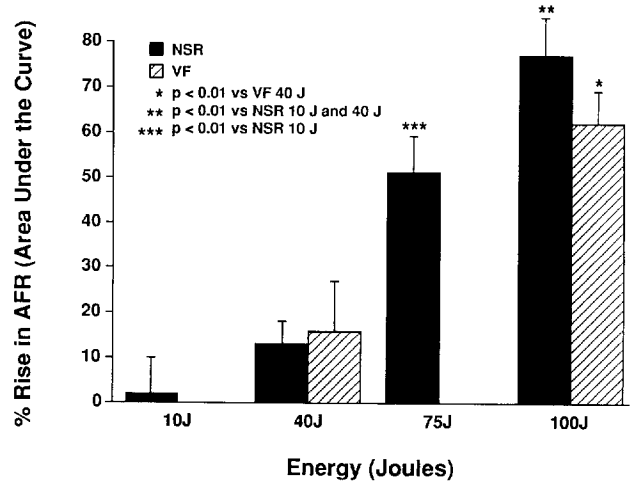


Figure 3. Relation of DC shock energy to peak percent increase in AFR concentration (shocks given to hearts in NSR only). There was a significant relation between the two.

reperfusion (no VF was induced). This procedure allowed us to compare the effect of a 30-s sequence of ischemia–reperfusion with the effect of an equal-length 30-s sequence of fibrillation–defibrillation on AFR generation.

Experiment 3. In six open chest dogs, we studied the effect of the peak versus cumulative energy of DC epicardial shocks on AFR generation. The dogs were either given two 100-J shocks (n = 3) or five 100-J shocks (n = 4) in rapid succession (1 dog received two 100-J shocks and, later, five 100-J shocks). The results were compared with single 100-J shocks delivered in the same dogs to determine whether the cumulative energy of the rapidly applied successive shocks produced a greater increase in free radical generation. Of the six dogs receiving the initial 100-J single shocks, three received the shock while in normal sinus rhythm (NSR), and three received the shock to terminate electrically induced VF. The subsequent double and quintuple shocks in rapid succession were all delivered while the animals were in NSR.

Figure 2. Effect of DC shock energy and cardiac rhythm on AFR generation. Increasing shock energy caused increasing AFR generation (integrated area under percent change in AFR concentration vs. time curve). There was no significant difference in AFR generation from shocks delivered to hearts in NSR versus shocks delivered to terminate VF.



Experiment 4. In seven open chest dogs, we studied the effect of administration of the antioxidant enzymes SOD and Cat before shock delivery on the magnitude of AFR generation. These enzymes were given as a continuous infusion: 15,000 U/kg of SOD (bovine erythrocyte SOD, 4,200 U/mg protein, Sigma Chemical Co.) and 55,000 U/kg of Cat (bovine liver suspension, 58,000 U/mg protein, Sigma). Before initiating the SOD/Cat infusion, we first administered 75-J and, subsequently, 100-J DC shocks to each dog. After all the appropriate recordings, we began the SOD/Cat infusion. Ten minutes after initiating the SOD/Cat infusion, 75-J and, subsequently, 100-J DC shocks were readministered to each dog. In four additional dogs, control studies were performed, whereby 75- and 100-J shocks were delivered, followed by a 10-min time period during which saline instead of SOD/Cat was infused, and 75- and 100-J shocks were then readministered.

Experiment 5. In three open chest dogs, we placed preformed conductive gel-polymer pads (3M) between the metal electrodes and the epicardial surface of the heart. Shocks of 75 and 100 J were delivered, and the usual AFR recordings were obtained. This procedure was done to demonstrate that direct epicardium–electrode contact was not necessary for AFR generation to occur.

Experiment 6. In three dogs we studied the effects of transthoracic shocks on AFR generation. Thoracotomy, coronary sinus and femoral artery and vein cannulation was performed as described earlier. A thoracotomy was neces-

Table 2. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Shocks Given to Terminate Ventricular Fibrillation and After Brief Coronary Occlusion–Reperfusion Sequences

	Coronary Venous AFR Concentration (nmol/liter)					
	VF+40 J (n = 6)		VF+100 J (n = 8)		LAD 30-s Occ. (n = 4)	
	Mean	SEM	Mean	SEM	Mean	SEM
Before shock	7.89	0.77	7.28	0.35	8.41	1.08
Minutes after shock						
3	8.02	0.92	7.85	0.38	8.17	1.04
4	7.87	0.79	8.06	0.59	8.46	1.10
5	8.59	0.88	7.96	0.61	8.53	1.17
6	8.06	0.73	7.99	0.51	8.24	1.08
7	8.26	0.72	8.28	0.51	8.50	1.10
8	8.26	0.72	8.24	0.40	8.57	1.14
9	7.97	0.86	8.24	0.39	8.28	1.07
10	8.26	0.56	8.23	0.40	8.14	1.15
11	7.99	0.68	7.88	0.31	8.35	1.10
12	7.99	0.58	7.87	0.37	8.14	1.15
13	7.97	0.82	7.96	0.44	8.32	0.96
14	7.85	0.74	7.70	0.38	9.02	0.96
15	7.78	0.76	7.38	0.28	9.31	0.69
16	7.73	0.71	7.31	0.28	9.17	0.91
	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)*					
	VF+40 J (n = 6)		VF+100 J (n = 8)		LAD 30-s Occ. (n = 4)	
Minutes After Shock	Mean	SEM	Mean	SEM	Mean	SEM
3–4	0	2	8	9	−1	2
5–6	6	3	8	11	0	2
7–8	5	4	15	7	1	1
9–10	3	3	15	10	−3	2
11–12	2	3	8	10	−2	2
13–14	0	3	13	9	−2	3
15–16	−1	2	−6	6	0	2
Integrated area under AFR conc vs. time curve	16	13	63†	18	−6	2

*For ascorbate free radical (AFR) percent change comparisons, see Figure 2. †$p < 0.01$ versus 40 J. conc = concentration; LAD Occ. = left anterior descending coronary artery occlusion; VF = ventricular fibrillation.

sary in this experiment because we could not accomplish percutaneous coronary sinus cannulation with a sufficiently large cannula to allow an adequate coronary sinus blood withdrawal rate. The thoracotomy was then sutured closed while as much air as possible was aspirated. After baseline measurements of coronary sinus and systemic arterial AFR were obtained, we delivered 200-J shocks from hand-held paddle electrodes pressed firmly against the shaved chest in a lateral–lateral placement. The AFR recordings were obtained as discussed earlier.

Statistical analysis. Data were analyzed for statistical significance using repeated measures analysis of variance to determine whether there was a significant difference among the multiple measurements of each variable tested, followed by a Bonferroni test to determine which specific variables were significantly different. Results are expressed as mean value ± SEM. We correlated the peak of each shock and cumulative energy (when more than one shock was administered) with the peak percent change from baseline in AFR levels and the integrated area under the percent change in AFR concentration versus time curves.

Results

In Tables 1 to 7 we present absolute coronary venous AFR concentrations (nmol/liter) and the percent change from baseline; the latter are shown as mean value ± SEM of all data during each 2-min interval.

Experiment 1. After epicardial DC shocks, the coronary venous AFR concentration increased directly with shock energy (Table 1, Fig. 1 and 2). In the 40-J NSR group, the peak AFR increase, 5 ± 3%, was reached at 9 to 10 min after the shock was delivered. In comparison, the 100-J NSR group had a higher ($p < 0.01$) peak AFR increase of 14 ± 2%, which occurred earlier, 5 to 6 min after shock delivery (Fig. 1). Figure 2 shows that the integrated areas under the AFR concentration versus time curves increased with higher energy shocks: the 10-, 40-, 75- and 100-J areas were 2 ± 8,

Table 3. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Single Versus Multiple Shocks*

	Coronary Venous AFR Concentration (nmol/liter)					
	100 J (n = 6)		100 J × 2 (n = 3)		100 J × 5 (n = 4)	
	Mean	SEM	Mean	SEM	Mean	SEM
Before shock	6.78	0.28	7.07	0.14	7.78	0.44
Minutes after shock						
3	7.44	0.38	7.58	0.25	7.92	0.45
4	7.15	0.45	7.87	0.38	8.42	0.27
5	7.78	0.44	7.58	0.25	8.50	0.56
6	7.44	0.40	8.06	0.29	8.35	0.42
7	7.63	0.41	8.35	0.29	8.42	0.54
8	7.49	0.38	8.38	0.30	8.42	0.25
9	7.39	0.32	7.97	0.42	8.57	0.54
10	7.39	0.16	8.16	0.42	8.86	0.70
11	7.58	0.35	8.06	0.00	8.06	0.69
12	7.44	0.40	7.97	0.51	8.60	0.51
13	7.51	0.41	8.06	0.33	8.57	0.54
14	7.23	0.42	8.16	0.48	8.14	0.54
15	7.25	0.45	7.39	0.25	8.35	0.81
16	6.96	0.34	7.30	0.10	7.92	0.56
	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)					
	100 J (n = 6)		100 J × 2 (n = 3)		100 J × 5 (n = 4)	
Minutes After Shock	Mean	SEM	Mean	SEM	Mean	SEM
3–4	8	4	9	4	5	4
5–6	12	5	11	3	9	4
7–8	12	3	18	2	9	5
9–10	10	4	14	3	12	3
11–12	11	4	13	4	7	3
13–14	9	4	15	5	7	4
15–16	5	2	4	3	4	5
Integrated area under AFR conc vs. time curve	67	11	82	7	54	18

*None of these comparisons are significantly different. 100 J × 2 = two shocks of 100 J in rapid succession; 100 J × 5 = five shocks of 100 J in rapid succession; other abbreviations as in Table 1.

13 ± 6, 51 ± 7 and 77 ± 8%, respectively. Figure 3 shows the relation between epicardial DC shock energy and peak percent AFR generation. There was a significant linear relation between the two: %AFR generation = 0.18 (Shock energy) + 2.9 ($r = 0.73$, $p < 0.0001$). There was a similar relation between the integrated area under the AFR concentration versus time curve and DC shock energy: Area = 0.89 (Shock energy) − 13.9 ($r = 0.70$, $p < 0.0001$). In the "sham" group, there was no increase in AFR; the maximal change was −5 ± 2% (Table 1). There was no relation between percent AFR increase and the order in which the varying energy shocks were delivered.

Experiment 2. Epicardial DC shocks given to terminate VF did not result in higher coronary venous AFR levels than shocks delivered to hearts in NSR (Table 2, Fig. 2). The peak AFR increase in the VF+40-J group was 6 ± 3%, reached at 5 to 6 min after the shock, which was not significantly different from the 40-J NSR group peak of 5 ± 3% (see Table 1 for NSR data). The peak AFR increase in the VF+100-J group was 15 ± 7%, reached at 7 to 8 min after the shock, also not significantly different from the 100-J NSR group peak of 14 ± 2%. When the integrated areas under the AFR concentration versus time curves were compared, neither the VF+40-J group (16 ± 13) nor the VF+100-J group (63 ± 18) were significantly different from their NSR counterparts (Fig. 2). In the four dogs in which the coronary artery was briefly occluded for 30 s, followed by reperfusion, the peak AFR increase was only 1 ± 1% at 9 to 10 min after occlusion (Table 2).

Experiment 3. Multiple epicardial DC shocks did not result in higher coronary venous AFR concentrations than single DC shocks at the same energy (Table 3). In the 100-J×2 group, a peak AFR increase of 18 ± 2% was reached at 7 to 8 min after the shocks, and in the 100-J×5 group, a peak AFR increase of 12 ± 3% was reached at 9 to 10 min after the shocks. These results were not significantly different from the single 100-J

Table 4. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Shocks: Before Versus After Superoxide Dismutase/Catalase (n = 7)

	Coronary Venous AFR Concentration (nmol/liter)							
	75-J NSR Group		75-J NSR+SOD/Cat Group		100-J NSR Group		100-J NSR+SOD/Cat Group	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Before shock	7.32	0.54	7.63	0.43	6.91	0.13	7.77	0.36
Minutes after shock								
3	7.82	0.59	8.02	0.56	7.69	0.29	7.94	0.36
4	7.94	0.35	7.69	0.55	8.11	0.32	8.13	0.40
5	8.41	0.55	8.11	0.47	7.78	0.32	8.15	0.34
6	7.98	0.62	7.65	0.60	7.80	0.19	8.04	0.37
7	7.99	0.71	7.73	0.46	7.80	0.19	8.13	0.29
8	7.90	0.53	7.86	0.48	8.27	0.36	7.92	0.39
9	8.08	0.69	8.00	0.48	8.13	0.14	8.15	0.36
10	8.02	0.70	7.73	0.37	7.82	0.20	7.96	0.40
11	7.53	0.70	7.78	0.51	7.69	0.16	7.88	0.32
12	8.02	0.76	7.65	0.43	7.90	0.28	8.19	0.30
13	7.45	0.66	7.78	0.43	7.34	0.18	8.11	0.32
14	7.45	0.67	7.71	0.42	7.28	0.20	7.98	0.32

	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)*							
	75-J NSR Group		75-J NSR+SOD/Cat Group		100-J NSR Group		100-J NSR+SOD/Cat Group	
Minutes After Shock	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
3–4	9	4	3	3	15	5	4‡	3
5–6	12	3	3†	2	13	4	4	3
7–8	9	2	2	2	17	5	4‡	2
9–10	10	3	3	1	16	3	4‡	3
11–12	6	3	1	2	13	3	4‡	3
13–14	1	2	2	2	6	2	4	2
Integrated area under AFR conc vs. time curve	46	9	15†	5	85	14	25‡	8

*For ascorbate free radical (AFR) percent change comparisons, see Figure 4. †$p < 0.01$ versus 75 J. ‡$p < 0.01$ versus 100 J. Cat = catalase; SOD =superoxide dismutase; other abbreviations as in Table 1.

group peak AFR increase of 12 ± 5% at 5 to 6 min. The integrated areas under the AFR concentration versus time curves were 82 ± 7 for the 100-J×2 group and 54 ± 18 for the 100-J×5 group compared with 67 ± 11 for the 100-J group (p = NS).

Experiment 4. The free radical scavenging enzymes SOD and Cat attenuated the increase in AFR coronary venous concentration after epicardial DC shocks (Table 4, Fig. 4). The peak AFR increase in the 75-J NSR group before SOD/Cat was 12 ± 3% at 5 to 6 minutes and only 3 ± 1% at 9 to 10 min ($p < 0.01$) after SOD/Cat infusion. In the 100-J NSR group, the peak increase before SOD/Cat administration was 17 ± 5% at 7 to 8 min, and with SOD/Cat the peak was 4 ± 3% at 5 to 6 min ($p < 0.01$) (Fig. 4). A similar attenuation was found in the integrated areas under the AFR concentration versus time curve with the presence of SOD/Cat during shock administration. In the four control dogs that received saline instead of SOD/Cat, there was no significant difference in AFR generation between shocks given 10 min apart without infusion of SOD/Cat (Table 5).

Experiment 5. When epicardial DC shocks were delivered from electrodes separated from the epicardium by preformed conductive gel-polymer pads, coronary venous AFR concentrations increased in a manner similar to the increases after DC shocks from electrodes in direct contact with the epicardium (Table 6). Peak AFR increases of 9 ± 6% (75-J shocks) at 9 to 10 min and 12 ± 5% (100-J shocks) at 5 to 6 min after the shock were demonstrated. These data are similar to the AFR increases seen when the metal electrode paddles were in direct contact with the epicardium (compare with Table 1 and Fig. 1).

Experiment 6. After 200-J transthoracic shocks, the peak AFR increase was 7 ± 5% (Table 7). Hemodynamic (blood pressure and heart rate) changes both before and after DC shocks with and without SOD/Cat are shown in Table 8. The effect of SOD/Cat on systolic blood pressure (SBP) before and after shocks is shown in Figure 5. The 75-J shocks caused a significant ($p < 0.05$) decline in SBP; when repeated after SOD/Cat, the decrease in SBP was smaller and no longer significant. The effect of SOD/Cat was less on SBP after 100-J shocks; SOD/Cat did not

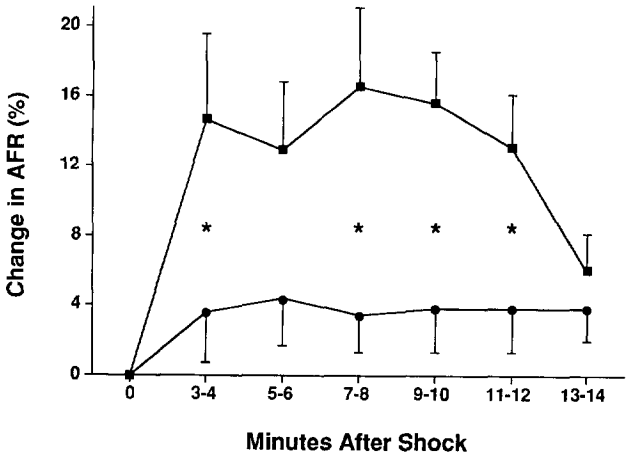


Figure 4. Modification by SOD and Cat of AFR generation after DC shock. Peak percent increase in AFR concentration was significantly reduced by SOD/Cat. **Squares** = 100-J NSR group; **circles** = 100-J NSR+SOD/Cat group; **vertical lines** = SEM. *p < 0.01.

significantly alter the decline in diastolic blood pressure (DBP) or heart rate induced by DC shocks.

Discussion

The *major findings* of this study are that 1) DC epicardial shocks produce an increase in AFR concentration, indicating free radical generation; 2) the magnitude of the AFR increase shows a linear correlation with the energy level of the shock delivered. A high energy shock (e.g., 100 J) produces a greater increase in AFR concentration than a lower energy shock (e.g., 40 J); 3) there is no significant difference in the increase in AFR concentration induced by shocks delivered to beating hearts versus shocks delivered to terminate VF of short duration; 4) when multiple shocks are given in rapid succession, the peak energy of any individual shock is more important than the cumulative energy in determining AFR generation; 5) the antioxidant enzymes SOD and Cat markedly attenuate the increase in AFR generation when they are infused before shock delivery; and 6) transthoracic shocks increase AFR concentration but to a lesser degree than epicardial shocks.

Previous studies of defibrillation injury. Many previous studies (1–5) have shown evidence for defibrillation injury, both morphologic and functional. Weaver et al. (18) showed, in patients, that higher shock energies were more likely to produce atrioventricular block after ventricular fibrillation was terminated. We (5) used sonomicrometers to demonstrate subepicardial contraction abnormalities after direct epicardial shocks. Not only is ventricular function disturbed by DC shocks, but atrial contraction has also been shown to be abnormal after cardioversion (19–21). Transesophageal echocardiographic techniques have demonstrated (19,20) lower left atrial appendage emptying velocities in the left atrium and atrial appendage and spontaneous contrast formation after electrical cardioversion for atrial fibrillation. Manning et al. (21) found a more prompt return of atrial function after pharmacologic than electrical cardioversion of atrial fibrillation, suggesting that atrial "stunning" is more pronounced after electrical cardioversion.

Mechanisms of DC shock injury. Those earlier studies did not establish the mechanism of DC shock injury. Jackson et al. (10) suggested that electrical current passed through a physiologic solution could generate free radicals. Trouton et al. (9) first raised the possibility of a myocardial free radical–mediated mechanism of injury by demonstrating organic lipid peroxyl radicals in hearts of three dogs subjected to DC shocks. Other studies have also shown metabolic and cellular changes in the myocardium after DC countershocks. Trouton et al. (22) demonstrated negative myocardial lactate extraction (signifying lactate production) after DC shocks, indicating that oxidative metabolism is depressed after damaging countershocks. Tovar and Tung showed that both monophasic and biphasic pulses of 1 V, 0.2 to 0.4 ms and 0.4 V, 5 ms make myocardial tissue more permeable, causing alteration in cellular ionic composition, leading to depressed or unexcitable tissue, a precursor for cardiac arrhythmia (23). Finally, Trouton et al. (24) demonstrated that reduction in mitochondrial oxygen consumption after transthoracic shocks is probably not due to depressed mitochondrial function, but may be secondary to other mechanisms, including free radical formation. Doherty et al. (4) suggested that increases in intramyocardial temperature caused by repeated shocks may play a role in myocardial damage.

In our study, shock-induced free radical generation occurred even in the absence of preexisting cardiac injury or arrhythmias; we showed that the administration of a DC shock to a healthy (nonischemic) beating heart generates free radicals. The presence of very short duration electrically induced VF did not further increase the free radical generation. The duration of VF was only 30 s, which may have been too brief to generate additional AFR after defibrillation. Thirty seconds of ischemia produced by coronary artery occlusion was also not long enough to produce AFR on reperfusion, whereas we know from our previous studies (13) that 5 min of coronary occlusion followed by reperfusion does produce AFR. Furthermore, the extent of regional ischemia created by the occlusion of one coronary artery may not be equivalent to the global derangements of perfusion and metabolism associated with ventricular fibrillation. Thus, defibrillation after a longer period of VF would very likely result in an additional increment of AFR generation.

Role of electrode–epicardial contact. In one set of experiments, shocks were delivered to beating hearts from handheld epicardial paddles, but the electrodes were separated from direct contact with the epicardium by preformed conductive gel-polymer pads (3M). These pads are designed to be used as couplants between metal electrodes and the

Table 5. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Shocks: Comparison of Shocks Delivered 10 Minutes Apart (with vs. without superoxide dismutase/catalase) (n = 4)*

	Coronary Venous AFR Concentration (nmol/liter)							
	75-J NSR Group				100-J NSR Group			
	With SOD/Cat		Without SOD/Cat		With SOD/Cat		Without SOD/Cat	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Before shock	8.33	0.62	8.41	0.91	8.69	0.94	9.12	0.85
Minutes after shock								
3	8.86	0.91	9.14	1.33	9.00	1.14	10.01	0.80
4	9.14	1.03	8.78	1.39	9.14	0.83	10.01	0.52
5	9.72	0.81	9.43	1.03	9.65	1.00	10.01	0.65
6	9.14	0.95	9.43	1.21	9.94	1.47	10.01	0.94
7	9.50	1.16	9.86	1.03	9.40	1.11	10.33	0.73
8	9.29	0.83	9.29	1.21	9.43	1.30	9.72	1.11
9	9.22	1.00	9.72	1.25	9.72	1.14	10.08	0.91
10	9.14	1.20	10.22	0.96	9.58	1.23	9.79	0.78
11	9.72	0.80	9.29	0.83	9.40	1.04	10.01	0.74
12	8.78	1.14	9.54	0.98	9.29	1.05	9.14	0.90
13	9.36	0.63	9.36	0.96	9.58	1.07	9.50	0.81
14	9.29	1.03	9.50	1.07	9.07	0.87	9.32	0.70
15	8.86	1.07	9.14	0.85	9.22	0.81	9.36	0.69
16	8.71	0.96	9.00	0.89	8.93	0.92	9.60	0.86

	Percent Change From Baseline in AFR Concentration (mean± SEM of all data during each 2-min interval)							
	75-J NSR Group				100-J NSR Group			
	With SOD/Cat		Without SOD/Cat		With SOD/Cat		Without SOD/Cat	
Minutes After Shock	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
3–4	7	4	5	5	4	3	11	5
5–6	13	4	12	3	12	3	10	2
7–8	12	5	14	4	8	3	10	4
9–10	9	5	19	4	11	4	9	3
11–12	10	5	13	5	7	3	5	5
13–14	12	3	13	7	8	4	4	2
15–16	5	4	9	4	5	2	2	2
Integrated area under AFR conc vs. time curve	66	19	80	21	53	4	50	11

*None of these comparisons are significantly different. Abbreviations as in Tables 1 and 4.

skin in transthoracic defibrillation as a nonslipping, nonspreading substitute for electrode creams or pastes. We used these pads to determine whether direct contact of the electrode with the cardiac tissue (tissue–electrode interface) was required to generate free radicals. The peak AFR increases produced by the shocks delivered with pads to separate the electrodes from the epicardium are comparable to the AFR increases that we demonstrated with epicardial paddle electrodes in direct contact with the epicardium. This finding indicates that a metal–tissue interface is not required to generate free radicals by shocks; transcardiac current appears to be the major determinant.

Transthoracic shocks. Transthoracic shocks of 200 J caused an AFR increase, but of a magnitude less than that induced by 100-J epicardial shocks. The more modest increase in AFR generation despite the higher energy used in the transthoracic shocks is not surprising because only a portion of the current generated by a transthoracic shock actually traverses the heart (25,26). Furthermore, because we could not accomplish percutaneous coronary sinus cannulation with a sufficiently large cannula to allow adequate coronary sinus withdrawal, we had to perform a thoracotomy and accomplish coronary sinus cannulation with direct manual assistance and then reclose the thorax before delivering shocks. The inevitable trapping of air (a poor conductor of electricity) in the thorax after closure of the thoracotomy probably further reduced transthoracic and transcardiac current and thus AFR generation. Transthoracic shocks delivered to an intact chest

Table 6. Coronary Venous Ascorbate Free Radical Concentration After Direct Current Shocks: Use of Preformed Conductive Gel-Polymer Pads (n = 3)

	Coronary Venous AFR Concentration (nmol/liter)			
	75-J NSR Group		100-J NSR Group	
	Mean	SEM	Mean	SEM
Before shock	6.59	0.27	10.32	1.27
Minutes after shock				
3	6.72	0.00	10.07	1.33
4	6.13	0.88	10.80	1.34
5	7.45	0.15	11.92	1.65
6	6.57	0.73	11.29	1.76
7	7.01	0.29	11.87	1.70
8	7.15	0.15	11.29	1.60
9	7.45	0.15	11.78	1.69
10	6.86	0.15	11.19	1.98
11	7.01	0.29	11.00	1.87
12	6.72	0.59	10.80	1.83
13	6.42	0.86	10.90	2.01
14	6.72	0.29	10.80	1.92
15	6.28	0.15	11.10	1.79
16	6.57	0.15	10.95	1.83

	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)			
	75-J NSR Group		100-J NSR Group	
Minutes After Shock	Mean	SEM	Mean	SEM
3–4	−3	7	1	3
5–6	6	7	12	5
7–8	8	4	12	4
9–10	9	6	10	6
11–12	4	3	4	6
13–14	−1	6	3	6
15–16	−2	4	6	5
Integrated area under AFR conc vs. time curve	22	2	46	13

Abbreviations as in Table 1.

might well yield more myocardial AFR generation; to demonstrate this hypothesis, the experimental model will need to be refined and thoracotomy avoided.

The levels of shock energy applied to the epicardium in this study—up to 100 J—are substantially higher than the typical clinical intraoperative levels of 10 to 20 J (27). Whether lower energy epicardial shocks generate free radicals in human hearts was not determined in this study.

Biphasic shock waveforms have been found to be less injurious to the myocardium than monophasic waveforms (28,29). Whether biphasic or other waveforms generate fewer radicals than monophasic waveforms was not addressed in this study; all shocks in these experiments were delivered using a standard damped sinusoidal waveform.

Prevention of shock injury. Antioxidant enzymes have been shown (30–32) to ameliorate the myocardial stunning associated with brief coronary occlusion–reperfusion sequences. In this study the free radical scavenging enzymes SOD and Cat, given before DC shocks, markedly reduced the magnitude of free radical generation. Although functional protection against DC shock injury was not the major focus of this study, SOD/Cat did attenuate the decline in SBP caused by 75-J shocks. However, the preshock SBP was lower after the dogs had already received one previous shock plus SOD/Cat, which renders interpretation difficult. Whether SOD/Cat or other free radical scavenging agents would prevent or ameliorate the functional myocardial toxicity resulting from DC shocks would require sophisticated measures of left ventricular global and regional function and myocardial injury, and a dose–response study.

Conclusions. Because DC shocks to the heart generate free radicals, and free radicals are known to be toxic to the myocardium, our study implies that shock-induced free radical generation is a mechanism of defibrillation injury. However, free

Table 7. Coronary Venous Ascorbate Free Radical Concentration After Transthoracic Direct Current Shocks (200 J) (n = 3)

	Coronary Venous AFR Concentration (nmol/liter)	
	Mean	SEM
Before shock	7.97	0.45
Minutes After Shock		
3	8.12	0.77
4	7.83	0.54
5	8.12	0.84
6	7.93	0.78
7	7.93	0.51
8	8.03	0.59
9	7.83	0.52
10	8.32	0.76
11	8.32	0.35
12	8.71	0.71
13	8.56	0.18
14	8.22	0.45
15	8.61	0.20
16	8.17	0.56

	Percent Change From Baseline in AFR Concentration (mean ± SEM of all data during each 2-min interval)	
Minutes After Shock	Mean	SEM
3–4	0	5
5–6	1	6
7–8	0	3
9–10	1	5
11–12	7	5
13–14	5	2
15–16	5	2
Integrated area under AFR conc vs. time curve	17	7

Abbreviations as in Table 1.

radicals may not be the sole or even major mechanism. Previous investigators have shown (1–4) myocardial damage from DC shocks to be directly related to the cumulative energy rather than the peak individual shock energy, as we found; the time interval between shocks and intramyocardial temperature increases may also be important. Defibrillation injury may be multifactorial.

Table 8. Hemodynamic Effects of Direct Current Shocks Delivered Before and After Superoxide Dismutase/Catalase

	75-J NSR Group (n = 7)				100-J NSR Group (n = 7)			
	Before SOD/Cat		After SOD/Cat		Before SOD/Cat		After SOD/Cat	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Preshock SBP (mm Hg)	97	10	81	7	92	9	80	7
Postshock SBP (mm Hg)	81*	9	73	8	78†	5	69†	6
ΔSBP (mm Hg)	16	5	9	4	13	5	11	4
Preshock DBP (mm Hg)	59	8	48	6	59	8	49	7
Postshock DBP (mm Hg)	39‡	5	39§	5	39‖	6	40¶	7
ΔDBP (mm Hg)	20	4	9	3	20	4	8	3
Preshock HR (beats/min)	124	5	128	5	131	5	126	4
Postshock HR (beats/min)	128	3	129	4	126	5	128	5
ΔHR (beats/min)	4	4	1	4	5	3	2	2

*$p < 0.05$ versus preshock systolic blood pressure (SBP) (75 J). †$p < 0.05$ versus preshock SBP (100 J). ‡$p < 0.01$ versus preshock diastolic blood pressure (DBP) (75 J). §$p < 0.05$ versus preshock DBP (75 J). ‖$p < 0.01$ versus preshock DBP (100 J). ¶$p < 0.05$ versus preshock DBP (100 J). HR = heart rate; Δ = change in; other abbreviations as in Tables 1 and 4.

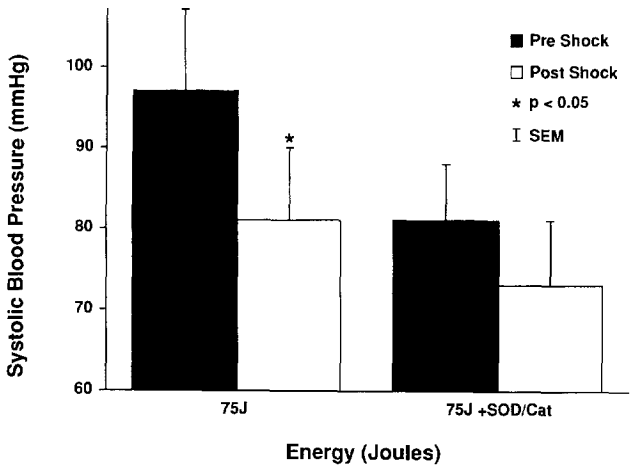


Figure 5. Systolic blood pressure changes induced by DC shocks before and after SOD/Cat; 75-J shocks caused a significant decline in SBP. When 75-J shocks were repeated after SOD/Cat, the decline in SBP was smaller and no longer significant.

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References

1. Dahl CF, Ewy GA, Thomas ED. Myocardial necrosis from direct current countershock. Circulation 1974;50:956–61.
2. Warner ED, Dahl CF, Ewy GA. Myocardial injury from transthoracic defibrillator countershock. Arch Pathol 1975;99:55–9.
3. Ebsani A, Ewy GA, Sobel BE. Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity. Am J Cardiol 1976;37: 12–8.
4. Doherty PW, McLaughlin PR, Billingham M. Cardiac damage produced by direct current countershock applied to the heart. Am J Cardiol 1979;43:225–32.
5. Kerber RE, Martins JB, Gascho JA, Marcus ML, Grayzel J. Effect of direct current countershocks on regional myocardial contractility and perfusion. Circulation 1981;63:323–32.
6. Hearse DJ, Humphrey SM, Naylo WG, Slade A, Border D. Ultrastructural damage associated with reoxygenation of the anoxic myocardium. J Mol Cell Cardiol 1975;7:315–24.
7. Arroyo CM, Kramer JH, Leiboff RH, Mergner GW, Dickens BF, Weglicki WB. Spin trapping of oxygen and carbon-centered free radicals in ischemic canine myocardium. Free Rad Biol Med 1987;3:313–6.
8. Zweier JL, Flaherty JT, Weisfeldt ML. Direct measurement of free radical generation following reperfusion of ischemic myocardium. Proc Nat Acad Sci USA 1987;84:1404–7.
9. Trouton TG, Allen JD, Yong LK, Rooney JJ, Adgey AAJ. Metabolic changes and mitochondrial dysfunction early following transthoracic countershocks in dogs. PACE Pacing Clin Electrophysiol 1989;12:1827–34.
10. Jackson CV, Mickelson JK, Stringer K, Rao PS, Lucchesi BR. Electrolysis-induced myocardial dysfunction: a novel method for the study of free radical-mediated tissue injury. J Pharmacol Meth 1986;15:305–20.
11. Bolli R. Oxygen-derived free radicals and postischemic myocardial dysfunction ("stunned myocardium"). J Am Coll Cardiol 1988;12:239–49.
12. Kloner RA, Przyklenk K, Whittaker P. Deleterious effects of oxygen radicals in ischemia/reperfusion: resolved and unresolved issues. Circulation 1989; 80:1115–27.
13. Sharma MK, Buettner GR, Spencer KT, Kerber RE. Ascorbyl free radical as a real-time marker of free radical generation in briefly ischemic and reperfused hearts. Circ Res 1994;74:650–8.
14. Buettner GR, Jurkiewicz BA. The ascorbate free radical as a marker of oxidative stress: an EPR study. Free Radic Biol Med 1993;14:49–55.
15. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys 1993; 300:535–43.
16. Buettner GR, Kiminyo KP. Optimal EPR detection of weak nitroxide spin adduct and ascorbate free radical signals. J Biochem Biophys Meth 1992;24: 147–51.
17. Pansegrau DG, Abboud FM. Hemodynamic effects of ventricular defibrillation. J Clin Invest 1970;49:282–97.
18. Weaver WD, Cobb LA, Copass MK, Holstrom AP. Ventricular defibrillation- a comparative trial using 175-J and 320-J shocks. N Engl J Med 1982;307:1101–6.
19. Grimm RA, Stewart WJ, Maloney JD, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993;22:1359–66.
20. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Card 1994;23:307–16.
21. Manning WJ, Silverman DI, Katz SE, et al. Temporal dependence of the return of atrial mechanical function on the mode of cardioversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1995;75:624–6.
22. Trouton TG, Allen JD, Adgey AA. Oxidative metabolism and myocardial blood flow changes after transthoracic DC countershocks in dogs. Eur Heart J 1992;13:1431–40.
23. Tovar O, Tung L. Electroporation of cardiac cell membranes with monophasic or biphasic rectangular pulses. PACE Pacing Clin Electrophysiol 1991; 14:1887–92.
24. Trouton TG, Barry JJ, Allen JD, Adgey AA. Failure of countershock-type pulses in vitro to adversely alter mitochondrial oxidative phosphorylation. Ann Emerg Med 1992;21:132–6.
25. Lerman BB, Deale OC. Relation between transcardiac and transthoracic current during defibrillation in humans. Circ Res 1990;67:1420–6.
26. Camacho MA, Lehr JL, Eisenberg SR. A three-dimensional finite element model of human transthoracic defibrillation: paddle placement and size. IEEE Trans Biomed Eng 1995;42:572–8.
27. Kerber RE, Carter J, Klein S, Grayzel J. Open chest defibrillation during cardiac surgery: energy and current requirements. Am J Cardiol 1980;46: 393–6.
28. Oswald S, Trouton TG, O'Nunain SS, Holden HB, Ruskin JN, Garan H. Relation between shock-related myocardial injury and defibrillation efficacy of monophasic and biphasic shocks in a canine model. Circulation 1994;90: 2501–9.
29. Jones JL. Waveforms for implantable cardioverter defibrillators and transchest defibrillation. In: Tacker WA, editor. Defibrillation of the Heart. St. Louis: Mosby, 1994:46–81.
30. Jolly SR, Kane WJ, Bailie MB, Abrams GD, Lucchesi BR. Canine myocardial reperfusion injury. Its reduction by the combined administration of superoxide dismutase and catalase. Circ Res 1984;54:277–85.
31. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R. Enhancement of recovery of myocardial function by oxygen free-radical scavengers after reversible regional ischemia. Circulation 1985;72:915–21.
32. Ambrosio G, Becker LC, Hutchins GM, Weisman HF, Weisfeldt ML. Reduction in experimental infarct size by recombinant human superoxide dismutase: insights into the pathophysiology of reperfusion injury. Circulation 1986;74:1424–33.