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A Novel Low-Energy Electrotherapy That Terminates Ventricular Tachycardia With Lower Energy Than a Biphasic Shock When Antitachycardia Pacing Fails

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Objectives The authors sought to develop a low-energy electrotherapy that terminates ventricular tachycardia (VT) when antitachycardia pacing (ATP) fails.

Background High-energy implantable cardioverter-defibrillator (ICD) shocks are associated with device failure, significant morbidity, and increased mortality. A low-energy alternative to ICD shocks is desirable.

Methods Myocardial infarction was created in 25 dogs. Sustained, monomorphic VT was induced by programmed stimulation. Defibrillation electrodes were placed in the right ventricular apex, and coronary sinus and left ventricular epicardium. If ATP failed to terminate sustained VT, the defibrillation thresholds (DFTs) of standard versus experimental electrotherapies were measured.

Results Sustained VT ranged from 276 to 438 beats/min (mean 339 beats/min). The right ventricular–coronary sinus shock vector had lower impedance than the right ventricular–left ventricular patch (54.4 ± 18.1 Ω versus 109.8 ± 16.9 Ω; $p < 0.001$). A single shock required between 0.3 ± 0.2 J to 5.9 ± 2.5 J (mean 2.64 ± 3.22 J; $p = 0.008$) to terminate VT, and varied depending upon the phase of the VT cycle in which it was delivered. By contrast, multiple shocks delivered within 1 VT cycle length were not phase dependent and achieved lower DFT compared with a single shock (0.13 ± 0.09 J for 3 shocks, 0.08 ± 0.04 J for 5 shocks, and 0.09 ± 0.07 J for 7 shocks; $p < 0.001$). Finally, a multistage electrotherapy (MSE) achieved significantly lower DFT compared with a single biphasic shock (0.03 ± 0.05 J versus 2.37 ± 1.20 J; respectively, $p < 0.001$). At a peak shock amplitude of 20 V, MSE achieved 91.3% of terminations versus 10.5% for a biphasic shock ($p < 0.001$).

Conclusions MSE achieved a major reduction in DFT compared with a single biphasic shock for ATP-refractory monomorphic VT, and represents a novel electrotherapy to reduce high-energy ICD shocks. (J Am Coll Cardiol 2012;60: 2393–8) © 2012 by the American College of Cardiology Foundation

Randomized, prospective clinical trials have demonstrated that implantable cardioverter-defibrillators (ICDs) decrease mortality in patients with coronary artery disease or prior myocardial infarction (MI) who are at increased risk of ventricular tachycardia (VT) or ventricular fibrillation (1,2). More than 80% of victims of sudden cardiac death have coronary artery disease (3), with the most common arrhythmia being sustained monomorphic VT (4). A high-energy biphasic shock is the only existing electrotherapy when antitachycardia pacing (ATP) fails to terminate VT. However, ICD shocks have been shown to damage the myocardium and reduce the quality of life (5,6). Moreover, patients

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receiving high-energy shocks have a 2- to 3-fold increase in mortality (7,8) compared with those who do not receive shocks. Although it is unclear whether it is the shocks themselves or a change in underlying cardiac status that actually causes higher mortality, even inappropriate shocks (9) are associated with a higher mortality, for example, inappropriate shocks often occur during atrial fibrillation,

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Abbreviations and Acronyms

ATP = antitachycardia pacing
CL = cycle length
CS = coronary sinus
DFT = defibrillation threshold
ICD = implantable cardioverter-defibrillator
LV = left ventricle/ventricular
LVP = left ventricular patch
MI = myocardial infarction
MSE = multistage electrotherapy
RV = right ventricle/ventricular
VT = ventricular tachycardia

which itself can result in a higher mortality in patients with poor left ventricular (LV) function. Despite these disadvantages, alternative low-energy electrotherapies have not been introduced into ICD technology since the incorporation of ATP. The purpose of this study was to develop a novel electrotherapy that terminates VT with lower energy than a biphasic shock for ATP-refractory monomorphic VT.

Methods

Surgical procedures. All animal procedures were performed in accordance with the Position of the American Heart Association on the use of research animals (updated in 1985) and were approved by the Animal Studies Committee at Washington University. MI was created after anesthetization of mongrel dogs (n = 25) of either sex weighing 20 to 25 kg, by surgical ligation of the left anterior descending coronary artery for 2 h, as described previously (10). Four days after MI, animals were reanesthetized, a median sternotomy was performed, and cardiopulmonary bypass was initiated after the administration of heparin.

Electrode configuration. In the 24 dogs that survived MI (1 dog died suddenly 1 day after left anterior descending coronary artery ligation), a 15-cm^2 custom epicardial LV patch (LVP) was placed over the posterolateral LV, and an 8-F standard defibrillation/bipolar pacing lead (6935, Medtronic, Minneapolis, Minnesota) was implanted in the right ventricular (RV) apex (Fig. 1). In 5 animals, an additional 8-F standard defibrillation lead (6937A, Medtronic) was placed into the coronary sinus (CS) (Fig. 1). Pacing was delivered from the RV bipole. Shock therapies were delivered across the RV-LVP or RV-CS vectors; all shocks were RV anodal. A bipolar button electrode was sewn to the RV epicardium for ventricular sensing.

Defibrillation protocol. Four days after MI, loading (2 mg/kg) and maintenance (0.05 mg/kg/min) infusions of flecainide acetate (Sigma-Aldrich, St. Louis, Missouri) were administered intravenously. VT was induced by rapid RV pacing protocols (programmed electrical stimulation). Sustained, monomorphic VT was defined as a fast but organized ventricular rhythm <500 beats/min, lasting >30 s. Ventricular fibrillation was defined as an arrhythmia >500 beats/min, and if induced, terminated using an external defibrillator. The heart was allowed to recover for 5 to 10 min after any external defibrillation before reinduction of VT.

After monomorphic VT was induced, ATP was attempted. ATP consisted of 8 pacing stimuli, each of 2-ms duration delivered at a rate of 88% of the VT cycle length (CL), delivered from the RV bipole at an amplitude 4 times the ventricular pacing capture threshold current. If ATP failed to terminate VT, defibrillation thresholds (DFTs) of various electrotherapies (defined later in the text) were measured. DFT, in volts, was defined as the peak shock amplitude that terminated VT. DFT, in joules, was calculated by multiplying the energy of a single shock by the number of shocks applied (for multiple-shock and multistage electrotherapies).

Experimental and standard electrotherapies were delivered using a randomized protocol with respect to sequence to avoid time bias, using a voltage-regulated, step-up protocol. The amplitude of the peak shock voltage was increased after each unsuccessful termination, beginning at twice the minimum voltage required to capture the ventricle with a 10-ms monophasic shock, until VT was terminated. Reinduction of VT was attempted after a 5-min recovery period, according to the protocol. Electrotherapies were delivered from computer-controlled regulated power supplies (BOP 100-4M, Kepco, Flushing, New York). Impedances were calculated using a current probe (A622, Tektronix, Beaverton, Oregon).

Electrotherapies tested. The electrotherapies tested are shown in Figure 2. One (1MP), 3 (3MP), 5 (5MP), or 7 (7MP) monophasic shocks were delivered within 1 VT CL (Fig. 2A); each individual shock was 10 ms in duration. A single biphasic shock (1BP, 6-ms and 4-ms duration of the first and second phases, respectively; 2:1 ratio of the leading edge voltages of the 2 phases is shown in Fig. 2B). Multistage electrotherapy (MSE), shown in Figure 2C,

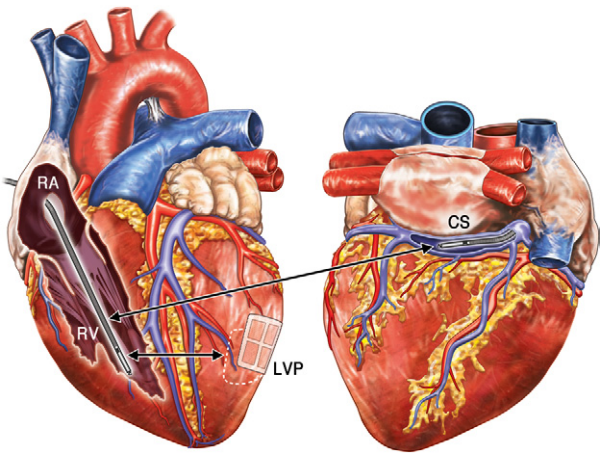

Figure 1 Anatomic Position of Defibrillation Electrodes

Schematic of a canine heart with the locations of the electrodes used for application of electrotherapies. Anteroposterior **(left)** and posteroanterior **(right)** views showing locations of the defibrillation leads and shock vectors **(black arrows)**. Shocks were delivered from the RV defibrillation coil (RV) to the CS defibrillation coil (CS), or from the RV coil to epicardial LV defibrillation patch (LVP). CS = coronary sinus; LVP = left ventricular patch; RA = right atrium; RV = right ventricle.

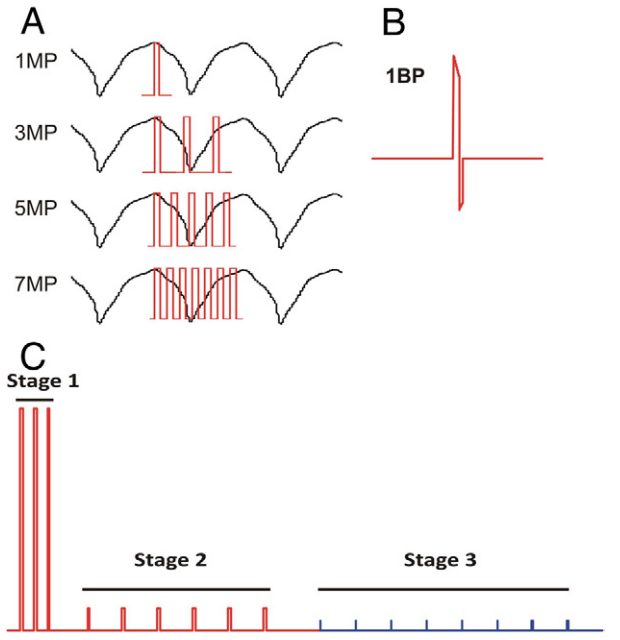

Figure 2 **Defibrillation Wave Forms and Low-Energy Electrotherapies**

Schematic diagrams of the electrotherapies applied. Pulse widths of individual shocks were 10 ms. **(A)** One (1MP), 3 (3MP), 5 (5MP), or 7 (7MP) monophasic shocks delivered within 1 VT cycle length (CL). **(B)** A single biphasic shock (1BP) with pulse widths of 6 ms for the first (positive) phase and 4 ms for the second (negative) phase. **(C)** Multistage electrotherapy (MSE). Stage 1 consisted of 3 monophasic shocks delivered in 1 VT CL, followed by a 100-ms delay. Stage 2 consisted of 6 lower-voltage monophasic shocks delivered at a rate of 88% of the VT CL, followed by a 100-ms delay. Stage 3 consisted of 8 pacing stimuli, each of 2-ms duration delivered from the endocardial RV lead (tip to ring) at a rate of 88% of the VT CL. BP = biphasic; MP = monophasic; VT = ventricular tachycardia; other abbreviations as in Figure 1.

consisted of 3 monophasic shocks delivered within 1 VT CL (Stage 1), followed by 6 MP shocks delivered with an interval of 88% of the VT CL at twice the ventricular shock capture voltage (Stage 2), followed by ATP (Stage 3); individual stages were separated by 100-ms delays.

Statistical analysis. The defibrillation protocol randomized the sequence of electrotherapies to prevent the confounding effects of treatments with respect to time. Recovery periods were observed after each termination to prevent carryover effects. DFTs for comparisons of electrotherapies tested were analyzed using a linear mixed-effects model with animal ID as a random effect and treatment as a fixed effect. Energy and voltage DFT values were log transformed to stabilize the variance. Estimates were calculated with the MIXED procedure in SAS (version 9.3, SAS Institute, Cary, North Carolina). Paired Student's *t* test was used to compare impedances of the 2 shock vectors tested, and performed in Prism 5.0c (GraphPad Software, La Jolla, California). Results are reported as mean ± SD. A p value of ≤0.05 was considered significant.

Results

Characteristics of monomorphic VT in canine hearts with 4-day-old infarct. One hundred and ninety episodes of monomorphic, sustained VT (lasting >30 s) were induced in 16 of the 24 dogs (66.7%) that survived MI; in 8 dogs, only ventricular fibrillation or polymorphic VT could be induced. VT ranged from 276 to 438 beats/min (mean 339 beats/min). ATP successfully terminated VT in 17 of 170 trials, a success rate of 10.0%.

Phase dependence of a single shock. The energy required for a single shock to terminate VT varied significantly depending upon the phase of the VT cycle in which it was delivered (DFT phase dependence) in this in vivo model. The DFT of a single 10-ms monophasic shock varied significantly when delivered at 0%, 20%, 40%, 60%, or 80% of the VT CL. Shocks were delivered between the RV coil and the LVP. Application of a single shock revealed that the DFT dramatically changed based upon the phase of application. Phase-dependent DFT for a single shock was seen in all dogs tested (n = 5). Across all dogs, the mean DFT of the optimal phase in each animal compared with the mean DFT of the least effective phase was 0.3 ± 0.2 J versus 5.9 ± 2.5 J, respectively (p = 0.008). Notably, the optimal phase varied between animals and could not be determined a priori.

DFTs of single versus multiple shocks. We hypothesized that multiple low-energy shocks applied evenly within 1 VT CL would not have phase dependence, thus enabling a reduction in the DFT compared with a single shock. After induction of sustained VT, ATP was attempted. If ATP failed, 1, 3, 5, or 7 MP shocks (1MP, 3MP, 5MP, or 7MP, respectively) were applied within 1 VT CL (Fig. 3A). A single (1MP) 1.1-J MP shock failed to terminate VT (upper tracing), whereas 3MP, 5MP, and 7MP shocks (of 0.24 J, 0.16 J, and 0.2 J, respectively) terminated VT. Mean DFTs across all dogs tested (n = 6) are summarized in Figure 3B. In all animals tested, multiple shocks significantly lowered the DFT compared with a single shock and did not exhibit phase dependence.

Multistage electrotherapy. Previous electrotherapies were applied from endocardium to epicardium (RV-LVP vector) (Fig. 1). To move toward the goal of developing a lead system that is practical in humans yet enables low DFT, we tested whether shocks applied entirely within the heart (RV-CS vector) (Fig. 1) would achieve low impedance. The mean impedance of shocks delivered between the RV-CS vector was significantly lower than the RV-LVP vector (54.4 ± 18.1 Ω versus 109.8 ± 16.9 Ω, respectively, p < 0.001). These results showed that low impedance can be achieved using transvenous electrodes rather than an epicardial patch electrode.

To further reduce the DFT, we expanded multiple shocks to a MSE (Fig. 2C). Using the RV-CS vector, MSE was compared to the existing clinical standard, a single biphasic shock. After induction of sustained monomorphic VT,

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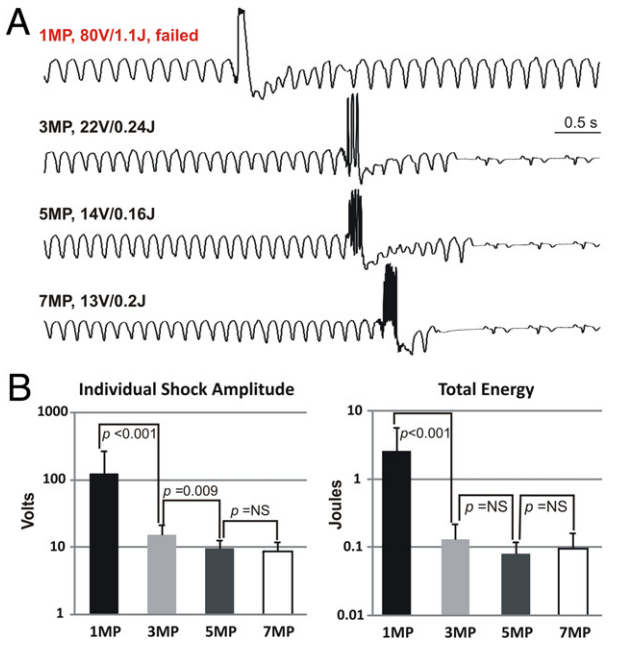

Figure 3 DFTs of Single and Multiple Monophasic Shock Electrotherapies

(A) Surface electrocardiogram tracings during applications of single and multiple monophasic shock electrotherapies. An 80-V (1.1 J) single monophasic shock (1MP) failed to terminate VT **(top panel)**. In the same animal, 3 monophasic shocks (3MP; **second panel**), 5 monophasic shocks (5MP; **third panel**), and 7 monophasic shocks (7MP; **lower panel**) delivered within 1 VT cycle terminated VT successfully with 22 V (0.24 J), 14 V (0.16 J), and 13 V (0.2 J), respectively. **(B)** Mean DFTs (logarithmic scale) of 1MP, 3MP, 5MP, and 7MP with respect to peak voltage **(left panel)** and total energy **(right panel)** over n = 6 dogs tested is shown. NS = not significant; other abbreviations as in Figures 1 and 2.

ATP was attempted, and if it failed, electrotherapies were delivered according to a randomized protocol. Sample terminations using a single biphasic shock and MSE are shown in Figure 4A, where the DFT of a single BP shock was 200 V (4.56 J) compared with 20 V (0.22 J) for MSE. Pooled results (n = 5 dogs) are shown in Figure 4B. The mean DFT of MSE was significantly lower than that of a single biphasic shock in terms of total energy (0.03 ± 0.05 J versus 2.37 ± 1.20 J, respectively; $p < 0.001$) and peak shock voltage (7.2 ± 6.9 V versus 137.7 ± 43.8 V, respectively; $p < 0.001$). At a peak shock amplitude of 20 V, MSE achieved 91.3% of terminations versus 10.5% for a biphasic shock ($p < 0.001$). Importantly, these results demonstrate that low DFT can be achieved using transvenously implanted leads, and does not require an epicardial electrode.

Discussion

Our study showed that the DFT of a single shock to terminate post-MI monomorphic VT in vivo was phase dependent, and that multiple low-energy shocks delivered within a single VT CL eliminated phase dependence. Expanding upon this concept, MSE dramatically reduced the DFT compared with a single biphasic shock for ATP-refractory monomorphic VT. Importantly, we showed that MSE (and a single biphasic shock) could be delivered endocardially using commercially available transvenous defibrillation leads placed in the RV and CS.

In this model, the success rate of ATP was 10%. This contrasts with human trials in which ATP terminated 78% to 94% of monomorphic VT <200 beats/min (11–13). In humans, the efficacy of ATP has been shown to be lower with increasing rate of VT, terminating 84% of VT episodes ranging from 188 to 214 beats/min, and only 69% of episodes ranging from 214 to 250 beats/min (14). Other studies have shown the success rate for fast VT to range from 47% to 79% (15–18). The average rate of VT in our model was 339 beats/min, significantly faster than those reported in human ATP trials, and likely explains why ATP was relatively unsuccessful in this model. Importantly, the low-energy MSE described in this report is not envisioned as an alternative to ATP. Rather, it is intended to complement ATP and provide an alternative

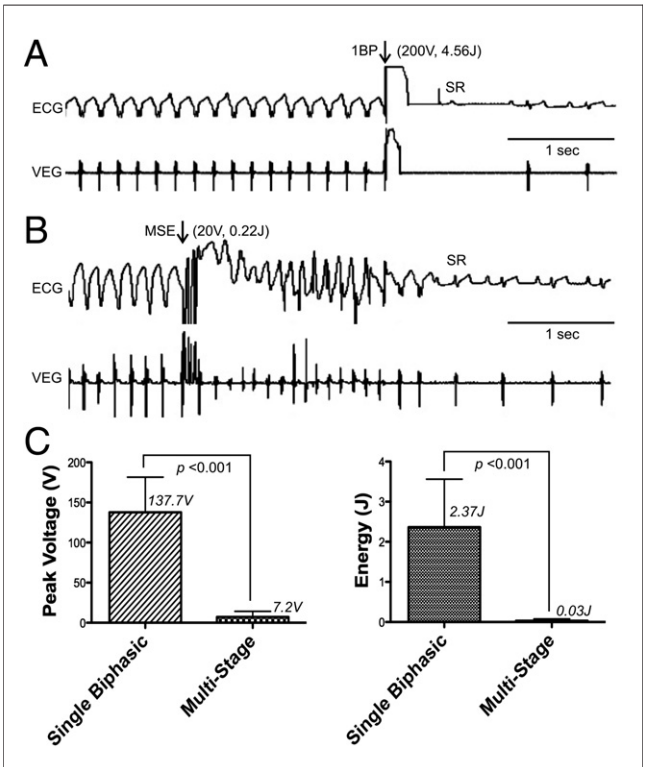

Figure 4 Sample Terminations and Mean DFTs of a Single Biphasic Shock Versus MSE

(**A**) Surface electrocardiogram (ECG) and ventricular electrogram (VEG) of a termination of monomorphic VT by a single biphasic shock (1BP) with peak leading edge voltage of 200 V (4.56 J). **Arrows** indicate the time of electrotherapy application. **(B)** Surface ECG and VEG of a termination of monomorphic VT by MSE with peak voltage of 20 V (0.22 J). **(C)** Mean DFTs of a single biphasic shock (Single Biphasic) and MSE (Multi-Stage) are shown with respect to peak voltage **(left panel)** and total energy **(right panel)**. SR = sinus rhythm; other abbreviations as in Figures 2 and 3.

to potentially damaging, high-energy biphasic shocks when ATP fails.

Our study agrees with in vitro studies in post-MI rabbit hearts showing the phase dependence of single monophasic and biphasic shocks (19,20). We found a 20-fold energy difference between single optimally and poorly timed shocks, similar to those reported in in vitro studies. Notably, in both the current in vivo canine study and previously in vitro rabbit studies, and the optimal phase for single-shock application could not be predicted a priori.

Lowering the DFT by repetitive shocks was first shown by Gurvich in 1945 (21). More recently, repetitive sub-threshold (below the ventricular capture threshold) pacing was shown to terminate VT in guinea pig hearts when applied to the endocardium (22). Previous studies in in vitro rabbit heart preparations showed that multiple shocks extinguished the re-entrant circuit by maintaining an area of myocardium refractory to activation, into which the re-entrant wave front collides (19). It is likely that the mechanism of defibrillation in the canine MI model of VT is similar.

The current standard ICD electrotherapy for ATP-refractory monomorphic VT is a high-energy biphasic shock. A low-energy electrotherapy would be desirable to replace the shock if it were effective. The mean DFT of the MSE in this report was nearly 80-fold lower in energy than that of a biphasic shock. Moreover, at low voltage (20 V), MSE achieved significantly more terminations than a biphasic shock, making it a suitable low-energy electrotherapy to reduce the need for full output ICD shocks.

Nearly all ICD shocks are delivered from the RV coil to an "active can"/superior vena cava coil configuration, delivering current, not only through the heart itself, but also through the chest wall musculature and sensory nerves, thereby dissipating energy over structures outside of the heart and causing pain. Implanting commercially available defibrillation leads in the CS (already Food and Drug Administration approved for defibrillation from the CS and azygous vein) and RV enables application of a shock vector that largely confines energy to the heart itself, and was shown to be effective for delivering MSE. Notably, this configuration would still allow ICD shocks to be applied via the traditional RV to superior vena cava/active can vector should MSE fail.

Though MSE may require design changes prior to incorporation into ICDs, such therapies require significantly lower voltage for defibrillation, which requires much less time for charging the capacitor than a full-output ICD shock. Reducing the number of full-output ICD shocks would likely prolong battery life and may reduce the malfunction rate of high-voltage components. Effective low-energy electrotherapy may be significantly less painful to patients, and importantly, reduce the likelihood of patients receiving a high-energy shock. Also, if high-energy shocks are themselves partially responsible for the increased mortality observed in patients who receive them, effective lower-energy electrotherapy may conceivably reduce mortality.

Conclusions

In the present study, we found that the DFT of a single monophasic shock to terminate VT in canine hearts with healing MI is phase dependent. Multiple shocks delivered within a single VT CL achieved lower DFTs than a single randomly timed shock without requiring a priori knowledge of phase dependence. MSE, which incorporated multiple MP shocks within the first stage, further reduced the DFT.

MSE is a low-voltage, low-energy electrotherapy that terminates VT with lower DFT than a single biphasic shock, yet it is significantly more effective than ATP in this model. If successful in humans, MSE may reduce the need for high-energy shocks.

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Key Words: defibrillation ■ ICD ■ multistage electrotherapy ■ myocardial infarction ■ ventricular tachycardia.