Burst Stimulation Improves Hemodynamics During Resuscitation After Prolonged Ventricular Fibrillation

Gregory Walcott, MD; Sharon Melnick, AAS; Cheryl Killingsworth, DVM, PhD; Raymond Ideker, MD, PhD

Background—Although return of spontaneous circulation is frequently achieved during resuscitation for sudden cardiac arrest, systolic blood pressure can then decrease, requiring additional myocardial support. Previous studies have shown that a series of 1-ms electric pulses delivered through the defibrillation patches during ventricular fibrillation can stimulate the autonomic nervous system to increase myocardial function after defibrillation. We hypothesized that a similar series of electric pulses could increase myocardial function and blood pressure during the early postresuscitation period.

Methods and Results—Six swine were studied that underwent 6 to 7 minutes of fibrillation. Each animal received 5, 10, 15, or 20 pulse packets consisting of six 10-A, 1-ms pulses every 3 to 4 s in random order whenever systolic blood pressure became <50 mm Hg. All 4 sets of pulse packets were delivered to each animal. Systolic blood pressure and cardiac function (left ventricular +dP/dt) were increased to above prestimulation levels or above by all 4 sets of pulse packets. The increases were significantly greater for the longer than the shorter number of pulse packets. The mean±SD duration of the time that the systolic pressure remained above 50 mm Hg after pulse delivery was 4.2±2.5 minutes.

Conclusions—Electric stimulation during regular rhythm after prolonged ventricular fibrillation and resuscitation can increase blood pressure and cardiac function to above prestimulation levels. (Circ Arrhythmia Electrophysiol. 2009;2:57-62.)

Key Words: ventricular fibrillation ■ resuscitation ■ electric stimulation

Sudden cardiac arrest is the leading cause of death in the United States with over 450 000 people suffering cardiac arrest each year.1 Survival after cardiac arrest is dismal, with only 5% to 10% of patients recovering well enough to leave the hospital alive. During resuscitation, 20% to 40% of arrest victims develop a palpable pulse. Therefore, 50% to 75% of all initially resuscitated victims of cardiac arrest die after medical help has arrived. In approximately one third of these deaths, poor myocardial function is an important contributing cause.3 Therefore, improved treatment for postresuscitation myocardial dysfunction could have a significant beneficial effect.

Postresuscitation myocardial dysfunction starts almost immediately after return of spontaneous circulation (ROSC).4 Global myocardial dysfunction progressively worsens over the first few hours after resuscitation, but often improves almost to prearrest levels after 48 hours.3,6 Therefore, early myocardial support, even in the prehospital setting, may be necessary to improve survival after resuscitation.

Previously, we have shown that delivering a series of 1-ms pulses during short duration (10 to 20 s) ventricular fibrillation (VF), stimulates the autonomic nervous system to increase myocardial function after defibrillation.7 Further, we have shown that myocardial catecholamine levels are at near toxic levels after defibrillation and reperfusion after several minutes of VF.8 After a few minutes of reperfusion, catecholamine levels, and arterial blood pressure begin to decrease. Arterial blood pressure often drops below 50 mm Hg, the minimum level for a palpable carotid pulse in humans. We hypothesized that electrically stimulating the autonomic nervous system with a series of 1-ms pulses synchronized to the R wave of the ECG after the blood pressure dropped below 50 mm Hg during resuscitation would increase cardiac function and blood pressure. In this study, we tested this hypothesis in swine and determined the effect of varying the number of stimulation pulses on the magnitudes of the subsequent rise in arterial blood pressure and increase in cardiac function.

Methods

Animal Preparation

All procedures were approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham. Further, all preoperative and operative care for animals complied with section 6 of the Animal Welfare Act of 1989 and adhered to the principles outlined in the “Guide for the care and use of animals,” National Institutes of Health publication No. 85 to 23. All authors...
Fourteen domestic swine of either sex, were studied. Animals were preanesthetized with telazol/xylazine (4.4 mg/kg of each) and atropine (0.04 mg/kg), then intubated, anesthetized with isoflurane (1.2% to 3%) and supported on a pressure-controlled mechanical ventilator (Ohmeda Modulus II, BOC Healthcare, N.J.) with a tidal volume of 10 to 15 mL/kg and a respiratory rate of 10 breaths/min. Normal saline was administered IV at a rate of 5 to 10 mL kg\(^{-1}\) h\(^{-1}\).

Blood gases and electrolytes were measured every half hour and respiratory parameters and infusion fluid composition were adjusted accordingly (potassium and calcium added if measured levels were low). ECG lead II was monitored throughout the study.

The animal was placed in dorsal recumbency. The left and right chest walls were shaved. Self-adhesive defibrillation electrodes were placed on the anterior left and right chest walls. The right jugular vein was isolated and a fluid filled pressure catheter was advanced under fluoroscopy to the junction of the right atrium and superior vena cava. A quadripolar catheter was inserted into the left jugular vein and advanced into the apex of the right ventricle for VF induction. The left carotid artery was isolated and a high fidelity pressure catheter (Mikro-tip, Millar Instruments, Houston, Tex) was inserted and advanced into the left ventricular cavity. The left femoral artery was isolated and a fluid filled pressure catheter was advanced into the ascending aorta.

After induction of anesthesia, ventilator oxygen fraction was decreased until the animals’ \(pO_2\) was \(<150\) mm Hg. After recording 30 s of baseline data, VF was induced by applying 60-Hz alternating current to the endocardium of the right ventricle. Fibrillation was allowed to persist unsupported for 6 to 7 minutes, after which the animal was defibrillated with a 200-J biphasic shock (LifePak 12, Physio-Control Corp, Redmond, Wash). Ventilation and chest compressions were then initiated. Ventilation was performed by restarting the ventilator at the same rate and tidal volume as before VF induction. Chest compressions were performed using a mechanical chest compressor (LUCAS, Jolife, Lund, Sweden) at a rate of 100 compressions/min.

Chest compressions and ventilation were continued until ROSC occurred or 30 minutes of resuscitation had elapsed. Compressions were stopped every 90 s to determine cardiac rhythm and whether the animal maintained a systolic arterial blood pressure \(>50\) mm Hg without chest compressions. If the ECG showed VF, the animal was defibrillated again with a 200-J shock.

**Experimental Procedures**

To be enrolled in the study, the animal must first have achieved ROSC, defined as a systolic arterial blood pressure \(>50\) mm Hg, followed by a decrease in arterial pressure to \(<50\) mm Hg (Figure 1). At this time, in the animals that met the above criteria, a series of electric stimuli was delivered. The stimuli were delivered in packets of six 1-ms pulses spaced 9 ms apart (Figure 2). The amplitude of each pulse was 10 A. The first pulse of each packet was delivered synchronized with the R wave of the local electrogram recorded from the right ventricular endocardium. Delivery of 5 stimulation packets is shown.
Table. Animal and Resuscitation Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>30±4</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>4/2</td>
</tr>
<tr>
<td>Time to ROSC (min)</td>
<td>3.6±1.8</td>
</tr>
<tr>
<td>No. of shocks</td>
<td>2.0±0.8</td>
</tr>
<tr>
<td>No. of refibrillation episodes</td>
<td>0.7±0.7</td>
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</table>

ROSC indicates return of spontaneous circulation.

elapsed between the delivery of each packet of stimuli. After a series of packets was delivered, the systolic blood pressure was monitored while it increased for a time period to above 50 mm Hg and then again fell to below 50 mm Hg. After the blood pressure decreased to <50 mm Hg, the next series of packets was delivered. This pattern was repeated until all 4 series of packets had been delivered to each animal.

Data Collection and Analysis

Surface ECG lead II, an intracardiac electrogram, and left ventricular, aortic, and right atrial pressures, were recorded on a personal computer-based data acquisition system (Dataq, Akron, Ohio) at a sampling rate of 250 samples/s. Data were analyzed off-line using Matlab (Mathworks, Natick, Mass). Systolic arterial pressure was determined by identifying the peak value in the aortic pressure recording on a beat-by-beat basis. Systolic arterial pressure was determined at baseline before the induction of fibrillation and at the time of peak response after delivery of the electric packets by averaging the beat-by-beat systolic arterial pressure over a 5-s interval. Cardiac function was evaluated by examining \( \frac{dp}{dt} \) of the left ventricular pressure. The derivative of left ventricular pressure was calculated using a 5-point parabolic fit. Maxima and minima of \( \frac{dp}{dt} \) were determined at baseline before the induction of fibrillation and at the time of peak response after delivery of the electric packets. Baseline animal comparisons were made using ANOVA (SPSS, Chicago, Ill). Burst stimulation hemodynamic data were compared using repeated-measures analysis of variance. Postburst hemodynamic values were included in the model as one of the levels tested. Post hoc comparisons were made using Tukey’s method. Significance was defined as \( P<0.05 \). Values are given as mean±SD.

Results

Six swine met the criteria to be included in the data analysis. The other 8 animals were not included because either they were not resuscitated (6 animals) or the systolic arterial blood pressure never fell below 50 mm Hg after achieving ROSC (2 animals). Animal and resuscitation characteristics are shown in the Table. The 6 animals were not significantly different with respect to the duration of chest compressions, the number of refibrillation episodes, and the number of defibrillation shocks delivered.

Figure 2 shows an example of the increase in systolic aortic blood pressure caused by all 4 stimulus packets. Before VF induction, systolic aortic blood pressure was \( \approx 110 \) mm Hg. It then dropped nearly to zero during VF (time 0 to 7 minutes). After defibrillation, chest compressions were performed from \( \approx 7 \) to 16 minutes. Chest compressions were halted when ROSC occurred at \( \approx 16 \) minutes. Systolic aortic blood pressure rose to a peak of \( \approx 125 \) mm Hg, presumably secondarily to the surge of intrinsic catecholamines that occurs after prolonged VF and resuscitation. Systolic aortic blood pressure then fell to 50 mm Hg at which time delivery of a series of packets of electric stimuli was begun each time the pressure decreased to 50 mm Hg. Each of the 4 series of packets increased the systolic pressure.

A similar pattern was seen in all 6 animals. The time from the beginning of resuscitation until ROSC was 3.6±1.8 minutes. The time from ROSC until peak systolic arterial pressure after ROSC was 5.4±2.4 minutes. The time from this peak blood pressure to delivery of the first series of stimulation packets was 9.7±1.4 minutes.

Figure 3 shows the systolic arterial pressure response to electric stimuli. Systolic arterial blood pressure was significantly higher for all 4 numbers of packets tested compared with the prestimulation systolic arterial blood pressure. Ten or more packets were required to return systolic arterial pressure to prearrest levels, which was 122±15 mm Hg. There was a positive dose-response relationship. Post hoc multiple comparisons testing grouped the arterial blood pressure response into 2 groups: the response to 5 and 10 pulses were not different and the response to 10, 15, and 20 pulses were not different. This data suggests that the arterial pressure
response reaches a plateau after 10 pulses. The duration of the response (the time from the onset of the stimuli until the systolic blood pressure dropped below 50 mm Hg or reached a minimum if the pressure remained above 50 mm Hg) was 4.2±2.5 minutes. There was no significant difference in the duration of this response time among any of the 4 pulse packets tested.

Figure 4 shows the cardiac function (±dP/dt) response to the electric stimuli. Maximum +dP/dt was 1687±157 mm Hg/s and minimum −dP/dt was −2547±422 mm Hg/s before the initiation of VF. Both +dP/dt and −dP/dt were significantly greater after delivery of electric stimulation compared to the prestimulation levels. Again there was a positive dose-response relationship. Post hoc multiple comparisons testing grouped the + and −dP/dt response into 2 groups: the response to 5 and 10 pulses were not different and the response to 10, 15, and 20 pulses were not different. Fibrillation was never induced by the electric stimuli.

Discussion
The major finding of this study is that electric stimulation during regular rhythm after a period of prolonged VF and resuscitation can increase blood pressure and cardiac function (dP/dt) to above prearrest levels.

Resuscitation after cardiac arrest can be divided into 2 stages. The first stage is the period when attempts are made to establish ROSC. Treatments before ROSC include performance of chest compressions, rhythm analysis, and delivery of defibrillation shocks if necessary. The second stage is the period when cardiac and neurological function is decreased and needs to be supported. This period may extend from a few minutes to several days.

That cardiac function is decreased after ROSC has been observed in a number of species including rat, pig, dog, and human. This decrease in cardiac function occurs without continuing myocardial ischemia caused by coronary occlusion and is likely due to the combination of ischemia induced by the no blood flow state during VF and the high cardiac metabolic rate caused by the rapid activations during VF. Certain types of defibrillation shock waveforms and of drugs during cardiac arrest have been shown to modify the degree of cardiac dysfunction. If the cardiac arrest victim does not have a fixed coronary blockage, this dysfunction often improves over the next 24 to 48 hours.

Our study shows that frequently arterial blood pressure falls and cardiac function decreases soon after ROSC in swine after 6 to 7 minutes of VF. The time from the beginning of resuscitation until the systolic arterial blood pressure dropped below 50 mm Hg was ≈19 minutes. If the time course of human resuscitation follows the time course of resuscitation in our animal model, and because ROSC most often occurs before transport of the victim to the hospital begins, cardiac support may need to be begun in the prehospital setting. The electric therapy described here can be delivered simply without the need for IV or other vascular access and can be performed in a moving ambulance.

In a previous study, we showed that burst stimulation delivered during short duration VF just before the shock improved hemodynamics after defibrillation. Further, β-adrenergic blockade before electric stimulation blocked the hemodynamic improvement, showing that the electric burst was stimulating the sympathetic nervous system. The current study has 2 important differences from our previous work. First, the burst stimuli were delivered from defibrillation electrodes on the chest wall rather than from defibrillation electrodes in the heart. This difference is likely to change the amount of sympathetic nervous stimulation the pulses induce, but is not likely to change the mechanism of the effect. Second, the pulse packets are delivered during regular rhythm after ROSC rather than during VF. A previous study from our group showed that myocardial tissue catecholamines rise to potentially toxic levels in the first few minutes of reperfusion after prolonged VF and defibrillation. Therefore, we chose to deliver the pulses at a time when the intrinsic catecholamine
surge is waning and cardiac function is decreasing. This choice required that we deliver the electric stimuli synchronized with the intrinsic cardiac electric signal so that the pulses would not induce VF. We limited our packets to six 1-ms pulses 9 ms apart so that the entire packet of 6 pulses (60 ms) would be delivered before the T wave of the electrogram occurred. We spaced the packets a minimum of 3 s apart so that the electrogram that we were synchronizing the packets to had time to recover from the previous packet(s). This resulted in no VF induction by any of the packets, suggesting that if sufficient care is taken to synchronize the delivery of packets to the QRS, the therapy can be delivered safely.

The response to the stimulating packets reached a plateau for 15 to 20 packets, and only 5 or 10 packets were needed to return systolic arterial blood pressure and cardiac function to prearrest levels. We chose to deliver the therapy intermittently whenever the systolic arterial blood pressure dropped below 50 mm Hg. A better approach might be to deliver the pulse packets more frequently at a rate that maintains a constant arterial blood pressure. Future study is needed to determine the most appropriate way to implement this therapy, whether or not it improves survival or changes functional status after resuscitation. Further study is also necessary to compare survival and functional status of this therapy with current conventional therapies such as catecholamine infusion.

Limitations
Our electric therapy never induced VF, but this required careful synchronization with the intrinsic cardiac electric signal. In this case, we used an electrophysiology catheter in the right ventricle to synchronize our therapy with the heart. This therapy significantly distorts the body surface ECG, especially the defibrillation patch electrogram. Development of signal processing algorithms will be necessary to deliver this therapy synchronized to the defibrillation patch electrogram.

Though not tested in this experiment, it is likely that this therapy would cause discomfort in an awake patient. It is likely that subjects requiring this type of support are likely to be unconscious at the time of therapy and so will not feel the delivery of the burst stimulation.

This study was performed in animals that had received anesthesia, including atropine at the beginning of the study. Our previous work has suggested that burst stimulation is a sympathetic nervous system effect rather than a parasympathetic nervous system effect. The effect of anesthesia may change the underlying physiology slightly, but should not affect the relative changes in hemodynamics and cardiac function that we observe with delivery of the burst stimulation.

Another limitation of our study is that we only measured pressures and not blood flow. Cardiac output measurements at low flows (before burst stimulation) are problematic as it determining the cardiac output at the peak of the response to the burst stimulation. We hope to improve future studies in part by solving this issue.

Our study has not answered the question of whether or not burst stimulation improves survival after ROSC. Our therapy might lead to short-term hemodynamic improvements but not have long-term survival benefits. The question of appropriate postresuscitation hemodynamic optimization has not been well addressed in the literature. A recent review by Jones et al.\(^9\) states that to date no clinical trials have examined hemodynamic optimization in patients with cardiac arrest after ROSC. Some work in animals by the research group at the University of Arizona\(^10,11\) has examined the effect of dobutamine and aortic counterpulsation on postresuscitation myocardial dysfunction and found that dobutamine, but not aortic counterpulsation, improved postresuscitation myocardial dysfunction. Future studies are necessary to determine whether burst stimulation therapy improves morbidity or mortality following ROSC after sudden cardiac arrest.

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Disclosures
None.

References


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