Burst Stimulation Improves Hemodynamics During Resuscitation after Prolonged Ventricular Fibrillation

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Abstract

**Background** - Although return of spontaneous circulation (ROSC) 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 electrical pulses delivered through the defibrillation patches during ventricular fibrillation (VF) can stimulate the autonomic nervous system to increase myocardial function following defibrillation. We hypothesized that a similar series of electrical pulses could increase myocardial function and blood pressure during the early post-resuscitation period.

**Methods and Results** - Six swine were studied that underwent 6-7 min. Each animal received 5, 10, 15, or 20 pulse packets consisting of 6 10 A, 1-ms pulses every 3-4 s in random order whenever systolic blood pressure became less than 50 mmHg. All four sets of pulse packets were delivered to each animal.

Systolic blood pressure and cardiac function (left ventricular +dP/dt) were increased to pre-stimulation levels or above by all four 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 mmHg following pulse delivery was 4.2±2.5 min.

**Conclusions** - Electrical stimulation during regular rhythm following prolonged VF and resuscitation can increase blood pressure and cardiac function to above pre-arrest levels.

**Key Words**: ventricular fibrillation, resuscitation, electrical stimulation
Introduction:

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 following cardiac arrest is dismal, with only 5-10% of patients recovering well enough to leave the hospital alive. During resuscitation, 20-40% of arrest victims develop a palpable pulse. Therefore 50-75% of all initially resuscitated victims of cardiac arrest die after medical help has arrived.\(^2\) In approximately one-third of these deaths, poor myocardial function is an important contributing cause.\(^3\) Therefore, improved treatment for post-resuscitation myocardial dysfunction could have a significant beneficial effect.

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

Previously we have shown that delivering a series of 1-ms pulses during short duration (10-20 s) ventricular fibrillation, stimulates the autonomic nervous system to increase myocardial function following defibrillation.\(^7\) Further, we have shown that myocardial catecholamine levels are at near toxic levels after defibrillation and reperfusion following several minutes of ventricular fibrillation.\(^8\) After a few minutes of reperfusion, catecholamine levels and arterial blood pressure begin to decrease. Arterial blood pressure often drops below 50 mmHg, the minimum level for a palpable carotid pulse in humans.\(^9\) 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 mmHg 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 pre-operative 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. 85-23. All authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Fourteen domestic swine of either sex, were studied. Animals were pre-anesthetized with telazol/xylazine (4.4 mg/kg of each) and atropine (0.04 mg/kg), then intubated, anesthetized with isoflurane (1.2-3%) and supported on a pressure-controlled mechanical ventilator (Ohmeda Modulus II, BOC Healthcare, NJ) with a tidal volume of 10-15 ml/kg and a respiratory rate of 10 breaths/min. Normal saline was administered IV at a rate of 5-10 ml/kg/hr. 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 ventricular fibrillation induction. The left carotid artery was isolated and a high fidelity pressure catheter (Mikro-tip, Millar Instruments, Houston, Tx.) 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 less than 150 mmHg. After recording 30 s of baseline data, ventricular fibrillation was induced by applying 60Hz alternating current to the endocardium of the right ventricle. Fibrillation was allowed to persist unsupported for 6-7 min, after which the animal was defibrillated with a 200J biphasic shock (LifePak 12, Physio-Control Corp, Redmond, Wa.). Ventilation and chest compressions were then initiated. Ventilation was performed by restarting the ventilator at the same rate and tidal volume as before ventricular fibrillation 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 min of resuscitation had elapsed. Compressions were stopped every 90 s to determine cardiac rhythm and whether the animal maintained a systolic arterial blood pressure greater than 50 mmHg without chest compressions. If the ECG showed ventricular fibrillation, the animal was defibrillated again with a 200J shock.

**Experimental Procedure:**

To be enrolled in the study, the animal must first have achieved ROSC, defined as a systolic arterial blood pressure greater than 50 mmHg, followed by a decrease in arterial pressure to less than 50 mmHg (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 6 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 ventricle. The pulse packets were delivered through the defibrillation electrodes on the chest wall. A series of 5, 10, 15, or 20 packets was delivered in random order. A minimum of 3 seconds 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 mmHg and then again fell to below 50 mmHg. After the blood pressure decreased to less than 50 mmHg, the next series of packets was delivered. This pattern was repeated until all four 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 PC-based data acquisition system (Dataq, Akron, OH) at a sampling rate of 250 samples/s. Data were analyzed off-line using Matlab (Mathworks, Natick, MA.). 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 following delivery of the electrical packets by averaging the beat-by-beat systolic arterial pressure over a 5 sec interval. Cardiac function was evaluated by examining ± 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 $dP/dt$ were determined at baseline before the induction of fibrillation and at the time of peak response following delivery of the electrical packets.

Baseline animal comparisons were made using ANOVA (SPSS, Chicago, IL.) Burst stimulation hemodynamic data were compared using repeated measures analysis of variance. Pre-burst 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 the mean ± the standard deviation.
Results:

Six swine met the criteria to be included in the data analysis. The other eight animals were not included because either they were not resuscitated (6 animals) or the systolic arterial blood pressure never fell below 50 mmHg after achieving ROSC (2 animals). Animal and resuscitation characteristics are shown in table 1. The six 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 1 shows an example of the increase in systolic aortic blood pressure caused by all four stimulus packets. Before VF induction, systolic aortic blood pressure was about 110 mmHg. It then dropped nearly to zero during VF (time 0-7 min). After defibrillation, chest compressions were performed from about 7 min to 14 min. Chest compressions were halted when ROSC occurred at about 14 min. Systolic aortic blood pressure rose to a peak of about 125 mmHg, presumably secondarily to the surge of intrinsic catecholamines that occurs following prolonged VF and resuscitation. Systolic aortic blood pressure then fell to 50 mmHg at which time delivery of a series of packets of electrical stimuli was begun each time the pressure decreased to 50 mmHg. Each of the four series of packets increased the systolic pressure.

A similar pattern was seen in all six animals. The time from the beginning of resuscitation until ROSC was 3.6±1.8 min. The time from ROSC until peak systolic arterial pressure following ROSC was 5.4 ±2.4 min. The time from this peak blood pressure to delivery of the first series of stimulation packets was 9.7±1.4 min.
Figure 3 shows the systolic arterial pressure response to electrical stimuli. Systolic arterial blood pressure was significantly higher for all four numbers of packets tested compared to the pre-stimulation systolic arterial blood pressure. Ten or more packets were required to return systolic arterial pressure to pre-arrest levels, which was 122±15 mmHg. There was a positive dose–response relationship. Post-hoc multiple comparisons testing grouped the arterial blood pressure response into two 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. After the duration of the response (the time from the onset of the stimuli until the systolic blood pressure dropped below 50 mmHg or reached a minimum if the pressure remained above 50 mmHg) was 4.2±2.5 min. There was no significant difference in the duration of this response time among any of the four pulse packets tested.

Figure 4 shows the cardiac function (±dP/dt) response to the electrical stimuli. Maximum +dP/dt was 1687±157 mmHg/s and minimum -dP/dt was -2547±422 mmHg/s before the initiation of VF. Both +dP/dt and –dP/dt were significantly greater after delivery of electrical stimulation compared to the pre-stimulation 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 electrical stimuli.

Discussion:
The major finding of this paper is that electrical stimulation during regular rhythm following a period of prolonged VF and resuscitation can increase blood pressure and cardiac function (dP/dt) to above pre-arrest levels.

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

That cardiac function is decreased following 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 24-48 hours.

Our study shows that frequently arterial blood pressure falls and cardiac function decreases soon after ROSC in swine after 6-7 min of VF. The time from the beginning of resuscitation until the systolic arterial blood pressure dropped below 50 mmHg was ~19 minutes. If the time course of human resuscitation follows the time course of resuscitation in our animal model, and since ROSC most often occurs before transport
of the victim to the hospital begins\textsuperscript{18}, cardiac support may need to be begun in the pre-
hospital setting. The electrical 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 following defibrillation.\textsuperscript{7}
Further, beta-adrenergic blockade prior to electrical stimulation blocked the
hemodynamic improvement, showing that the electrical burst was stimulating the
sympathetic nervous system. The current study has two 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 following 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 following prolonged VF and
defibrillation.\textsuperscript{8} 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 electrical stimuli synchronized with the intrinsic cardiac electrical
signal so that the pulses would not induce VF. We limited our packets to 6 1-ms pulses
9-ms apart so that the entire packet of six 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 15-20 packets
and, only 5 or 10 packets were needed to return systolic arterial blood pressure and
cardiac function to pre-arrest 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 following 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 electrical therapy never induced VF, but this required careful
synchronization with the intrinsic cardiac electrical 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 (prior to burst stimulation) are problematic as is 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 following ROSC. Our therapy might lead to short term hemodynamic improvements but not have long-term survival benefits. The question of appropriate post-resuscitation hemodynamic optimization has not been well addressed in the literature. A recent review by Jones et al.\textsuperscript{19} states that to date no clinical trials have examined hemodynamic optimization in patients with cardiac arrest after return of spontaneous circulation. Some work in animals by the research group at the University of Arizona\textsuperscript{20, 21} has examined the effect of dobutamine and aortic counter-pulsation on post-resuscitation myocardial dysfunction and found that dobutamine, but not aortic counter-pulsation, improved post-resuscitation myocardial dysfunction. Future studies are necessary to determine if burst stimulation therapy improves morbidity or mortality following ROSC after sudden cardiac arrest.
Funding Sources:

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Conflict of Interest:

The authors have no conflict of interest associated with the work presented in this manuscript.
References:


Table 1: Animal and Resuscitation Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<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>Number of Shocks</td>
<td>2.0±0.8</td>
</tr>
<tr>
<td>Number of Refibrillation episodes</td>
<td>0.7±0.7</td>
</tr>
</tbody>
</table>
Figures and Legends:

Figure 1: An example from one animal demonstrating that the stimuli increase the systolic blood pressure. VF was induced and defibrillation was performed 7 min later. Chest compressions (CCs) were then performed for about 7 min until ROSC occurred after which CCs were halted. ROSC lasted for approximately 15 min with systolic pressure decreasing for approximately the last 10 min of this period. Stimulation packets were then delivered in random order whenever the systolic pressure decreased to 50 mmHg. After the fourth series of packets, systolic pressure remained above 50 mmHg. The peak values for 20, 15, 10, and 5 stimulation packets are labeled.

Figure 2: Diagram of the delivery of the electrical stimulation. Each packet consisted of 6 10-Amp 1-ms pulses 9 ms apart delivered through the defibrillation electrodes. Each packet of stimuli was synchronized with the R-wave of the local electrogram recorded from the right ventricular endocardium. Delivery of 5 stimulation packets is shown.

Figure 3: Systolic blood pressure response to stimulation. White bars show the left ventricular systolic blood pressure just before delivery of electrical stimulation. Black bars show the peak blood pressure response following delivery of electrical stimulation. For all four numbers of packets, the peak systolic pressure following stimulation was significantly different than the systolic pressure before stimulation.

Figure 4: Cardiac function response to electrical stimulation. Circles show left ventricular ± dP/dt just before delivery of electrical stimulation. Squares show the peak
± dP/dt response following delivery of electrical stimulation. For all four numbers of packets, ± dP/dt following stimulation was significantly different than before stimulation.
Figure 1: Systolic Arterial Blood Pressure (mmHg) vs Time (min). The graph shows the following events:

- **VF**: Ventricular Fibrillation
- **CC**: Cardiac Cessation
- **ROSC**: Return of Spontaneous Circulation

The graph indicates a series of peaks and troughs, with annotations at 5, 10, 15, 20, and 25 minutes, respectively.
Figure 2:
Figure 3:
Figure 4:
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