Effect of Burst Stimulation During Ventricular Fibrillation on Cardiac Function Following Defibrillation

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Abstract

**Background:** The purpose of defibrillation is to rapidly restore blood flow and tissue perfusion following ventricular fibrillation and shock delivery. We tested the hypotheses that (1) a series of 1-msec pulses of various amplitudes, delivered before the defibrillation shock, can improve hemodynamics following the shock and (2) this hemodynamic improvement is due to stimulation of cardiac or thoracic sympathetic nerves.

**Methods and Results: Part 1:** In ten anesthetized pigs, a burst of either 15 or 30 1-msec pulses ranging from 0.1 to 10 Amps in strength were given during ventricular fibrillation after which defibrillation was performed. ECG, arterial blood pressure and left ventricular pressure were recorded. Defibrillation shocks and burst pulses were delivered from a right ventricular coil electrode to superior vena cava coil and left chest wall electrodes. After an initial series of trials, sympathetic blockade was induced with timolol, 1 mg/kg, and the trials were repeated. **Part 2:** The first half of the above protocol was repeated in two animals that were pretreated with reserpine.

**Part 1:** Heart rate following 1, 2, 5, and 10 Amp pulses was significantly higher than following control shocks without preceding pulse therapy. Mean and peak left ventricular pressures increased 38% and 72% following shocks preceded by 5 and 10 Amp pulses when compared to shocks preceded by no burst pulses. Mean and peak arterial pressures increased 36% and 43% following shocks preceded by 5 and 10 Amp pulses when compared to shocks preceded by no burst pulses. Following beta blockade, neither heart rate, mean nor peak arterial pressure or mean LV pressure was significantly different following pulses of any strength when compared to control shocks. LV peak pressure following the 10 Amp pulses was significantly higher than with no burst pulses but was significantly less than the the response to the 10 Amp pulses delivered without beta blockade. **Part II:** The heart rate, mean and peak arterial pressure, mean and peak LV pressure response following 15 or 30, 5 or 10 Amp pulses was similar to the response to the same pulses following beta blockade.

**Conclusion:** A burst of 15-30 1-msec pulses delivered during ventricular fibrillation can increase
heart rate, arterial pressure and LV pressure following defibrillation. Beta blockade or reserpininepretreatment prevents most of this post-shock increase in heart rate, arterial pressure and LV pressure.

**keywords:** defibrillation, cardiac function
Introduction

The goal of defibrillation is to rapidly restore blood flow and tissue perfusion following an episode of ventricular fibrillation by restoring a regular rhythm. Both the shock itself as well as the preceding ventricular fibrillation can contribute to depressed myocardial function following successful defibrillation. If ventricular fibrillation continues long enough, about 120 seconds in dogs, pulseless electrical activity can result and the subject will die if hemodynamic support is not started. The mechanism for this depressed myocardial function is not well understood.

Electrical therapy can be used to improve cardiac contractility in several possible ways. Post-extrasystolic potentiation causes the contraction following a premature stimulus to be augmented compared to baseline or to the contraction associated with the premature stimulus. Field stimulation that alters the transmembrane potential without initiating a new action potential can either increase or decrease cardiac contractility depending on the timing and polarization of the pulse. The activation sequence of patients with congestive heart failure and a prolonged QRS can be altered by pacing from one or more sites to increase the synchrony of contraction and improve cardiac function.

The autonomic nervous system can be stimulated to either increase or decrease cardiac contractility. Post-ganglionic fibers in sympathetic cardiac nerves are distributed over the heart. Extra-cardiac stimulation of these nerves increases both heart rate and the strength of cardiac contraction. Field stimulation of intrinsic cardiac nerves in isolated myocardium also can increase cardiac contractility.

We tested the hypotheses that (1) a series of 1-msec pulses of various amplitudes delivered during fibrillation before defibrillation can improve hemodynamics following the shock and (2) this improvement in hemodynamics following the shock is due to stimulation of cardiac or thoracic sympathetic nerves. To test these hypotheses we examined the ability of these pulse trains to change hemodynamics following a defibrillation shock before and after beta blockade and following reserpine pre-treatment.
Part I

Ten pigs, 25-30 kgs, were premedicated with Telazol, 4.4 mg/kg, xylazine, 2.2 mg/kg and atropine, 0.04 mg/kg. Animals were intubated with a cuffed endotracheal tube and were ventilated at a rate of 10-15 ml/kg/min. Anesthesia was maintained using 1-3% isoflurane. A 7-Fr hemostatic sheath was placed in the left femoral artery and an 8-Fr hemostatic sheath was placed in the right femoral artery and left jugular vein. Both the left and right jugular veins was isolated. A 5-Fr high fidelity pressure catheter (Millar Instruments) was advanced retrograde across the aortic valve into the left ventricle. A 3-Fr high fidelity pressure catheter was placed via a femoral sheath into the abdominal aorta. A transvenous defibrillation catheter (Endotak model DSP, Guidant Corp.) with a 6 cm distal coil, a 7 cm proximal coil, and an interelectrode spacing of 12 cm was advanced into the right ventricular apex. A defibrillation can electrode was placed under the skin of the anterior left chest wall overlying the 2nd intercostal space. The distal defibrillation electrode was the anode for all burst stimulation and the first phase of the biphasic defibrillation shock. The proximal defibrillation catheter electrode connected to the can electrode served as the cathode.

A defibrillation threshold was determined using a three reversal up-down protocol using a log(0.1) Joule step size.15 VF was induced using 60-Hz current applied to the right ventricular apex. Defibrillation shocks were delivered after 10 seconds of VF. An external cardiovertor-defibrillator (VENTAK ECD, Guidant Corp.) was used to deliver all defibrillation shocks. The defibrillator was triggered by a pulse generator (WPI). All subsequent defibrillation shocks were delivered at approximately 1.5X energy of the measured threshold. If a shock failed to defibrillate the heart, the trial was discarded and repeated.

The animal was challenged with 10 ug/kg/min of dobutamine, a beta agonist,16 for 4 minutes. Heart rate and arterial blood pressure were recorded before and at the end of the dobutamine infusion. Following the dobutamine challenge, a 20 minute washout period was observed before
any testing was performed.

**Pulse Therapy**

Prior to defibrillation shock delivery, a series of therapy pulses were delivered using a linear power amplifier (Guidant Corp.). Burst stimulation was delivered through the defibrillation electrodes. The distal electrode in the right ventricular apex was the cathode for all stimuli. Burst stimulation pulses were 1 msec in duration. Six pulse strengths were used: 0.1, 0.3, 1, 2, 5, and 10 Amps. Either 15 or 30 pulses were delivered. Time between pulses was 30 msec for 0.1 and 0.3 Amp pulses and 10 msec for all the rest. A 3 second delay was allowed between the burst therapy and the defibrillation shock. A total of 12 different pulses therapies was tested. Trial order was randomized across each animal. A control trial with no burst stimulation prior to defibrillation was performed before any burst therapy trials and after every 4th therapy trial.

**Beta blockade**

After the initial 16 burst stimulation and control trials, the animal was given timolol, 1 mg/kg. After 10 minutes, the dobutamine challenge was repeated. The dobutamine challenge was given to test the effectiveness of beta blockade. The initial dobutamine challenge was given as a control. Following a 20 minute washout period for the dobutamine, the 12 burst therapy trials and 4 control trials were repeated.

At the end of the study, the animal was euthanized with KCl while still anesthetized. The heart was removed, weighed and examined grossly.

**Data Collection and Analysis**

Lead II ECG and the two pressure signals were collected with an 8-channel data acquisition system (Windaq, Dataq Co.) at a minimum sampling rate of 500 samples/sec. Data were analyzed using Matlab (Mathworks Co.). The investigator performing the analysis was blinded to the amplitude of
the burst stimulation at the time of analysis. Values are given as the mean ± the standard deviation.

Repeated measures analysis of variance was used to compare mean values (SPSS, SPSS Inc.). When the repeated measures analysis of variance showed a significant difference, a Student-Newman-Keuls post-hoc test was used to determine differences between the response to each burst stimulation level and the response during control episodes without burst stimulation. A p-value ≤ 0.05 was considered significant.

Part II

In two additional animals, reserpine, 1 mg/kg, was given 24 hrs prior to study in order to chemically sympathectomize them. The animals subsequently underwent the control portion of the above protocol, including defibrillation threshold determination, dobutamine challenge, and pulse therapy testing. Following pulse therapy testing, the animals were challenged with tyramine, 1 mg/kg, to test the effectiveness of the chemical sympathectomy.
Results

Animal weight was 34±3 Kg. Heart weight was 160±20 gms. Mean defibrillation threshold was 488±55 Volts. Mean defibrillation shock strength delivered during pulse therapy testing was 732±89 Volts. VF was induced an average of 44 times/animal. Baseline hemodynamics did not change significantly over the duration of each half of the protocol. Heart rate and hemodynamic response to the four control episodes in the first half of the study before the animal received timolol were not significantly different from each other. Gross pathologic examination at the end of each study showed no unusual changes in any of the hearts studied.

Pulse Therapy prior to Beta Blockade

For control shocks, heart rate did not change significantly over the 30 seconds following the shock from the baseline value of 110±17 beats per minute (figure 1). For shocks preceded by pulse therapy, heart rate was significantly higher following the 1, 2, 5 and 10 Amp pulses at 1, 10, and 20 seconds after the shock compared to baseline but was not different from baseline at 30 seconds. There was a trend toward a greater increase in heart rate with 30 pulses than with 15 pulses, but this difference did not reach significance.

For control shocks, systolic left ventricular pressure fell from 130±20 mmHg at baseline to 51±10 mmHg 1 second after the shock. By 30 seconds, systolic left ventricular pressure had increased to 91±12 mmHg, which was still significantly different than the baseline pressure (figure 2). For shocks with pulse therapy, systolic left ventricular pressure was significantly higher for pulse strengths of 2, 5, and 10 amps than for the control shocks. Thirty seconds after the shock, systolic left ventricular pressure was still significantly higher than for control shocks. Again there was a trend toward a greater increase in systolic left ventricular pressure for 30 than for 15 therapy pulses, but this did not reach significance.

For control shocks, left ventricular mean pressure dropped from 42 ± 9 mmHg at baseline to 18 ± 5 mmHg at 1 second following the shock (figure 2). Left ventricular mean pressure
was significantly higher for either 15 or 30 pulses at pulse strengths of 2, 5, and 10 Amps than for control episodes. Thirty pulses did not significantly increase left ventricular mean pressure compared to 15 pulses.

For control shocks, systolic arterial pressure dropped from 115±17 mmHg at baseline to 51±14 mmHg one second following the shock. By 30 seconds, systolic arterial pressure had increased to 87±10 mmHg (figure 3). Systolic arterial blood pressure was significantly increased over baseline for 2, 5, and 10 Amp pulses at 1, 10, 20 and 30 seconds. There was no significant difference in the systolic arterial pressure response to 15 and 30 pulses.

For control shocks, mean arterial pressure dropped from 84±14 mmHg to 45±16 mmHg at 1 second following the shock. By 30 seconds, mean arterial pressure had increased to 73±13 mmHg (figure 3). For shocks with pulse therapy, mean arterial blood pressure was significantly higher for either 15 or 30 pulses for pulse strengths of 5 and 10 amps than for control episodes at 1, 10, 20 and 30 seconds. There was no significant difference in the response of mean arterial pressure to 15 and 30 pulses.

**Dobutamine test**

Prior to any burst stimulation testing, dobutamine changed heart rate from 110±12 bpm to 134±18 bpm and systolic blood pressure from 112±24 mmHg to 158±24 mmHg (p ≤ 0.05). Following beta blocker administration, dobutamine changed heart rate from 107±17 mmHg to 111±17 mmHg and systolic blood pressure from 106±18 mmHg to 113±22 mmHg (p = NS).

**Pulses during Beta Blockade**

Beta blockade caused a significant decrease in heart rate from 114±17 to 107±12 bpm. Systolic blood pressure was lowered from 115±17 to 100±19 mmHg, and mean arterial blood pressure was lowered from 86±13 to 70±15 mmHg. Systolic LV pressure was lowered from 132±21 to 116±16 mmHg and mean LV pressure was lowered from 43±9 to 36±8 mmHg. All of these changes were significant. Heart rate and hemodynamic response to the four control episodes in the
the second half of the study after the animal received timolol were not significantly different from each other.

After beta blockade, heart rate 1, 10, 20, or 30 seconds following defibrillation for control episodes did not change significantly from the 110±17 beats per minute value before fibrillation induction (baseline) 1, 10, 20, or 30 seconds following the shock. None of the pulse therapy changed heart rate from the control values (figure 4).

For control episodes, systolic left ventricular pressure dropped from a baseline of 116±16 mmHg to 66± mmHg 1 second following the shock. By 30 seconds, systolic left ventricular pressure had increased to 113±17 mmHg (figure 5). Only the 10 Amp pulses increased systolic left ventricular pressure above control shock values. There was no significant difference in the response to 15 and 30 pulses.

For control episodes, mean left ventricular pressure dropped from a baseline value of 42±9 mmHg to 33±10 1 second following the shock. By 30 seconds, mean left ventricular pressure had increased to 38±10 mmHg (figure 5). None of the pulse therapies changed mean left ventricular pressure significantly differently than for control episodes.

For control episodes, systolic arterial pressure dropped from 98±15 mmHg at baseline to 58±15 mmHg 1 second after the shock. By 30 seconds, systolic blood pressure had returned to 98±15 mmHg (figure 6). None of the pulse therapies changed systolic arterial pressure significantly differently than for control episodes.

For control episodes, mean arterial pressure decreased from 84±13 to 45±16 mmHg 1 second following the shock. By 30 seconds following the shock, mean arterial pressure had returned to 73±15 mmHg (figure 6). None of the pulse therapies changed mean arterial pressure significantly from the control episode values.

**Part II**

In the two animals that received reserpine, dobutamine increased heart rate by 40% and systolic blood pressure by 80%. The defibrillation threshold was 452 ± 113.
We limited our analysis to control episodes and either 15 or 30 pulses of 5 or 10 amps. These burst stimulation combinations showed the greatest changes in heart rate and hemodynamics in Part 1 prior to timolol administration. Heart rate increased approximately 10% with pulse therapy compared to control episodes in the 30 seconds following the shock. Systolic arterial pressure, mean arterial pressure, systolic LV pressures and mean LV pressure also rose approximately 10% with pulse therapy compared to controls. These results are similar to those observed when timolol was given to the animal in part 1 prior to pulse therapy at these pulse strengths and numbers.
Discussion

The findings in this paper are two-fold. First, pulse stimulation that is too weak to defibrillate, when given during ventricular fibrillation prior to the defibrillation shock increases heart rate, arterial pressure and left ventricular pressure following successful defibrillation compared to that following defibrillation without prior stimulation. Second, the effect on post-shock cardiac hemodynamics can be blocked by beta blockers or by reserpine pretreatment, suggesting that the pulses delivered during ventricular fibrillation stimulate the sympathetic nervous system.

This study showed that following 10 seconds of ventricular fibrillation and defibrillation with a shock of a strength 1.5 times the defibrillation threshold, left ventricular and arterial pressures drop transiently followed by recovery that was still not complete by 30 seconds following defibrillation. This decrease in hemodynamics following the shock is thought to be primarily due to the episode of ventricular fibrillation rather than to the shock itself. Panegrau and Abboud showed that, similar to our results, following 15 to 30 seconds of fibrillation and a 400 W-sec capacitor discharge defibrillator shock delivered to the chest wall, heart rate and mean arterial pressure were significantly lower than at baseline. Over the next 2-3 minutes, heart rate returned to baseline. However at one minute following the shock, mean arterial pressure had overshot baseline. It subsequently returned to baseline over the next 2-3 minutes. In contrast, when the same shock was delivered to the chest wall during sinus rhythm, changes in hemodynamics were small and not statistically significant, with the exception of minimal reductions in mean arterial pressure. Kerber et al. showed that there was no significant change in heart rate and aortic mean pressure following shocks of up to 100 J delivered to the epicardial surface or following shocks up to 460 J delivered to the chest wall during sinus rhythm. When shocks of the same strength were delivered following 10-15 seconds of fibrillation, heart rate and mean arterial pressure transiently decreased. Park et al. have shown in humans that there is a negative logarithmic relationship between the duration of ventricular fibrillation and the return of systolic arterial pressure following defibrillation. Longer periods of ventricular fibrillation were followed by longer periods of arterial pressure recovery.

This study shows that the decrease in cardiac hemodynamics can be moderated or reversed
by delivering a series of short pulses during ventricular fibrillation before the defibrillation shock. Further, the change in post-shock heart rate and hemodynamics caused by the pulse therapy is abolished either by sympathetic blockade by acute timolol treatment or chemical sympathectomy by pretreatment with reserpine. It is well known that sympathetic nervous system stimulation can alter cardiac contractility and hemodynamics. Post-ganglionic sympathetic fibers arise from the dorsal sympathetic trunk and travel to the heart and other thoracic viscera through cardiac nerves. Direct electrical stimulation of the thoracic anterior roots T1-T5 can elicit large changes in blood pressure, left ventricular pressure, and heart rate. Stimulation of left-sided cardiac efferent nerves augment ventricular contractile force, left ventricular pressure and arterial pressure with minor changes in heart rate. Our results showed both an increase in heart rate and an increase in left ventricular and arterial pressure suggesting that we stimulated all or most of the sympathetic nervous system in the heart.

The pulse train that we used was very similar to pulse trains that have been used to increase cardiac contractility in isolated tissue preparations. Blinks has shown that field stimulation of isolated tissue with “strong pulses of electric current” increased cardiac contractility. Isolated tissue was field stimulated at a field strength of approximately 5 volts/cm with 1-2 msec pulses spaced 10 msec apart during the refractory period. Graded responses in contractility were produced by delivering various numbers of pulses per unit time to muscles paced at regular intervals. Similar to the study presented here, Blinks showed that either bathing the isolated tissue with propanolol or taking the tissue from animals which had previously been treated with reserpine eliminated the increase in contractility induced by the field stimulation. Brady et al. performed similar studies and showed similar results. They showed that 0.5 msec pulses were ‘optimal’ in increasing cardiac contraction and that after stimulation, the potentiation of contraction approached a maximum with a rate constant of approximately 10 seconds.

While several studies have shown that autonomic tone can modulate the defibrillation threshold, we are not aware of any previous study that has examined the effect of beta blockade
on hemodynamics following the shock. This study showed that a beta blocker did not change the hemodynamic response following defibrillation compared to the response without beta blockade.

**Limitations**

There are several limitations to our study. Testing in the presence of beta blockade always occurred following testing without beta blockade. This was necessary because of the half-life of the beta blocker, timolol. The fact that the hemodynamic responses during control episodes without beta blocker were not significantly different from each other and the hemodynamic responses during control episodes with beta blocker were not significantly different from each suggests that the order of testing did not affect the results. Since the high dose of timolol in this study probably completely blocked the beta receptors, further studies are needed to determine the effect of pulse therapy under partial beta blockade. Further, we chose to use the non-selective beta blocker, timolol, rather than a more selective beta₁ blocker in order to best test our hypothesis that sympathetic nerve stimulation was the mechanism through which the burst stimulation was increasing arterial and LV pressures. Further studies are necessary to determine the effect of the burst stimulation following defibrillation in more clinically relevant situations. We did not vary pulse duration and timing between pulses. As noted above, the values for pulse duration and timing between pulses were near the optimal values determined in isolated tissue. Further studies are needed to determine the optimal pulse duration and timing during VF. Further, we only studied heart rate and hemodynamic changes soon after the defibrillation shock. Studies are needed to determine the long term effect on cardiac function of sympathetic surge following defibrillation.

Testing is also needed to determine the pro-arrhythmic effects of burst stimulation if it is inadvertently delivered during a non-shockable rhythm rather than during ventricular fibrillation. Thirty pulses extend over a period of 300 msec. If these pulses are delivered during sinus rhythm, it is highly likely that one or more of the pulses will be delivered during the t-wave and induce ventricular fibrillation. This outcome is somewhat mitigated because the burst therapy would be delivered by an implantable defibrillator and so if ventricular fibrillation was inadvertently induced,
it could be quickly reversed. Studies are also needed to determine the effect of burst stimulation on the defibrillation threshold.
References


Figure Legends

**Figure 1:** Heart rate response to pulse therapy. Panel A: Heart rate following 15 pulses. Panel B: Heart rate following 30 pulses. Heart rate was significantly higher following 1, 2, 5, and 10 Amp pulse therapy than following defibrillation with no burst stimulation (control). There was no significant difference in heart rate following 15 therapy pulses compared to following 30 therapy pulses.

**Figure 2:** Left ventricular pressure response to pulse therapy. Panel A: Systolic left ventricular pressure following 15 1-msec pulses. Panel B: Systolic left ventricular pressure following 30 1-msec pulses. Left ventricular systolic pressure was significantly higher for 2, 5, and 10 Amp pulses compared to that for control episodes. There was no significant difference between the response to 15 and 30 pulses. Panel C: Mean left ventricular pressure following 15 pulses. Panel D: Mean left ventricular pressure following 30 pulses. Left ventricular pressure was significantly higher for 2, 5, and 10 Amp pulses than for control episodes. There was no significant difference between the response to 15 and 30 pulses.

**Figure 3:** Arterial pressure response to pulse therapy. Panel A: Systolic arterial pressure following 15 pulses. Panel B: Systolic arterial pressure following 30 pulses. Systolic arterial pressure was significantly higher for 2, 5, and 10 Amp pulses than for control episodes. There was no significant difference between the response to 15 and 30 pulses. Panel C: Mean arterial pressure following 15 pulses. Panel D: Mean left ventricular pressure following 30 pulses. Mean arterial pressure was significantly higher for 5 and 10 Amp pulses than for control episodes. There was no significant difference between the response to 15 and 30 pulses.

**Figure 4:** Heart rate response to pulse therapy without (Panel A) and with beta blockade (Panel B). The 15 and 30 pulse results have been combined. Heart rate response did not change significantly with delivery of pulses before the shock with beta blockade as it did for the 1-10 Amp pulses without beta blockade.
**Figure 5:** Systolic left ventricular pressure response to pulse therapy without (Panel A) and with beta blockade (Panel B). The 15 and 30 pulse results have been combined. Only the response to the 10 Amp pulses was significantly higher than that for control episodes. Mean left ventricular pressure response to pulse therapy without beta blockade (Panel C) and with beta blockade (Panel D). Mean left ventricular pressure did not change significantly with delivery of pulses before the shock with beta blockade.

**Figure 6:** Systolic arterial pressure response to pulse therapy without (Panel A) and with beta blockade (Panel B). Mean arterial pressure response to pulse therapy without beta blockade (Panel C) and with beta blockade (Panel D). The 15 and 30 pulse results have been combined. Neither systolic or mean arterial pressure changed significantly with delivery of pulses before the shock with beta blockade.
A 15 Pulses

B 30 Pulses

heart rate (beats/min)

Baseline 1 sec 10 sec 20 sec 30 sec

control

0.1 Amps

0.3 Amps

1 Amp

2 Amps

5 Amps

10 Amps