

Maximum Cardiac Assistance by Latissimus Dorsi Muscle Stimulation by Optimization of Delays, Frequencies and Pulses

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Abstract

To determine optimal parameters for vascular delayed latissimus dorsi muscle (LDM) stimulation, we hypothesized that appropriate pattern of synchronization delay, frequency and number of pulses per burst would improve benefits in cardiomyoplasty. In six dogs, vascular delay of left LDM and induction of myocardial dysfunction were performed 2 weeks before standard cardiomyoplasty. LDM was progressively conditioned for 9 weeks. The interventions were divided into 3 groups of Delay (25, 50, 75, 100 ms; between QRS and muscle stimulation), Frequency (20, 30, 40, 50, 60 Hz; each examined at 6 pulses), and number of Pulses (4, 6, 8, 10 burst-pulses at 50 Hz). With LDM stimulation, pressures and flows were significantly increased in all except 100 ms delay group. 25 ms synchronization delay at 50 Hz and 6-10 pulses, LDM stimulation caused the highest increases in peak aortic pressure (18.3 ± 1.4 mmHg), peak left ventricular pressure (22.4 ± 2.4 mmHg), LV +dP/dt (276.3 ± 166.4 mmHg/sec), stroke volume (8.0 ± 3.3 ml), stroke work (13.0 ± 2.8 gm-m), stroke power (135.0 ± 17.8 gm-m/sec), and peak aortic flow (4.5 ± 0.8 l/min) when assisted beats were compared to unassisted beats. At prolonged synchronization delay and highest burst pulses, the diastolic properties are compromised and at a relative shorter delay, higher frequency and bursts pulses showed maximum systolic improvements.

Key words: cardiomyoplasty, chronic stimulation, delay, frequency, pulses.

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LDM stimulation for myocardial assistance depends on many factors. Appropriate synchronization of the cardiac and LDM contraction cycles, adjustment of delay between the QRS waveform and LDM stimulation, inter-pulse frequency and the number of pulses per pulse-train affect optimum results. However, most experimental cardiomyoplasty (CMP) studies show minimal systolic augmentation with latissimus dorsi muscle (LDM) stimulation. Without augmentation, determining optimal LDM stimulation parameters is almost impossible. In fact, previous studies have proposed that the major benefits of cardiomyoplasty are passive, the external constrain or girdling effect of wrapping the muscle around the heart [4, 7, 13]. In previous studies, we showed that a two-stage vascular delay of LDM increased myocardial assistance contrary to standard cardiomyoplasty approach [1-2].

Using vascular delay of the LDM preparation, the present study determined the optimal frequency, delay and

number of pulses in cardiomyoplasty following vascular delay of LDM.

Methods

All the animals underwent the surgical procedure in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health [NIH publication 85-23, revised 1985]. All the animals were previously healthy and received human care and this study was approved by the University Animal Care and Use Committee.

All sterile surgical procedures were carried out in designated operating suites with animals receiving 500 mg of cefazolin sodium (Marsam Pharmaceutical Inc., Cherry Hill, NJ) and 75 mg of gentamicin (Gentocin[™] Ayerst Laboratories Inc., Rouses Point, NY) given

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parentally before the incision. ECG (Hewlett Packard Model N0. 78346A) and oxygen saturation was monitored continuously. Animals received Lactated Ringer's solution intravenously (250 ml - 350 ml/hr) during surgery. All the animals were fasted overnight and anesthesia was induced by intravenous short-acting barbiturate, sodium thiopental (Pentothal sodium 25 mg/kg) and intramuscular atropine (0.01 mg/kg). After intubation and ventilation by a ventilator (Quantiflex, VMC Anesthesia Machine, Orchard Park, NY), anesthesia was maintained by 2% isoflurane (Isoflurane Vaporizer, Oharda, Isotec 3, Aushell, GA), 0.5-1% nitrous oxide, and 4 L/min of oxygen.

Overview

In dogs (27-31 kg, n = 6), left ventricular dysfunction was induced by intracoronary microspheres injections [14]. Vascular Delay procedure of left latissimus dorsi muscle (LDM), where all the costal and spinal vascular supplies were severed and ligated, was performed to stimulate LDM revascularization [2, 19]. Two weeks later, all the animals underwent a standard cardiomyoplasty. After CMP surgery, the LDM was progressively conditioned over 9 weeks. In a terminal study, the effects of Delay (25, 50, 75, 100 ms), Frequency (20, 30, 40, 50, 60 Hz), and number of Pulses (4, 6, 8, 10, 12 burst-pulses) on cardiac assistance was examined.

LV dysfunction

In all animals, left ventricular dysfunction was induced by intracoronary microspheres injection [14]. Under general anesthesia, as described earlier, left femoral artery was cannulated by a 7 Fr. Catheter sheath through which a 6 Fr. left coronary Amplatz #1 catheter was advanced into the left anterior descending coronary artery under fluoroscopy. Contrast material (Renografin® -76 Bristol-Myers-Squibb Co) was injected to verify the catheter position. Latex microspheres ($3.0-6.0 \times 10^5$, 90 ± 2 μ diameter, latex microspheres, Polyscience Inc. Warrington, PA), mixed in 10 ml of normal saline, were injected into coronary artery in bolus dosages until left ventricular end-diastolic pressure was increased by 50-80%, and peak left ventricular and aortic pressure decreased by 20%.

All the animals survived the intra-coronary microspheres injections. The animals were treated with intravenous injection of Lasix 0.75 mg/kg and rapid infusion of 500 ml Ringer's Lactated saline solution. Post-operatively, the animals were treated with sedatives, (Acepromazine 0.5 mg, I.V.) and analgesics (Buprenex hydrochloride, 0.3 mg, I.V.), as needed.

Vascular delay

The dogs had a vascular delay procedure performed on the LDM, prior to CMP surgery. Under general anesthesia and in sterile surgical condition, a 15-20 cm long

oblique cutaneous incision was made from left axillary region towards the posterior iliac crest. Anterior border of the LDM was identified and then all the perforating collateral branches supplying the muscle were severed and ligated [1, 2, 19]. The spinal border of the muscle was identified and partially mobilized. The wounds were closed in layers using absorbable sutures. All the animals were allowed to 2 weeks for recovery and vascular remodelling.

Surgical procedure

In all animals, a standard cardiomyoplasty procedure was performed by the technique well established in our laboratory [4, 6, 12]. With the animal in the left lateral decubitus position, a transverse oblique incision (15-20 cm long) in the mid-axillary line was employed after the induction of the general anesthesia [12]. The left LDM was dissected out and mobilized from the surrounding tissue and from its distal insertions, proximally preserving the thoracodorsal neurovascular bundle. The tendon of the LDM was then carefully isolated and severed. Two epimysial leads (model YY38403403 Medtronic Inc., Minneapolis, MN) were implanted on the pedicle with nylon sutures; the cathode was placed proximally on the muscle and with the anode placed 6 to 8 cm distally. The stimulation threshold was determined by A-V Pacing System Analyzer 5311 (Medtronic Inc., Minneapolis MN).

A 4-5 cm section of anterior portion of the left 2nd rib, including periosteum, was resected to allow the translocation of the LDM flap into the anterior mediastinal space. A sensing myocardial lead was implanted into the right ventricular anterior free wall of each animal. All the epimysial and myocardial leads were tunnelled and connected to a dual chamber synchronous cardiomyostimulator (SP 1005, Medtronic Inc., Minneapolis, MN) which was implanted in a subcutaneous pocket fashioned in the left side. The LDM flap was then fixed to the periosteum of the second rib by poly-braided suturing materials, 3/0 dexan to avoid the tension to the muscle. The wound was closed in layers.

With the animals in supine position, the heart was exposed through a median sternotomy. After pericardiotomy, the ascending aorta was mobilized and an aortic flow probe (A-series 16-20 mm flow probes; Transonic Systems Inc., Ithaca, NY) was positioned around the ascending aorta with merocel sponge placed between probe and aorta. The distal end for the aortic flow probe was placed subcutaneously for later access. The LDM was wrapped around the heart in a clockwise manner covering the ventricular surfaces of the heart with the costal surface of the muscle. The paravertebral and superior edges of LDM were fixed into the pericardium opposite to the level of the posterior atrioventricular line approximating the costal surface of the LDM to epicardium. Bilateral chest tubes were inserted and connected

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to a water-seal drainage system. The tubes were placed by the thymic tissues superiorly and between pericardiopleural tissues and the undersurface of the sternum laterally. The sternum was closed using four or five wire sutures parasternally on both sides. All the wounds were then closed in layers.

All the animals survived the procedure and were extubated though two required intra-operative catecholamines (Dopamine hydrochloride, $3\mu\text{g/kg/min}$) due to their severe depressed myocardium resulting in severe left ventricular hypokinesis. Intravenous buprenorphine hydrochloride (0.3-0.6 mg, Buprenex™ Reckitt & Coleman Pharmaceuticals Inc., Richmond, VA) was used for analgesia every 3-4 hour as needed during the first 48 hr. Acepromazine maleate (0.25-0.5 mg I/M, PromAce™ Fort Dodge Lab. Inc., Fort Dodge, IA) was used every 10-12 hours for sedation in the initial 24 hours. Animals were positioned to lie on their right side overnight. Chest tubes were removed on the first post-operative day. Antibiotics (cefazolin 500 mg and gentamicin 75 mg every 12 hours) were used for 72 hours post-operatively.

On the 2nd postoperative week, the cardiomyostimulator was turned on and the LDM was progressively conditioned over 9 weeks using pulse width = 210 μs ; pulse-train duration 185 ms; synchronization delay = 40-to-60 ms.

Hemodynamic evaluation

Experimental preparation

At 9 weeks after surgery, the dogs were anesthetized with sodium pentothal (10-15 mg/kg IV) followed by 2% isoflurane and 0.5-1% nitrous oxide. Each dog was ventilated via endotracheal tube with a positive-pressure respirator. Analgesia was given prior to intubation with Buprenex (Buprenorphine HCl, Reckitt & Coleman, Richmond, VA, 0.3-0.6 mg IV) avoiding atropine. Two 7 Fr. catheter sheath were introduced into the left femoral and carotid artery. A 6F pigtail micromanometer tipped catheter with lumen (MILLAR® Instruments Inc. Houston, TX, model no. SPC 464D) was advanced through the catheter sheath in femoral artery, and placed into the left ventricle under fluoroscopic guidance. Another 6F pigtail micromanometer tipped catheter with lumen (MILLAR® Instruments Inc. Houston, TX, model no. SPC 464D) was advanced through the catheter sheath in left carotid artery, and placed into the ascending aorta under fluoroscopic guidance. Analog signals from the pressure transducers were obtained using an amplifier (PM-1000, CWE Inc., Admore, PA). To measure aortic flow, the aortic flow probe lead was dissected out and connected to a flow meter (Model No. 206T, TRANSONIC® Systems Inc., Ithaca, NY). The epimysial leads were disconnected from the SP1005 pacemaker and connected to an external muscle stimulator (GRASS Model 8800, Grass Systems Inc.,

Quincy, MA). A cardi tachometer (Model 1000 CWE Inc. Admore, PA) detected the QRS waveform from the analogue ECG signal. The cardi tachometer signal was sensed by an Apple computer. The apple computer triggered the external muscle stimulator and controlled train duration, frequency, pulse duration, inter-pulse interval, pulse train delay. The muscle was stimulated on every 4th beat using at least four times the threshold voltage.

Data acquisition

Data were recorded simultaneously on a chart recorder (Model TA-11, Gould Instrument Systems Inc. Cleveland, OH) as well as on a PC computer (Micron Inc., model no. M55PLUS2-P200-MT). The pressure, flow, and ECG signals were digitized using an A/D circuit board (model AT-MIO 16.0E-10, low-pass and antialiasing filters, National Instruments, Austin, TX). The data were acquired using software LABVIEW, version 4.0.

Delay, frequency, and pulses data acquisition

Four synchronization delays (SD = 25, 50, 75, 100 ms) between the QRS and LDM stimulation were examined. Each pulse train consisted of 6 pulses at 50 Hz interpulse spacing with pulse duration of 0.5 ms. Each data run was 30 seconds long and 3 data runs were obtained for each intervention. The ventilator was switched off during data acquisition to avoid respiratory variations. Similarly, five different frequencies of inter-pulse spacing (F_n = 20, 30, 40, 50, 60 Hz with 6 pulses per train) and 4 to 10 pulses per pulse train (P_s = 4, 6, 8, 10) at a frequency of 50 Hz with a 50 ms delay were examined.

Data analysis

Using software developed in Visual Basic for Excel (Microsoft Excel 7.0, Microsoft Inc., Redwood, WA), hemodynamic variables were extracted from a digitally stored data file. Ectopic beats and post ectopy beats were excluded from the analysis. For each beat, the end-diastolic pressure, the peak ventricular systolic pressure, the peak positive and negative first derivative of the left ventricle pressure (+dP/dt, -dP/dt), peak and end-diastolic aortic pressures were determined, and stroke volume, stroke work and stroke power were calculated. The hemodynamic parameters of stimulated beats using delay, frequencies, and pulses were compared with the non-stimulated beats immediately preceding it. Both absolute magnitudes of the changes and percent changes caused by LDM stimulation were calculated. Data were expressed as mean $\pm$ standard error of the mean.

Statistical analysis

Software for statistical analysis StatView 4.5 [Abacus™ Concepts; Berkley, CA] was used for statistical analysis. Within each group, the stimulated beats were compared with the immediately preceding non-stimulated beats using paired Student's *t* test. *p* is considered as significant when less than 0.05. The compari-

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son between and within delay (SD), frequency (Fn) and pulse (Ps) groups was performed to find out significant increases in the absolute and percent changes. This analysis indicated significant effects and interaction between (SD), (Fn) and (Ps) groups. Statistical significance was determined using ANOVA.

Results

Figure 1 shows data traces from one typical experiment, for aortic flow, aortic and left ventricular pressures, left ventricular dP/dt, and ECG with 25 and 50 ms delay between the QRS waveform and LDM stimulation. The LDM was stimulated on every 4th beat as seen on the ECG. At synchronization delay (SD) = 25 and 50 ms, LDM stimulation caused large increases in peak aortic flow, left ventricular and aortic pressure.

Figure 2 shows the percent changes of the hemodynamic parameters with LDM stimulation at different delays. In general, shorter delays were associated with greater LDM myocardial assistance. With a 100 ms delay, LDM stimulation caused only minor increases of pressure, stroke volume, stroke work, and flow whereas with 25ms delay, LDM stimulation provided greater myocardial assistance. Absolute changes at 25 ms delay compared to 100ms delay showed significant hemodynamic improvements in peak left ventricular pressure (16.5 ± 2.4 vs. 7.1 ± 1.4 mmHg; $p < 0.001$), stroke volume (5.4 ± 1.0 vs. 1.7 ± 1.0 ml; $p < 0.05$), stroke work (11.3 ± 2.0 vs. 2.7 ± 1.0 gm.m; $p < 0.001$), peak aortic pressure (15.2 ± 2.4 vs. 5.8 ± 1.1 mmHg; $p < 0.001$), peak aortic flow (3.4 ± 0.7 vs. 0.1 ± 0.1 l/min; $p < 0.001$) and stroke power (105.1 ± 23.3 vs. 6.5 ± 3.2 gm.m/sec; $p < 0.001$).

Figure 3 shows percent changes of the peak left ventricular and aortic pressures, stroke volume, stroke work

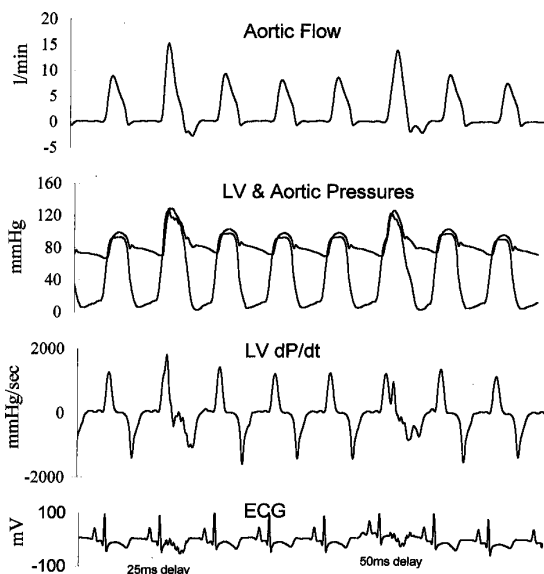


Figure 1. Data trace for aortic flow, aortic and left ventricular pressure, LVdP/dt and ECG with different delays starting from 25 ms to 50 ms.

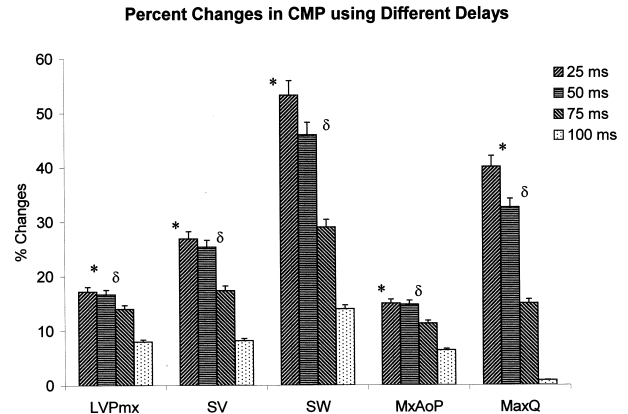


Figure 2. The percent increases of hemodynamics with different delays. LVPmx: maximum peak left ventricular systolic pressure; MxAoP: maximum peak aortic systolic pressure; SV: stroke volume; SW: stroke work; and MaxQ: maximum peak aortic flow. * $p < 0.05$; 25 ms compared to 100 ms SD. $\delta p < 0.05$; 50 ms compared to 100 ms SD.

and peak aortic flow after LDM stimulation using different frequencies. Higher frequencies were associated with larger improvements in cardiac function. At frequencies of 50 and 60 Hz, LDM stimulation showed significant greater increases in hemodynamics compared to 20 Hz LDM stimulation ($p < 0.05$ and $p < 0.01$, respectively).

Figure 4 shows the percent changes of the peak left ventricular and aortic pressures, stroke volume, stroke work and peak aortic flow after LDM stimulation using 4-10 burst pulses. The number of pulses had minimal effect on LDM assistance. Only 4 pulses per burst showed less LDM augmentation compared with 6, 8, or 10 pulses.

Discussion

Since the first clinical case in 1985, cardiomyoplasty has been performed in over 700 patients worldwide as a surgical treatment for congestive heart failure [3]. Results were variable, and controversies still remained re-

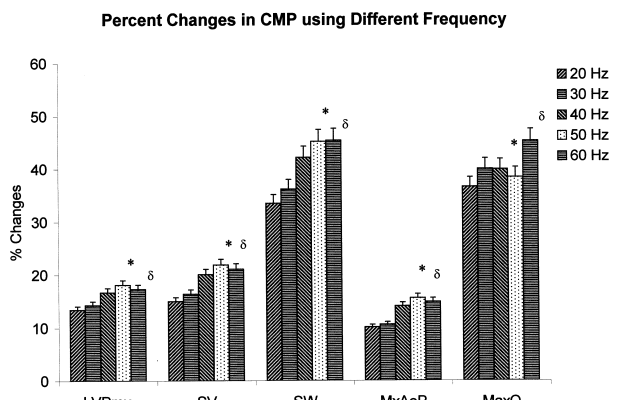


Figure 3. The percent increases of hemodynamics at different pulse frequencies. NS: not significant. * $p < 0.05$ when 50 Hz is compared to 20 Hz. $\delta p < 0.05$ when 60 Hz is compared to 20 Hz.

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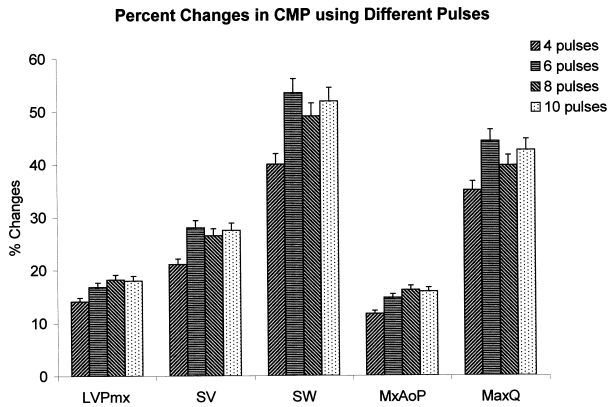


Figure 4. The percent increases of hemodynamics in the different burst pulses group (Ps).

garding the efficacy of the procedure [6]. Functional class improvement was seen in most patients but the procedure had not demonstrated consistent hemodynamic augmentation [3, 7, 8]. Most experimental and clinical studies showed minimal hemodynamic benefits in standard cardiomyoplasty procedure.

Effect of vascular delay

In our previous study, we established that vascular delay procedure prior to CMP resulted in increased systolic myocardial assistance [1, 12]. Other groups have examined intramuscular vascular territories from canine LDM and from fresh human cadavers [2, 11, 19]. They also determined the necessity of the vascular delay of the LDM in cardiomyoplasty [2, 11, 19].

Effect of synchronization delay

In 3 patients, Molteni and colleagues have shown that changes in the delay time between the QRS sensing and single-pulse stimulation in cardiomyoplasty significantly affect the peak flow velocity of blood in the ascending aorta [18]. Using Doppler echo, they measured the flow velocity at the aortic root with QRS-LDM stimulation delay ranging from 75 ms to 250 ms. They found the maximal flow velocity of 0.83 m/s at 150 ms in one patient and 1.45 m/s at 100 ms delay in another patient. These delays are much higher than we and the other BAM paper [15] have observed. Their use of single-pulse stimulation is a severe limitation of their study.

In 3 patients, Helou and coworkers compared three different modes to determine the delay period between the R-wave sensing and LDM stimulation [10]. Fixed-time mode consisted of fixed timing of the burst stimulation at 25 ms, corresponding to the usual time interval between the R-wave and the onset of mechanical cardiac systole. Two-dimensional echocardiography was used to start LDM stimulation at mitral valve-synchronized closure. The flow-optimized mode adjusted the burst stimulation programming to obtain the maximal aortic flow velocity as measured by the Doppler echocardiography. Helou and coworkers suggested that valve-

synchronized mode ensures the prevention of interference with diastolic ventricular filling since the burst stimulation is delivered at the start of the mechanical cardiac systole [10]. Using the flow-optimized mode, to they showed a 30% increase of flow velocity when 75 ms delay period was compared with a 45 ms.

In an experimental study, Tsukube et al used 20-60 ms different delay periods to find out the maximum benefits during cardiomyoplasty surgery [20]. With an untrained LDM, the maximal benefits and effects on the hemodynamics occurred with a 40 ms synchronization.

Geddes and associates [9] studied the timing of the muscle contraction in a canine cardiomyoplasty and found the optimal delay period to average of 58 ms (range 40-80 ms). Within this range, maximal augmentation of the left ventricular function and stroke volume was achieved. They hypothesized that to obtain the maximum precontraction load on the muscle encircling the ventricle, the contraction should be occurred late in isovolumic period when the ventricle bulges maximally outside.

Vural et al investigated the effects of very short (0 ms) or prolong delay (150 ms) on cardiac function in 10 patients [20]. Left ventricular ejection fraction and peak aortic flow velocity were higher with a prolong delay as compared to shorter (45 to 60 ms) or no delay (0 ms). However, diastolic parameters and isovolumic relaxation time were better without a delay.

Li et al [15] investigated the lag period between the onset of stimuli to peak muscle contraction using m-mode echocardiography. They suggested that m-mode echocardiography overestimate the ideal delay period. In their study, they showed that despite the lowest set delay period, the cardiomyostimulator (8 msec), peak muscle contraction still occurred 70-100 msec after peak LV pressure in most of the animals studied. They also demonstrated that the muscle contraction curve profile does not always follow that of the ventricle.

Our study examined different synchronization delays, frequencies and bursts-pulse in a vascular delay model of cardiomyoplasty. Shorter delays (25 and 50 ms) were most effective and significant when compared to longer (100 ms) delays. Using 20 Hz-frequency stimulation, LDM caused minimal augmentation of hemodynamics whereas using 50 or 60 Hz-frequency, there were significant improvements. After 6 pulses, the number of pulses per pulse train had minimal effect on hemodynamic augmentation.

In summary, LDM stimulation with a the synchronization delay of 25 ms, 50 Hz of frequency, and 6 to 10 pulses showed the optimal hemodynamic augmentation. In the current clinical practice, the synchronization delay may be too long and the stimulation frequency may be too low in some patients.

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