

Novel Functions (Work-Rest and Day-Night Regimens) in a New Cardiomyostimulator for Cardiac Bioassist

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Abstract

The LD-PACE II, a new cardiomyostimulator was manufactured by CCC del Uruguay with the support of the Illini Group, Chicago, Illinois. The LD-PACE II was designed for use in cardiomyoplasty, aortomyoplasty, and skeletal muscle ventricle. All parameters specified as programmable can be changed in a noninvasive manner (using a programming interface wand connected to a computer using the Windows 95/98 environment). Most of the functions of the new stimulator are similar to functions of previously used devices (Transform, Medtronic; EKS 445, Russia).

In the case of bradycardia or atrio-ventricular blockage, the LD-PACE II will act as a pacemaker with a basic pacing rate between 36 and 120 BPM. In order to prevent the stimulator from inappropriately sensing events, there is a ventricular refractory period (195-480 ms). Hysteresis (0-20%) allows the patient's heart rate to temporarily fall below the lower rate without inducing immediate pacing. Synchronization delay (2-350 ms) obtains the optimal time of muscle contraction. Adaptive delay allows the automatic change in the delay time with a change of heart rate. The cardiosynchronization ratio is programmed from 1:1-1:16. Muscle output is inhibited if the heart rate is higher than the synchronization upper rate (120-226 BPM). The adaptive ratio allows for the automatic change of the cardiosynchronization ratio with an increase in heart rate. Delivery of a muscle pulse train is triggered by paced or sensed ventricular events. Characteristics of the pulse train are changes in pulse amplitude (0.44-0.75 V), pulse width (0.061-0.076 ms), pulses per burst (1-8), and pulse interval (15.6-132.8 ms). The adaptive pulse train duration will automatically decrease the train duration with an increase in heart rate and inhibit muscle contraction during the diastolic phase. The LD-PACE II does however have two new functions which prove to be extremely important for clinical use based on experimental research.

1. Work-rest regimen. In the conventional stimulation regimen, the latissimus dorsi muscle (LDM) works 24 hours daily with no rest except for short periods between contractions. The LD-PACE II is able to deliver alternating periods of muscle contractions and rest. Work and rest periods may be programmed independently between 1 and 120 minutes in increments of one minute. The work-rest regimen may be useful clinically if muscle contractions are needed for cardiac assist postoperatively. Morphological (light microscopy, transmission electron microscopy) and electrophysiological data show that a short period of work followed by a long period of rest does not damage the ischemic muscle.

2. Day-night regimen. This feature is also brand new. It allows for a change in the ratio of muscle contractions according to a patient's activity level. During the day the cardiosynchronization ratio may be set from 1:1 to 1:4 and during the night it may be set for 1:8 to 1:16. This allows the LDM to have a long rest period, prevents overuse, and prolongs bat-

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tery life. Data confirmed that there is no depression in hemodynamics when the ratio is slowed or turned off during the night.

The first experimental tests of the LD-PACE II (in Milwaukee, Wisconsin, Detroit, Michigan and Paris, France) showed good functional ability of a high caliber. The first clinical cardiomyoplasty with the LD-PACE II was performed on April 2, 2000 at the Bahamas Heart Center.

Key words: LD-PACE II, dynamic cardiomyoplasty, aortomyoplasty, skeletal muscle ventricle, heart failure.

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Continuous improvement in cardiomyoplasty enhances the ability of the failing heart to contract by using the latissimus dorsi muscle (LDM), however in some patients hemodynamic results are inconsistent and correlate poorly with considerable clinical improvement [14, 33]. In 1999, Acker summarized the results of cardiomyoplasty performed in over 300 patients randomized for three different phases of a study sponsored by Medtronic, Inc [1]. One hundred eighteen patients underwent the Phase I feasibility study (1985-91). An additional 250 patients were studied in Phase II (1991-94). Starting in 1994, a prospective randomized trial comparing dynamic cardiomyoplasty with medical therapy was initiated under FDA approval, with a calculated sample size of 400 cases. The operative mortality of cardiomyoplasty had steadily decreased from over 20% in Phase I to 12% in Phase II, and to only 3% of 51 patients in Phase III (1). Several different mechanisms and conditions are known to effect long term results, although we do not yet know which are more important in individual patients, since the heart's condition, the right variation of the operation [31], the condition of the LDM [29], and an appropriately cardiosynchronized electrical stimulation (ES) protocol [1, 35] can all influence hemodynamic results.

I tried to find a regimen of muscle stimulation that would allow the muscle to rest more than conventional stimulators used worldwide for cardiac bioassist. Several investigations were performed on how to allow the latissimus dorsi muscle to rest during continuous stimulation without stopping contractions for months and years. It was our concept that overuse of the LDM leads to weakness and aggravation of cardiomyoplasty results [2, 3, 18, 19]. There are several variants of LDM rest: 1) continuous contractions with prolonged rest periods between contractions (1:4 or 1:5 regimen); 2) a work-rest regimen (i.e. several minutes of ES contraction followed by several minutes of rest); and 3) day-night regimen when contractions are stopped or slowed down for several hours daily. However, only one function (regimen of stimulation using a ratio of greater than 1:2) was included in conventional stimulators: first in the Soviet stimulator Stiminak 805, and after that in the Medtronic stimulator TransformTM. It was necessary to

create a new stimulator which could automatically work in a work-rest regimen and a regimen with cessation or slow down of the stimulation for several hours each day.

The LD-PACE II Cardiomyostimulator for Cardiac Bioassist

The LD-PACE II is a brand new stimulator slated to be used in cardiomyoplasty, aortomyoplasty, and skeletal muscle ventricle procedures. It was designed and manufactured by CCC del Uruguay and is exclusively distributed by the Illini Group (Chicago, Illinois). The first experimental testing of the LD-PACE II were performed in August 1999 at Sinai Samaritan Medical Center in Milwaukee, Wisconsin. Further tests were conducted in September 1999 at Wayne State University in Detroit, Michigan, and in October 1999 at the Hospital Broussais in Paris, France. The first clinical cardiomyoplasty using LD-PACE II was performed at the Bahamas Heart Center in April 2000 (V. Chekanov, H. Spencer, D. Sands, and C. Brown).

Novel functions of the LD-PACE II

Work-rest regimen

The LD-PACE II is able to deliver alternating periods of muscle contractions and rest ("work time" vs. "rest time"). This feature is programmable as ON or OFF. When ON, the work and rest periods may be programmed independently between 1 to 120 minutes in increments of one minute. Using this regimen, it is therefore possible to rest the LDM after a programmed period of work.

The work-rest regimen is a novel concept for cardiomyostimulators and may prove very useful clinically in several situations [18]. This feature may help prolong good muscle performance, and may extend the life of the stimulator. In the conventional stimulation regimen, the LDM works 24 hours daily with no rest except for the short periods between contractions. The work-rest regimen allows muscle contractions to stop (for example for 10 minutes) after every 60-120 minutes of work. Over a 24 hour period, the LDM will have rested at least two hours.

The work-rest regimen may also be useful during the postoperative period if muscle contractions are needed

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for cardiac assistance. For a short period of time, the LDM could be stimulated with 6 pulses per burst followed by up to two hours of rest. Even immediately after LDM mobilization, a short period of work followed by a long rest period would not likely damage the ischemic muscle.

Clinical evidence and weight of tradition (just over a decade) have already established fixed principles in cardiomyoplasty. One established principle of cardiomyoplasty is based on the assertion that electrical stimulation applied to newly mobilized LDM invariably leads to muscle necrosis and ensuing ischemic shock. Thus, electrical stimulation training is begun only after a 2-week recovery period using single impulses/burst. Training continues for 8 weeks before the muscle can contract strongly enough (using 6 impulses/burst) to contribute to cardiac performance. Therefore, 8-10 weeks are required before any hemodynamic benefit is available to the patient. A second principle is an adjunct to the first: for several weeks after cardiomyoplasty, the LDM, which has not completed its full training course, cannot be used even for partial cardiac assist because it lacks the strength and contraction rate necessary for the task. Although providing cardiac assistance full time is a worthy aim, reason dictates that any amount available is better than none at all. Therefore our hope was to establish an electrical stimulation training regimen that could be applied to the mobilized LDM immediately after surgery, decreasing the length of time before the LDM could provide assistance to the failing heart, yet doing so without aggravating the ischemic state of the muscle. Data from recent studies demonstrated that the LDM might not only suffer from ischemic injury during mobilization, but also from the ensuing rest period [22]. Immobilization rapidly results in atrophy and may lead not only to a loss of muscle mass, but also to fatty infiltration and fibrosis. You et al. [36] also showed that delayed stimulation in partially unstretched LDM may result in atrophy and loss of function. These investigations seem to support our hypothesis that a cautious electrical stimulation protocol would prepare the LDM for cardiac assist. With the goal of applying electrical stimulation for training and partial cardiac assistance (if needed) immediately after LDM mobilization, we investigated several approaches that would allow the muscle to rest for longer periods than in conventional protocol. Investigations performed in Milwaukee [19] yielded results that contradict the conventional wisdom that any electrical stimulation damages newly mobilized LDM and will cause a considerable decrease in contractile force. Intensive stimulation regimens using continuous contractions at 30 and 60 contraction per minute for 30 minutes were damaging to the LDM. Contractile force also dropped significantly and returned slowly to baseline values: at 60 CPM, contractile force dropped to

50% and did not return to baseline even after 90 minutes of rest; at 30 CPM, contractile force dropped to 61% and baseline was restored after 80 minutes of rest. Electrical stimulation using continuous contractions at a slower rate (15 CPM) was tolerable, although a 23% decrease in contractile force was noted ($p < 0.05$ when compared to 60 CPM). These results showed that such a regimen would not be useful for cardiac assistance immediately after cardiomyoplasty. The next investigation focused on the use of a work-rest regimen — the LDM rested one minute after every one minute of work. However 30 CPM even in a work-rest regimen gave poor results: contractile force after an intensive 30 minute testing decreased to 75% and baseline was restored after 80 minutes of rest. However, promising results were seen when utilizing a work-rest regimen at 15 CPM. The newly mobilized LDM showed no visible signs of fatigue: contractile force decreased minimally to 92% ($p < 0.05$ when compared to 30 CPM), and light microscopic analysis of biopsies revealed no morphological damage exceeding that typically seen after subtotal mobilization. Such results open avenues for beginning electrical stimulation immediately after cardiomyoplasty, beginning partial cardiac assistance immediately after cardiomyoplasty (if needed), and has inspired us to create a new cardiomyostimulator with these unique functions.

Day-night regimen

This feature of the LD-PACE II is also unique to cardiomyostimulators. It allows for a change in the ratio of muscle contraction according to a patient's activity level. A muscle contraction ratio of 1:2 or 1:3 may be necessary for day time when the patient is active, but during the night, when the patient is at rest, it may be enough to stimulate the muscle every sixth, seventh, etc. beat. The LD-PACE II is capable of detecting the application of a magnet over the implant site and modifying its functioning in the presence of this magnetic field. The magnet mode can be programmed as NO USE, ON/OFF, and NIGHT RATIO. If the device is programmed NO USE, the presence of a magnet will have no effect. If a change in contraction rates is not allowed, the LD-PACE II should be programmed in the NO USE mode. If the device is programmed as ON/OFF, the presence of a magnet will inhibit muscle contractions until the magnet is detected again. If the device is programmed to NIGHT RATIO, the detection of the magnet will change the basic ratio (for example, 1:3) to a pre-programmed ratio (for example, 1:10). When the magnet is detected again, the ratio goes back to the basic rate (1:3).

Because resting the LDM for prolonged periods after CMP might decrease the amount of fibrotic degeneration and fat deposits in the LDM [35], it is an appealing notion to be able to switch off the cardiomyostimulator

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during sleep when maximum assist is not needed. A protocol of intermittent ES could reduce muscle damage and preserve muscle function better than when ES is continuous (3). However, the effect of intermittent ES on the function of the cardiac muscle is difficult to predict and needs clinical and experimental investigation. In 1993, Magovern [32] made an admittedly biased, but intriguing statement “based partially on evidence and partially on intuition.” Magovern questioned whether the LDM was over-stimulated and the duration of stimulation was too long, stating that “asking the LDM to contract every beat or every other beat 24 hours a day, 365 days a year, is perhaps not realistic.” Accordingly, he suggested resting the LDM “perhaps 12 hours a day or 16 hours a day” to improve results. In 1996, Magovern and Simpson [31] investigated this idea in two cardiomyoplasty patients (the first one hospitalized for end-stage heart failure 18 months after CMP), turning the cardiomyostimulator off by “a magnet” daily for 2 two-hour intervals. The first patient was able to be discharged home to regular activities and had an increased LVED at his next evaluation. In the second patient, LVEF fell below baseline after “impressive” early increases. One month after starting the rest regimen, LVEF increased 11 points. Jondeau et al. [28] also reported that discontinuation of LDM stimulation for one hour did not alter left ventricular systolic function in patients with congestive heart failure who underwent cardiomyoplasty 6 months earlier. In the series published from Italy [2, 3], it was shown that “the 24 hours per day stimulated latissimus dorsi muscle contain only type 1 myosin heavy chains (i.e., they are fully transformed), whereas muscle stimulated 10 hours/day still contained large amounts of fast type myosin heavy chain, in particular type 2A”. The authors made the conclusion that the activity-rest stimulation “could be the rationale for the need of a cardiomyostimulator whose discontinuous activity could offer patients the long-standing advantage of faster and more powerful muscle contractions”.

In Milwaukee an investigation was performed to confirm the possibility of switching off stimulation for 12 hours daily. To assess hemodynamic improvement after cardiomyoplasty, the following measurements were made in animals with chronic biventricular failure before and after cardiomyoplasty with continuous 24-hour ES. Statistically significant ($p < 0.05$) increases were seen in LV ejection fraction ($55 \pm 4\%$ vs. $38 \pm 6\%$) and decreases in heart rate (126 ± 23 vs. 142 ± 28 beats per min), right atrial pressure (8 ± 2 mmHg vs. 15 ± 3 mmHg), right ventricular pressure (25 ± 4 mmHg vs. 33 ± 2 mmHg), left ventricular end-diastolic area (10.8 ± 1.0 cm² vs. 15.3 ± 1.2 cm²) and left ventricular end-systolic area (4.2 ± 0.6 cm² vs. 11.0 ± 1.1 cm²), as well as decreases in left ventricular end-diastolic (21.1 ± 0.9 ml vs.

28 ± 1.4 ml) and end-systolic volumes (9.4 ± 0.9 ml vs. 24 ± 1.3 ml) were also noted.

The main goal of this investigation was to evaluate whether hemodynamic results after CMP were impaired when ES was stopped for 12 hours daily to allow the LDM to rest. There was no difference when ES continued nonstop 24 hours daily or when it was stopped for 12 hours daily. With the stimulator on similar heart rates (126 ± 3 bpm vs. 127 ± 4 bpm); right atrial pressures (8.2 mm Hg vs. 9 ± 2 mm Hg), right ventricular pressures (25 ± 4 mm Hg vs. 26 ± 3 mm Hg), pulmonary capillary wedge pressures (14 ± 2 mm Hg vs. 14 ± 3 mm Hg), left ventricular ejection fractions ($55 \pm 4\%$ vs. $55 \pm 5\%$), left ventricular end-diastolic volumes (21.1 ± 0.9 cm² vs. 22.3 ± 0.7 cm²), and left ventricular end-systolic volumes (9.4 ± 0.6 cm² vs. 9.8 ± 1.0 cm²) were seen. Results were similar when the stimulator was turned off [20, 21]. As in the previously cited study by Tasdermir et al. [35], in which no patient had cardiac decompensation during the day or night when LDM stimulation was stopped, there was no hemodynamic impairment when the stimulator was turned off for 12 hours daily after cardiomyoplasty. It therefore is not only logical to turn off stimulation nightly for sleep and to turn it back on during the day, but the evidence shows no reason to fear doing so. Hemodynamic results are not impaired; the LDM has a chance to rest and thereby overuse atrophy is avoided, and the cardiomyostimulator may function longer without needing to be replaced. Finally, hemodynamic results are better when LDM contractions are cardiosynchronized and there is systolic augmentation in addition to the girdling effect of a heart wrap.

Based on these experimental evidence in sheep, a pilot clinical study is conducted in Italy with excellent outcomes. The Italian Trial of Demand Dynamic Cardiomyoplasty is showing that under activity-rest pattern of stimulation LD wrap provides higher power than continually stimulated LD [4, 8, 9, 34]. Furthermore, the muscle is fast enough to contract and relax during cardiac systole [9]. LD wrap slowness reverses by the activity-rest regime even after years of standard stimulation (Tetanic fusion frequency of 11 ± 2 Hz after standard stimulation vs. 30 ± 3 Hz after demand regime, $p < 0.0001$). After Demand Dynamic Cardiomyoplasty there are no deaths (eight subjects, 42 ± 8 months post-operation, of which 14 ± 3 months of demand stimulation). Quality of life is substantially improved with significant reduction of heart failure symptoms (NYAH class: pre-op 3.0 ± 0.0 , post-Demand Dynamic Cardiomyoplasty 1.5 ± 0.2 , $p < 0.0001$). In the sub-group of patients light stimulated from LD conditioning, exercise capacity tends to increase over pre-op values more than two years after operation (VO₂ max: pre-op 12.3 ± 0.7 vs. 16.6 ± 1.7 post-Demand Dynamic Cardiomyoplasty, $p = 0.05$). In this group of patients the excitation threshold

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of the LD wrap is not increased throughout the two years of follow-up. The conclusions of the Italian Trial of Demand Dynamic Cardiomyoplasty, a phase two study, are that demand stimulation and mechanography of the LD wrap are safe procedures, which could offer long-term the benefits of Dynamic Cardiomyoplasty to patients with pharmacologically intractable heart failure [8].

Only future clinical investigations will answer which regimen is better: switching off stimulation during the night, or slowing stimulation to a rate between 1:8 and 1:16. Or determining which daily time interval is best for stopping electrical stimulation: 12, 8, or 4 hours. Its use will allow the cardiologist for the first time to be able to program a day/night regimen of stimulation based on the needs and condition of the cardiomyoplasty patient.

LD-PACE II as a Cardiomyostimulator

The LD-PACE II has two cardiac channels which sense cardiac activity or pace if necessary, and a myostimulation channel. All channels are coordinated by synchronization circuitry.

Cardiac channels

The LD-PACE II has the capability of sensing and pacing atrial and ventricular chambers. In cardiomyoplasty, aortomyoplasty and skeletal muscle ventricles, it is much more common to only sense the cardiac events rather than to pace the heart. The cardiac channels sense the R-wave from the left or right ventricle, depending on the placement of the myocardial leads. If a device is not able to sense an R-wave, the device begins to pace the ventricle in VVI mode. It does not matter if the R-wave is intrinsic or paced; when the ventricle is depolarized, the synchronization circuit is activated.

Modes of operation

The LD-PACE II can be operated in the following cardiac modes when used as a cardiomyostimulator: VVI, VVT, VDD, DDD. It may be programmed for atrial and/or ventricular operation, which may be conducted in unipolar or bipolar modes. Selection between unipolar and bipolar sensing modes provides greater flexibility in setting the device to achieve the best performance. Typically in cardiomyoplasty, myocardial leads are implanted into the right ventricle.

Ventricular sense amplifier sensitivity

The device is programmable from 1.0 to 8.0 mV in increments of 1.0 mV. This range allows for standard sensitivities for appropriate operation, as well as enabling the assessment of the performance of the implanted leads.

Atrial sense amplifier

The device also has an atrial sense amplifier which may be programmed from 0.5 to 4.0 mV in increments of 0.5 mV. It also has a special independent connector channel for atrial chamber sensing.

Ventricular refractory period

The device is programmable from 195 to 480 msec in increments of 7.8 msec. This range prevents the cardiomyostimulator from inappropriately sensing artifactual events. One such event is a pulse train delivered to the LDM from the muscle channel. The pulse train is delivered after the synchronization delay (the time between the beginning of the R-wave and the closing of the mitral valve). Therefore, the refractory period must be greater than the sum of the pulse train length and the synchronization delay.

Atrial refractory period

In a situation in which a dual chamber mode is selected, the device has a programmable atrial refractory period (195-484 msec) that disables atrial sensing after the ventricle is sensed or paced. The atrial sensing is also disabled during the AV period.

Synchronization circuitry

The synchronization circuitry coordinates the function of the muscle channel with the cardiac cycle, determining the time of delivery of the pulse train to the LDM, and prevents the muscle from excessively high contraction rates.

Ventricular-Latissimus Dorsi (V-LD) delay

The device is programmable from 5 to 350 msec in increments of 1 msec between 5 and 10 msec, and by 5 msec between 10 and 350 msec. The V-LD delay is the period of time after an occurrence of a ventricular event, but before the start of the next pulse train. High flexibility in the delay period is necessary to obtain good performance. A synchronization delay is necessary to obtain the optimal timing of the muscle contraction (just after mitral valve closing). A delay up to 350 msec is needed for aortomyoplasty and skeletal muscle ventricle procedures.

Adaptive V-LD delay

The LD-PACE II is capable of adapting the delay to a changing heart rate. This parameter may be programmed either as "ON" or "OFF". When turned "ON", the V-LD delay is calculated as a percentage of the programmed rate.

Ratio

The LD-PACE II can be programmed to deliver a pulse every n th ventricular event. The ratio can be programmed from 1:1 to 1:16 in increments of one. There are several advantages in a low cardiosynchronization

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ratio. When training is complete, some patients have better results from the cardiomyoplasty procedure when a ratio of 1:3 or 1:4 is used rather than 1:1 or 1:2. For many patients a slow rate of stimulation (1:8-1:16) during the night lets the LDM rest and also improves cardiomyoplasty results.

Synchronization Upper Rate (SUR)

The SUR prevents muscle stimulation during ventricular tachycardia or ventricular fibrillation. If ventricular cycling is too fast to allow for muscle contraction and relaxation, there are two options: change the synchronization rate, or completely inhibit the muscle output. With the LD-PACE II both options are available. Using the SUR, it is possible to inhibit any muscle contraction if the rate of ventricular contraction reaches the preset level. The rate is programmable in increments of 8 BPM from 120 to 226 BPM. Therefore, if the instantaneous ventricular rate is greater than the SUR, then muscle output is inhibited. The combined action of the ratio and the SUR is as follows: whenever a SUR is reached, the ratio count is set to zero.

Adaptive ratio

When ventricular tachycardia is less than the programmed SUR but greater than the programmed basic rate, the LD-PACE II automatically begins to work in the adaptive ratio regimen. The adaptive ratio prevents LDM overuse, minimizing muscle fatigue by preventing muscle contraction at rates that are too high by automatically slowing the ratio (from 1:2 to 1:3, or from 1:3 to 1:4 for example) whenever the heart rate exceeds the preset value. This parameter can be programmed as "ON" or "OFF". When the heart rate becomes greater than the SUR, muscle contractions are inhibited. This feature allows for great flexibility and it is easy to use.

Work-rest regimen

(see above)

Night ratio

(see above)

Muscle channel

The LD-PACE II has a generator capable of producing pulse trains suitable for LDM stimulation.

Output to muscle

The delivery of a muscle pulse train is triggered by ventricular events (sensed only, or either sensed or paced). The synchronization circuitry provides the very important synchronization between the ventricular activity and the delivery of muscle pulses. The output to the muscle is programmable in the following modes: "Off", "Ventricular Sense", "Ventricular Pace and Sense".

Pulse amplitude

This feature is programmable in a range off 0.63-7.5 V in increments of 0.63 V. The device provides a suitable range of pacing pulse amplitudes to allow for appropriate operational settings, as well as to enable assessment of the performance of implanted lead.

Pulse width

This feature is programmable from 0.061 msec to 0.976 msec. Like pulse amplitude, altering the pulse width also enables a gradation of muscle force by varying the number of activated motor units. The contractile force of the LDM increases with an increase in pulse width.

Pulses per burst

The number of pulses in the train is programmable from 1 to 10 in increments of one. High flexibility is needed to train the muscle in its transformation from a fatigable to a fatigue-resistant state, and for obtaining good cardiac contractions. Adjusting the burst duration by increasing the number of pulses in the burst also enables evoked muscle force to be sustained over a longer period.

Pulse interval

When a burst of impulses is used to stimulate the muscle, the interval between each pulse in the burst is programmable in increments of 7.8 msec from 15.6 msec to 132.8 msec. The interval is the time between the end of one impulse and the beginning of the next. There is a reciprocal relationship between the pulse interval and the frequency: when the pulse interval decreases the frequency increases. As the stimulation frequency increases (or pulse interval decreases), the generated muscular force increases to a plateau at which muscle contraction is smooth (fused contraction).

Adaptive pulse train duration

In order to prevent muscle contractions that extend into the diastolic phase, the burst duration can be correspondingly programmed to the heart rate. It is necessary to decrease the train duration, and the device does this automatically. It is better not to change the pulse width or pulse interval, but rather to modify the pulse train duration by decreasing the number of pulses as the heart rate varies.

Muscle response in the presence of a Premature Ventricular Contraction (PVC)

For reasons of safety, when a PVC is detected, the LD-PACE II will not attempt to stimulate the LDM.

LD-PACE II as a Pacemaker

The device has two pacing pulse generators, one for atrial stimulation (typically through a standard right

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atrial lead), and one for ventricular stimulation (typically through a standard right ventricular lead).

Modes of operation

The device has the following modes of operation: VVI, VVT, VOO DDD, VDD.

Basic Pacing Rate

The device is programmable in a range from 36-120 beats per minute in both single chamber and dual chamber modes. The normal setting of this parameter is 50 BPM.

Amplitude of pacing pulse

The range of amplitudes is 0.63-5.0 V in increments of 0.63 V.

Width of pacing pulse

The width of pacing pulse in both chambers is programmable in a range of 0.122-1.5 msec in increments of 0.122 msec.

Pacing polarity

The device can be programmed in unipolar or bipolar modes for both atrial and ventricular pacing. The availability of unipolar and bipolar pacing polarities provides higher flexibility in the setting of the device in order to achieve appropriate performance.

Atrial sensitivity

The atrial sensitivity is programmable from 0.5 mV to 4.0 mV in increments of 0.5 mV.

Ventricular sensitivity

The ventricular sensitivity is programmable from 1.0 to 8.0 mV in increments of 1.0 mV.

Blanking period

The refractory period to ventricular events when pacing the atrium is called the blanking period. It is programmable from 47-70 msec in increments of 7.8 msec. The blanking period is fixed, and during this time all sensing is inhibited.

Ventricular refractory period

This feature allows for the disabling of ventricular sensing after the ventricle was paced or sensed. It is programmable in a range from 195-480 msec in increments of 7.8 msec.

Hysteresis

This feature is programmable from 0-20%. It allows the patient's heart rate to temporarily fall below the programmed rate without immediately inducing pacing. It is valuable only for patients who tolerate bradycardia well.

Paced AV delay

The pace AV delay is programmable from 55-280 msec in increments of 7.8 msec.

Upper Tracking Rate (UTR)

The UTR limits the possibility that atrial tachycardia will be tracked by ventricular sensing. It is programmable at a rate of 80-140 BPM in increments of 2 BPM. UTR may be programmed in following modes: OFF, WENCKEBACH, and FIXED BLOCK. In the OFF mode, the only protection against atrial tachyarrhythmia is the atrial refractory period. In the WENCKEBACH mode, the AV delay is increased to maintain the UTR, such that during each cycle the ventricular rate is lower or equal to the UTR. In the FIXED BLOCK mode, the delivery of a ventricular stimulus is inhibited and an atrial refractory is begun when the V-V interval is lower than the UTR.

General Function and Physical Characteristics

The LD PACE-II has a bi-directional communication system to enable it to noninvasively communicate with a PC-based programmer. Incoming information comprises all programmable parameters of the device. Outgoing information comprises all currently programmed parameters, statistical information collected by the device, and telemetry of battery and lead condition.

The device has front-end protection from electromagnetic interference and high energy electromagnetic transients. The device will not be damaged by energy from commonly used surgical equipment (electrocautery, external defibrillation, etc.) or by the energy delivered by an automatic implantable cardioverter defibrillator (ICD) that may also be implanted in the same patient.

When the device is programmed with nominal settings and the LDM is paced at 25 BPM, the expected life of the device is greater than 10 years if no ventricular pacing occurs, and greater than 9 years if the ventricle is paced at 100%. Dimensions of the device are as follows: height - 47 mm, length - 67 mm and a width - 11 mm, and it weighs 56 g. The device is connected to the leads through a special connector block made of biocompatible material. The connector block is capable of receiving two standard bipolar VS-1 connectors for atrial or ventricular leads, and two unipolar connectors for muscle leads. The connectors for the muscle lead are smaller than the standard leads in order to prevent incorrect connection of the leads. Each terminal is identified through markings on the case of the stimulator as follows: "A" for atrial chamber pacing and sensing; "V" for ventricular chamber pacing or sensing; and "LD" for muscle pacing. Connectors are locked in place by set screws in the terminals. Electrical isolation is provided such that no current leakage occurs through the set screw.

Conclusions

One of the first multiple-pulse synchronous pacemakers was developed at the McGill University by Ray Chiu's group. This stimulator was a hybrid of a standard pacemaker and a frequency modulator [23-26]. George Magovern et al. [30] in Pittsburgh used R-wave synchronous pacemakers [tetanic muscle stimulator (Cortatomic, Inc.); SymbiosTM (Medtronic, Inc); DeltaTM (Cardiac Pacemakers)] that allowed the muscle graft to be stimulated in synchronous with the heart. Carpentier's group [5-7, 10-13, 15, 16] developed an implantable multiprogrammable double chamber stimulator with telemetry functions (SP 1005 cardiomyostimulator, Medtronic, Inc). It was designed primarily for cardiomyoplasty with ventricular sense/pace capability as well as muscle stimulation and could also be used for other muscle-cardiac assistance procedures. The original LDM pacing electrodes were also developed at the Broussais Hospital in France. About the same time (1987-88) in the former Soviet Union, the original Stiminak 805 cardiomyostimulator was constructed at the Moscow Engineering Physics Institute under the direction of I.A. Dubrovsky. This device had a wider range of cardiosynchronization ratios (1:1 to 1:8) which made it different from the first Medtronic device. A second generation Russian stimulator (EKS 445) was created in the Tochmash Design Bureau-Elestim (Moscow) that combined the functions of a cardiomyostimulator and a pacemaker [17].

A new cardiomyostimulator (TransformTM, Medtronic, Inc) was developed in the early 1990s which aimed at improving clinical results, increasing the length of time between replacements, and easing implantation and care procedures during follow-up [27]. At the same time several other stimulators were being manufactured and implanted in patients: Myostim (Teletronics Pacing Systems, Inc, Englewood, CO, USA), Myos (Biotronics, Berlin, Germany), LD-PACE I (CCC del Uruguay).

Experimental tests and the first clinical use of the LD-PACE II indicated that it can fulfil the requirements for generating biological energy from skeletal muscle to achieve cardiac bioassist. A number of advanced features have been incorporated into this new device based on the experience gained experimentally and clinically in the past decade. It is thought that the availability of this crucial device for cardiac bioassist will fill the gap created by the early termination of Medtronic Phase III trial. It is hoped that it will also revive further development in various cardiac bioassist approaches, allowing the investigators to achieve the ultimate goal of benefiting patients who suffer from severe heart failure.

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