Cardiac Contractility Modulation: A Technical Guide for Device Implantation

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This article provides a technical description of common implant practice for delivery of cardiac contractility modulation (CCM) therapy to heart failure patients. As of September 2016, the authors of this article collectively have been involved with more than 400 system implantations in five medical centers, beginning with the advent of CCM therapy approximately 12 years ago. CCM therapy has been evaluated in a variety of studies, and was shown to be safe and effective and of benefit to patient quality of life and exercise capacity. As the use of CCM therapy continuously expands among medical centers in Europe, this article describes the technical and practical aspects of the implant procedure, and additional special technical cases based on our cumulative experience.

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KEY WORDS

Heart failure • Cardiac contractility • Modulation • Cardiac contractility modulation • Implantation • Implantable pulse generator

This article provides a technical description of common implant practice of the Optimizer™ (Impulse Dynamics Inc., Orangeburg, NY) system for delivery of cardiac contractility modulation (CCM) therapy to heart failure (HF) patients.

Despite strong advances in cardiovascular care, HF remains one of the leading causes of death in the western world.[1] Cardiac resynchronization therapy (CRT) reduces hospitalizations and mortality in HF patients with prolonged electrical activation.[2] However, up to 30% of patients receiving CRT do not respond to the therapy; in HF patients with a narrow QRS complex (the majority of the HF population), CRT has failed to reduce mortality or hospitalization rates, and may even increase cardiac mortality rates.[3]

CCM is a device-based HF therapy that enhances contractile strength of the myocardium independent of the synchrony of myocardial contraction.[4-6] CCM signals are nonexcitatory high-voltage electric impulses that are applied during the absolute refractory period. These signals do not initiate a new contraction, but modify calcium homeostasis in the cardiomyocyte and enhance its contractility without increasing the myocardial oxygen consumption.

CCM signals are delivered via the Optimizer implantable pulse generator (IPG), which is comparable in its dimensions to a pacemaker (Figure 1). CCM therapy is normally programmed to deliver therapy over 7 or more hours per day (in US studies it is programmed to 5 h/d). The delivery schedule is typically several 1-hour segments, equally spaced throughout the day.

The CCM signal is delivered to the ventricular septum within the absolute refractory period of the cardiac cycle after the local

Figure 1. The OPTIMIZER™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY) measures 60 × 47 mm and has a volume of 29 mL.

electrical activity has been detected. The present Optimizer IV$_s$ system includes three leads (1 atrial, 2 ventricular), and its algorithm delivers the CCM signal only if it has detected cardiac electrical activity in a proper order, starting from the atrium and continuing to two locations on the ventricular septum, in accordance with programmed time windows among the sensed events.

During the implantation, one standard pacemaker lead (usually with a screw-in electrode) is placed into the right atrium to detect the right atrial electrical activity. CCM signals are delivered through two pacemaker leads (from specific models that are approved be used in CCM), positioned on the ventricular septum (Figure 2).

The typical CCM waveform is a double biphasic square pulse with an amplitude between 4 and 7.5 V and a total stimulation duration of approximately 20 ms. Because the CCM signal is applied during the absolute refractory period, as a pulse train at a short delay (typically 30 ms) after local sense in the ventricles, it typically shows on a body surface electrocardiogram (ECG) as stimulation artifacts around the R-wave (Figure 3).

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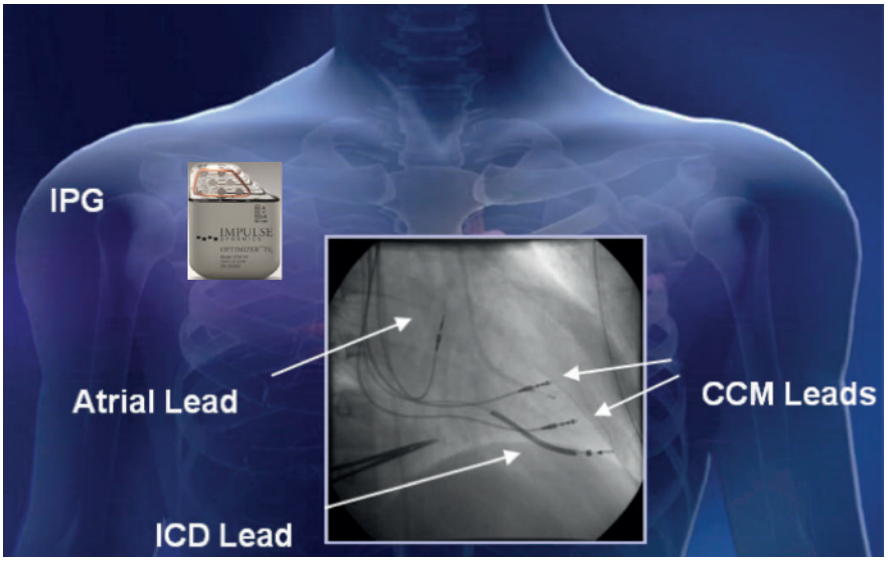
The Optimizer has a rechargeable lithium ion battery and patients recharge the battery using the portable Optimizer mini charger, typically once a week for approximately 1 hour (Figure 4). A fully charged battery typically lasts for approximately 3 to 4 weeks, though the patients are advised to recharge weekly, in order to maintain routine

Figure 2. OPTIMIZER™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY) in situ with two right ventricular septal electrodes and one atrial electrode. CCM, cardiac contractility modulation; ICD, implantable cardioverter-defibrillator; IPG, implantable pulse generator.



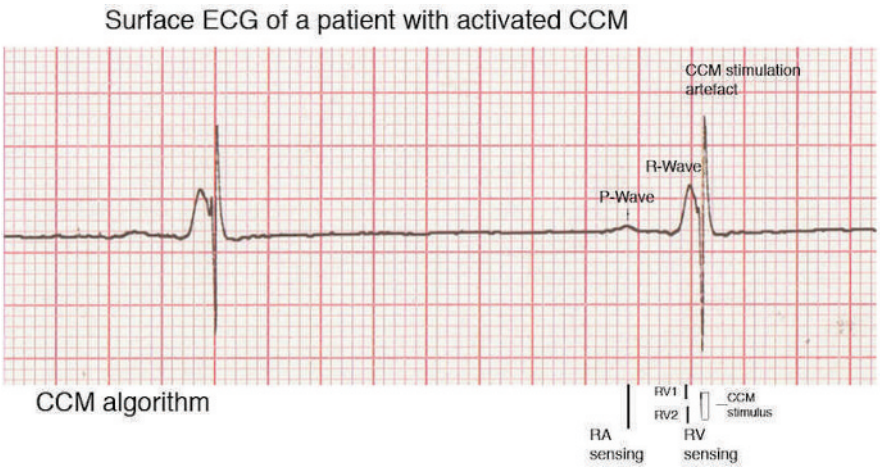


Figure 3. Body surface ECG of a patient in sinus rhythm with activated CCM. The corresponding timing of the CCM algorithm is illustrated at the bottom of the figure. ECG, electrocardiogram; CCM, cardiac contractility modulation; RA, right atrium; RV, right ventricle. Reprinted with permission from Röger S et al.[21]

charging. The battery can tolerate full discharge without damage.

Clinical Experience

CCM therapy delivered using the Optimizer system is currently being evaluated by the US Food and Drug Administration (FDA) and is investigational in the United States.

Two prospective randomized multicenter studies (Evaluate Safety and Efficacy of the OPTIMIZER® System in Subjects With Moderate-to-Severe Heart Failure [FIX-HF]-4 and -5) have demonstrated significant improvements in New York Heart Association (NYHA) functional classification, quality-of-life as indexed by the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), and peak oxygen uptake (peak VO_2) during cardiopulmonary exercise testing.[7,8] Furthermore, CCM contributes to left ventricular reverse remodeling and improves systolic ventricular function.[9] CCM therapy was evaluated for safety in all studies and was consistently found safe. As part of the safety analysis, no increase in arrhythmias or implantable cardioverter-defibrillator (ICD) shocks were observed during CCM therapy. This finding is consistent with the demonstrated benefit of CCM in raising levels of SERCA2a, which likely attenuates T-wave alternans and reduces the propensity for arrhythmias. CCM does not appear to interact with calcium directly (in contrast with many arrhythmogenic inotropic drugs); rather, it normalizes calcium handling via SERCA2a levels, increasing L-type calcium channels, improving sodium-calcium exchange, and increasing phosphorylation of phospholamban.[10]

To date, there are no prospective randomized data relating to reduction in mortality. Recent preliminary retrospective observations by sites that use the therapy over multiple years suggest that mortality rates in patients treated with CCM, especially in those with normal QRS intervals and with moderate disease stage, were lower than estimated by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) model and by the Seattle Heart Failure Model risk scores for those patients.[11,12] Currently, two prospective randomized multicenter studies are ongoing in the United States and in Europe (FIX-HF-5C FDA Confirmatory Study and IMPULSE-HF EU Randomized Efficacy Study) evaluating important clinical primary and secondary endpoints in different populations.[26] Additionally, mortality rates over a 3-year period are being investigated in a prospective, multicenter CCM-REG EU registry. A recent individual patient record meta-analysis of the randomized control trials, including 641 cases, concluded that CCM has favorable clinical effect in terms of peak VO_2, 6-minute walk, and MLWHFQ.[13] CCM has been evaluated in numerous studies and reports; Table 1 lists the major clinical publications regarding CCM. Recently, CCM therapy was reviewed in the European Society of Cardiology's Guidelines on Acute and Chronic Heart Failure,[14] in which it was stated that CCM may be considered in selected patients with HF.

Figure 4. OPTIMIZER™ IV_s (Impulse Dynamics Inc., Orangeburg, NY) mini charger and Optimizer IV_s device.

Patient Selection

CCM therapy is commonly used in patients with HF symptoms despite medication and who have normal QRS duration, and is particularly recommended for patients in sinus rhythm with a left ventricular ejection fraction (LVEF) ≥ 25% and NYHA class II-III symptoms—this subgroup of patients seems to

TABLE 1

Summary of Main Published Clinical Results

Study	Patients (N)	Follow-up	Major Findings
Pappone C et al[22]	18	Acute	Acute increase in dP/dt (9.1% ± 4.5%) measured with CCM stimulation; this was added to CRT
Stix G et al[23]	23	8 wk	Statistically significant improvement in NYHA class, LVEF, MLWHFQ, 6-min walk test
Neelagaru SB et al[24]	49	6 mo	Double-blind feasibility RCT showed nonstatistical reduction in hospitalizations: CCM vs control; VAT, peak VO_2, 6-min walk test, MLWHFQ and NYHA class had trend for improvement with CCM vs control subjects
Borggrefe MM et al[7]	164	6 mo	Double-blind crossover study showed CCM effect beyond sham in peak VO_2 and MLWHFQ
Yu CM et al[9]	30	3 mo	CCM improves global and regional LV contractility with reverse remodeling; increased LVEF
Schau T et al[25]	54	33 mo	All-cause mortality was equivalent to that predicted by the SHFM, and better than predicted by HFSS, in severe HF patients
Kadish A et al[8]	428	6 mo	In the whole cohort, changes in VAT could not be detected; peak VO_2 and MLWHFQ improved more with CCM vs OMT; in this study, CCM improved in all parameters and was most effective in patients with normal QRS, LVEF ≥ 25%, and NYHA class III HF
Abraham WT et al[15]	206	6 mo	
Röger S et al[21]	70	2.8 y	QRS duration does not prolong over time with CCM
Giallauria F et al[13]	641		Meta-analysis showing significant benefit from CCM in peak VO_2, MLWHFQ and 6-min walk test
Kuschyk J et al[11]	81	34 mo	Long-term clinical benefit with CCM vs baseline, long-term survival with CCM seem better than predicted by MAGGIC score
Kloppe A et al[12]	68	4.5 y	Long-term survival in patients with NYHA class II-III HF and normal QRS seem better with CCM than predicted by SHFM

CCM, cardiac contractility modulation; CRT, cardiac resynchronization therapy; dP/dt, rate of rise of left ventricular pressure in early systole; HF, heart failure; HFSS, Heart Failure Survival Score; LV, left ventricular; LVEF, left ventricular ejection fraction; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; MLWHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association; OMT, optimal medical therapy; RCT, randomized controlled trial; SHFM, Seattle Heart Failure Model; VAT, ventilatory anaerobic threshold.

benefit most from the therapy.[15,16] A subgroup of patients from the FIX-HF-5 study with an LVEF of 35% to 45% has shown even greater potential benefit.

Although CRT has been well established for symptomatic cases with an LVEF < 35% with left bundle branch block or QRS interval > 150 ms, the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study[3] has shown that CRT should not be applied in HF patients with a normal QRS interval. The recent European Society of Cardiology's Guidelines on Acute and Chronic Heart Failure[14] determined that CRT is contraindicated in patients with a QRS interval < 130 ms. Accordingly, Figure 5 illustrates a potential concept of a screening flow chart; the treating physician should diligently consider the

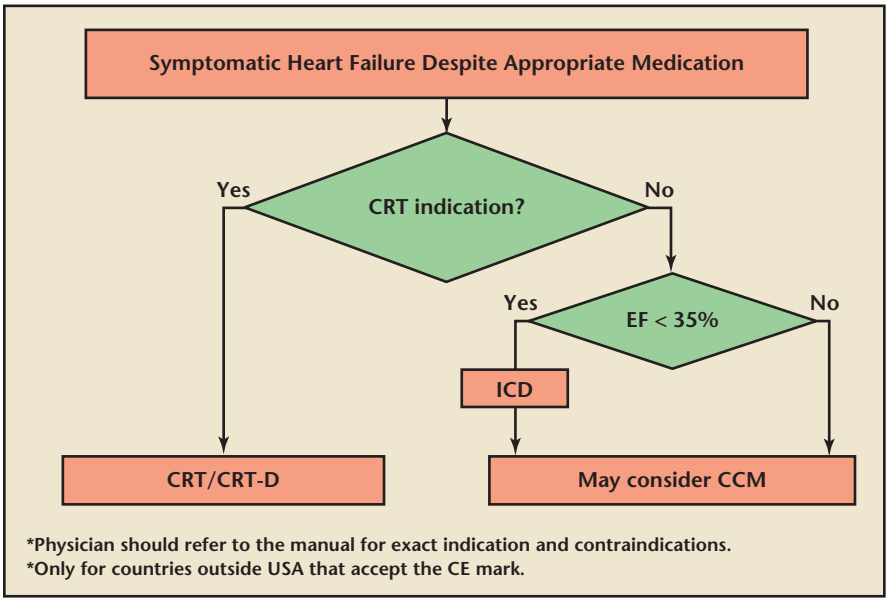


Figure 5. Potential patient screening flow chart. CCM, cardiac contractility modulation; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; EF, ejection fraction; ICD, implantable cardioverter-defibrillator.

indications, contraindications, evidence, and applicable guidelines before making the actual medical decision.

A small case series demonstrated that the combination of CCM therapy in addition to CRT is feasible and that CCM can be a possible useful adjunct in CRT-nonresponsive patients.[17] All patients are required to be on appropriate, stable medication for HF.[14] The current model of Optimizer (the Optimizer IV$_s$) contains a built-in algorithm that inhibits delivery of a CCM signal when irregular electrical activity is detected, such as premature atrial or ventricular complexes or sensing defects. Therefore, patients with multiple premature ventricular contractions benefit less from the therapy. The first studies excluded cases with > 8900 ectopic beats/24 h on a baseline Holter ECG; in routine use, CCM delivery in the presence of a slightly higher rate of premature ventricular contractions can be compensated by selecting more CCM hours per day (eg, up to 12 h/d). The current Optimizer IV$_s$ system implements an algorithm that requires sensing of proper atrial activity; therefore, the therapy is inhibited in patients with permanent or long-standing, persistent atrial fibrillation (AF). Accordingly, the use of the Optimizer IV$_s$ is contraindicated in those cases. Future devices that will not mandate atrial sensing are likely to enable CCM therapy for these patients. The new generation of the Optimizer system, the Optimizer Smart, includes an algorithm that does not require the implantation of an atrial lead (keeping the two ventricular leads only) thereby further simplifying the implantation procedure. The new model allows also the delivery of CCM therapy in patients with permanent atrial fibrillation.

Implant Technique

Preoperative Orders

The preoperative preparations for CCM implantation are generally similar to those recommended for pacemaker implantation. Preoperative routine testing includes chest radiograph, 12-lead ECG, complete blood cell count, prothrombin time measurement, and measurements of serum electrolyte and serum creatinine levels. In some institutions, these tests are performed in an outpatient setting at least 1 day before the operation. Preoperative transthoracic echocardiography, 24-hour Holter ECG monitoring to determine burden of premature ventricular beats, and, if possible, cardiopulmonary exercise testing to assess peak VO_2 are all recommended. Antiplatelet drugs such as aspirin or clopidogrel should not be interrupted. In patients receiving warfarin or phenprocoumon, an International Normalized Ratio of 2 to 2.5 is recommended. It is recommended that use of the new oral anticoagulants dabigatran, rivaroxaban, and apixaban be suspended 12 to 24 hours before the operation.

The patient is advised to fast for at least 6 hours before the procedure. A stable intravenous line is needed to provide subsequent venous access for anesthesia and adequate hydration of the fasting patient. Prophylactic antibiotic therapy is applied approximately 30 minutes before the operation, for example, administration of a broad-spectrum cephalosporin (cefazolin, 200 mg). Patients with allergies to penicillin or cephalosporin can receive clindamycin, 600 mg.

Preoperative Preparations in the Operation Room

In some centers, the CCM implantation is performed in an operating room reserved for cardiac device implantations, which guarantees a high hygienic standard. For fluoroscopy, a mobile C-arm radiographic image intensifier is used. Alternatively, the CCM implantation can be conducted in the catheterization laboratory. In most

centers, the operation is performed by an electrophysiologist specialized in cardiac device implantation, whereas in some centers the implant is performed by cardiac surgeons. The operator receives assistance of a scrub nurse familiar with the operator's surgical preferences. In some centers, a second cardiologist or an anesthesiologist is responsible for anesthesia and patient monitoring, and supports the personnel who have scrubbed in. Commonly, the team is further supported by a company technician skilled in the process of electrical testing of the electrodes and CCM configuration.

In the procedure room, patient monitoring consists of a multichannel electrocardiographic recording system, a transcutaneous oxygen monitor, and an automatic noninvasive blood pressure cuff. Patients eligible for CCM implantation who have an LVEF $<$ 35% typically already have implanted ICDs. The ICD is turned off before the procedure and patients are monitored by an external ICD throughout the procedure. Typically, the CCM is implanted at the right infraclavicular region, as most ICDs are placed on the left side. Shaving and skin cleansing should include the neck, supraclavicular fossae, shoulder, and chest. The operative site is widely disinfected with a povidone-iodine solution.

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In several studies and in cases in which the team wishes to monitor contractility changes by the CCM therapy during the procedure, online assessment of such changes can be implemented either by noninvasive systems or using a catheter-based approach.

One approach to assess acute changes in left ventricular pressure rise in early systole (dP/dt_{max}) is with a pressure-volume loop catheter. An arterial puncture of the superior femoral artery is performed and a standard 5F cardiac catheter sheath is placed in the vessel.

The draping process is a matter of personal preference. Commonly, two sterile preshaped plastic drapes with adhesives along one side are used. One adhesive drape is applied from shoulder to shoulder at the level of the clavicles, which serves to create a sterile barrier to the head of the patient. the patient's body is covered with the second sterile drape, leaving a sterile window at the operation site. There should be an attempt made to seal the room, limiting traffic and restricting access to personnel participating in the procedure. A table with customary sterile surgical material should be prepared in advance (Figure 6A).

Anesthesia and Related Considerations

Anesthesia can generally consist of a combination of local anesthesia, sedation, and pain reliever. There are several aspects to consider when deciding on which anesthesia protocol to use and for what duration. The main purpose of the anesthesia is to avoid pain and provide a comfortable environment for the patient, and allow proper performance of the procedure by the implanter.

Patient cooperation during the implant procedure is of high importance. In particular, part of the implant procedure includes testing of the leads with high-pacing voltage (10 V) and testing of proper CCM delivery. As part of these tests, the implanter is able to verify if acute hemodynamic effect of CCM appears, and if the CCM signals generate discomfort or sensation (eg, diaphragmatic or thoracic sensations). Therefore, careful planning of the implant steps (pocket preparation, lead positioning, and lead testing) and anesthesia protocol are needed, with a focus on minimal dose and selection of the time constant associated with the anesthesia, such that at the time of the pacing test and CCM test only local anesthesia is in effect, if clinically possible.

Substantial sedation during those tests may reduce the ability to evaluate acute contractility changes and detect potential sensation in advance, which can bother the patient postoperatively in some cases. For local anesthesia, up to 30 mL of a mixture of a short-acting (eg, effective for approx. 20 min) local anesthesia with acute effect, such as ropivacaine, and a long-lasting local anesthesia with a delayed effect, such as mepivacaine, are infiltrated (Figure 6B).

Sedation is commonly performed by successive injections of midazolam (approx. 2-3 and up to 10-15 mg); for pain relief, stepwise injections of fentanyl are administered to a maximum dose of approximately 100 µg. Sedation, if needed, should be kept at the lowest needed dose and for a short time, so that at the time of lead and CCM testing the anesthesia is mostly local. In some cases, additional administration of propofol (stepwise application of 10-200 mg) may be necessary. Resuscitation equipment, including a cardiac defibrillator, pericardial puncture set, pleural drainage system, intubation set, and anesthetic machine, are present in the operating room.

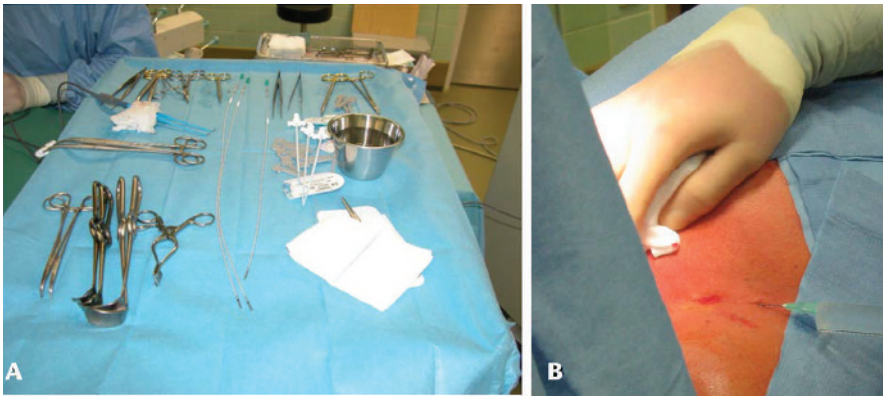


Figure 6. **(A)** Surgical instrument table. **(B)** Application of local anesthesia.

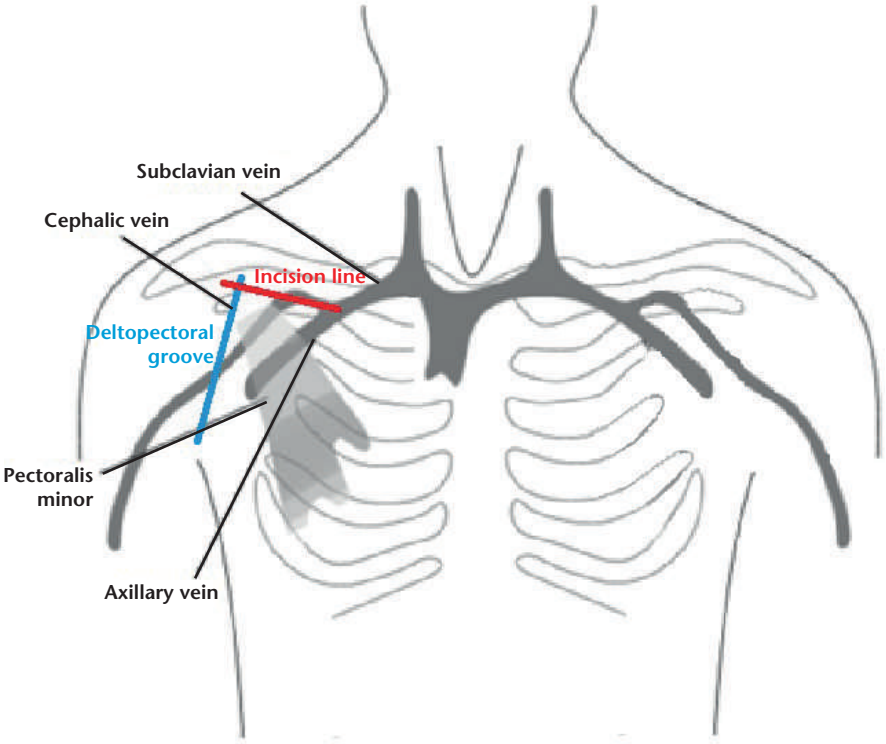
Operation

Incision and Pocket Preparation. The operator first identifies surface anatomic landmarks, including the clavicle, the coracoid process, and the deltopectoral groove. A 3- to 4-cm skin incision is made at the level of the coracoid process. The incision runs perpendicular and somewhat parallel to the deltopectoral groove, and approximately 2 to 3 cm beneath to the inferior border of the clavicle (Figure 7). This incision technique allows access to the subclavian and the cephalic vein.

The incision is extended to the anterior surface of the pectoral fascia. The device pocket is best created predominantly inferior and medial to the incision. The pocket can be either subfascial or submuscular, but it is recommended that it be no deeper than 2.5 cm from the skin, to enable effective communication and energy transfer to the IPG. The benefit of a subfascial pocket is in its simplicity, the avoidance of deep dissection, and reduced need for sedation and pain medication. The disadvantage of the subfascial approach is the concern of skin erosion. If the pocket is too superficial, the corners of the device (as with any implantable device) can create pressure points on the skin that might lead to skin erosion. Therefore, particularly in patients with little body fat, the submuscular approach may be preferred, while being careful not to exceed the maximal implantation depth, as defined in the Optimizer's physician manual. If the subfascial approach is used, a plane of dissection is created at the junction of the subcutaneous tissue and pectoral fascia using scissors (Figure 8A). The scrub nurse then holds back the subcutaneous tissue with a Senn retractor. After a plane of dissection has been established, the remainder of the pocket can be created with blunt dissection.

For the submuscular approach, the border between the clavicular and the sternal head of the pectoralis major muscle has to be identified, which usually contains fatty tissue. While the scrub nurse retracts the connecting tissue with a Senn retractor, the operator establishes a plane of dissection between the two heads of the muscle, which are gently peeled back until the surface of the chest wall is visualized as a glossy plane of fatty tissue (Figure 8B). The thoracoacromial neurovascular bundle can be identified on the outer surface of the pectoralis minor muscle and must be avoided. After the pocket is created, gauze soaked with local anesthesia is inserted for hemostasis and analgesia.

Figure 7. Illustration of the recommended incision line for surgical cardiac contractility modulation implantation.



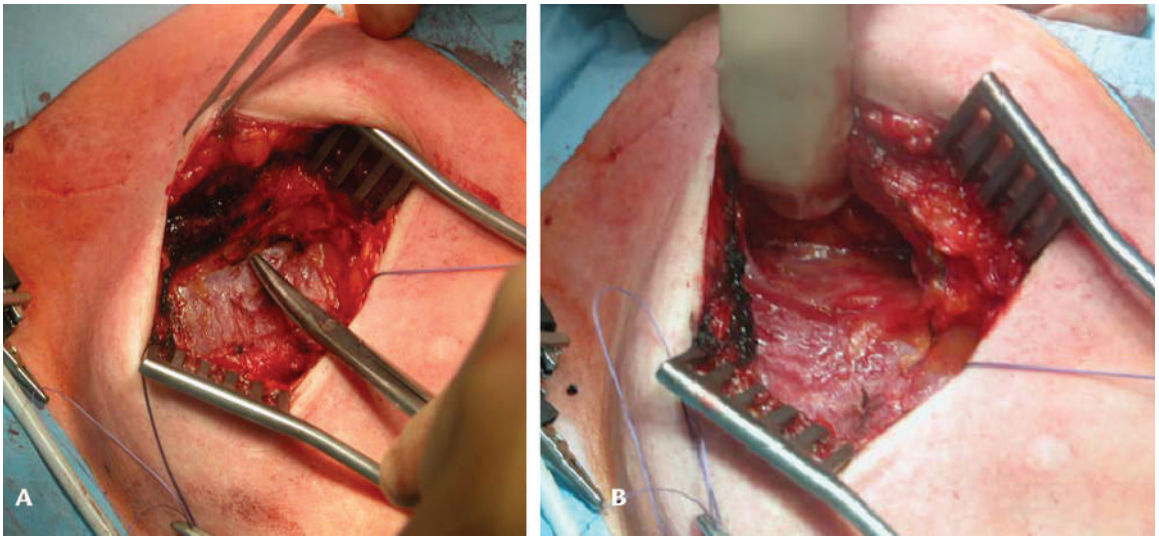


Figure 8. **(A)** Creation of a subfascial pocket. **(B)** Creation of a submuscular pocket.

Lead Positioning. Some implanters prefer to have the pocket prepared before venous access is achieved and leads are positioned, whereas some prefer the reverse order, beginning with lead positioning and followed by pocket preparation. The rationale for having leads positioned first is to use minimal anesthesia (predominantly local anesthesia) while testing the leads and CCM delivery, and later increase anesthesia for pocket preparation. The rationale for starting with pocket preparation is better handling of bleeding.

The current Optimizer IV$_s$ requires implantation of three leads. It is typically preferred to use the subclavian or cephalic vein. It is essential to puncture the subclavian vein from a lateral position in order to avoid lead crush (Figure 9A), or use the cephalic vein (Figure 9B). For the same reason, it is important to perform separate punctures for each lead. The wires are inserted under fluoroscopic control. Leads are inserted through standard peel-away 7F sheaths (Figure 9C).

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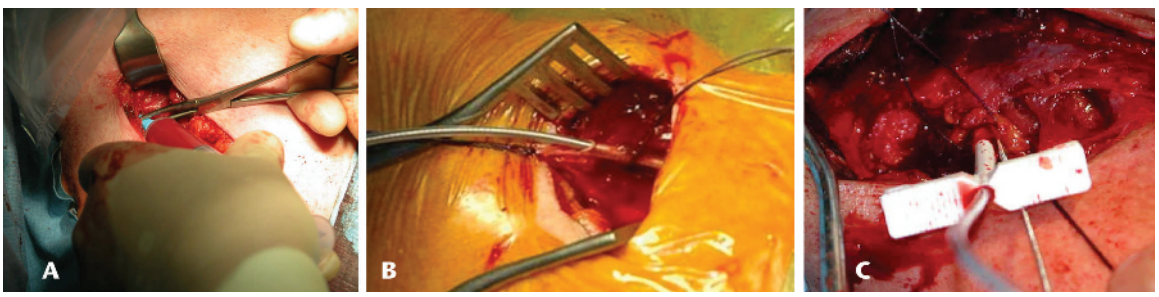
Two standard pacemaker leads with electrically active screw-in electrodes and low-polarization coating (eg, titanium nitride, fractal iridium, or iridium oxide) are used for ventricular delivery of CCM. Lead length selected for right-chest implantation is commonly approximately 58 cm. Currently, the lead types that are qualified for use for ventricular CCM delivery include the Tendril® 1888T/2088T/LPA1200M leads (St. Jude Medical, St. Paul, MN), Setrox S / Siello S / Solia S leads (Biotronik, Berlin, Germany), and Dextrus ventricular leads (Boston Scientific, Marlborough, MA).

The lead is advanced to the level of the right atrium under fluoroscopic control (posterior-anterior view) using a straight stylet. Afterward, the stylet is withdrawn and its distal 10 to 15 cm are manually shaped into a smooth 180° curve. The stylet is then reinserted and the electrode is carefully advanced through the tricuspid valve in the direction of the pulmonary artery. A stylet is then formed in order to reach a septal lead position. A smooth 180° curve is shaped over the distal 15 cm of the stylet.

Figure 9. **(A)** Puncture of the subclavian vein. **(B)** Lead insertion into the cephalic vein. **(C)** Lead insertion through a standard 7F sheath.



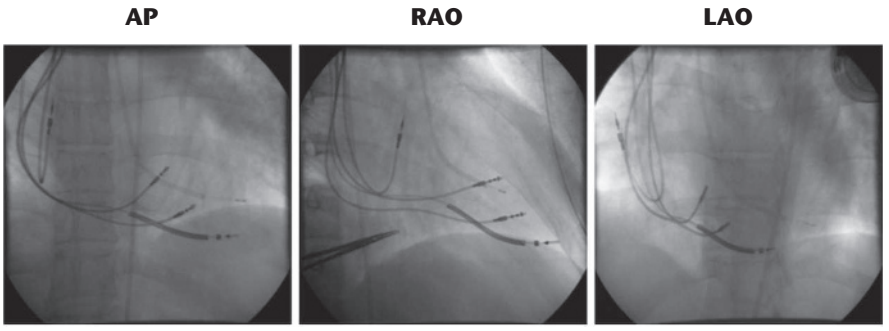


Figure 10. Exemplary anterior-posterior (AP), right anterior oblique (RAO), and left anterior oblique (LAO) views of leads placement.

Then, the stylet is rotated and a 90° curve is shaped over the distal 3 cm, giving it an additional posterior curve. Cautious counterclockwise torque is then applied while the lead is slowly withdrawn from the pulmonary artery. The lead then falls below the outflow tract of the right ventricle. At this point, the lead is advanced and applied against the septum to avoid it falling any further. This manipulation is controlled via the posterior-anterior view. It is also important to control the correct lead position in a left anterior oblique 40° to 60° view. At best, the septal position is additionally controlled in a right anterior oblique 30° to 40° view (Figure 10).

An anterior free-wall placement of the electrode must be avoided, as this position increases the risk of lead perforation and promotes thoracic palpitations during CCM signal delivery.

After placement of the first septal electrode, the second electrode is implanted in the same manner, at a distance of at least 2 cm from the first one. Both electrodes need an adequate distance from a formerly implanted ICD electrode in order to avoid crosstalk between the two devices. It is common to place the CCM ventricular electrodes at the mid septal area, one more anterior and the other more posterior.

A standard pacemaker screw-in electrode is placed in the right atrium (preshaped J-wire). The atrial electrode can either be placed in the atrial appendage or at the lateral wall of the right atrium.

Leads Testing. A pacemaker system analyzer is used for electronic measurements of signal, threshold, and impedance. In addition, 10 V pacing using the pacemaker system analyzer is used to check if there is an acute thoracic sensation by each of the ventricular leads.

After adequate placement of all three leads, they are connected to an external Optimizer test device using a sterile extension cable (Figure 11). Sensitivity level of each sensing channel is set to robustly detect local activity. CCM is delivered by the Optimizer using an algorithm that expects a specific sequence of detected events starting from the right atrium and continues in the right ventricular (RV) septum. Therefore, acceptable time windows among the electrical events sensed by the electrodes should be set using the OMNI II Programmer (Impulse Dynamics Inc.; Figure 12). CCM signal delivery is then initiated. If acute sensation is detected, the relevant lead needs to be repositioned and proper placement at the septal site should be confirmed.

Acute Hemodynamic Change Measurement. CCM is able to increase the contractile force of the muscle. Traditionally, in addition to fluoroscopy, implanting physicians often choose to ensure proper electrode positioning by acute measurement of the physiologic response to the CCM signal. However, it has not been shown that the magnitude of acute response or electrode position optimization based on the acute response is indicative of long-term clinical benefit; therefore, this measurement is optional. There are multiple ways to evaluate acute changes in cardiac function or contraction

Figure 11. Connecting an OPTIMIZER IV$_s$™ (Impulse Dynamics Inc., Orangeburg, NY) test device to the leads to test with a sterile extension cable.

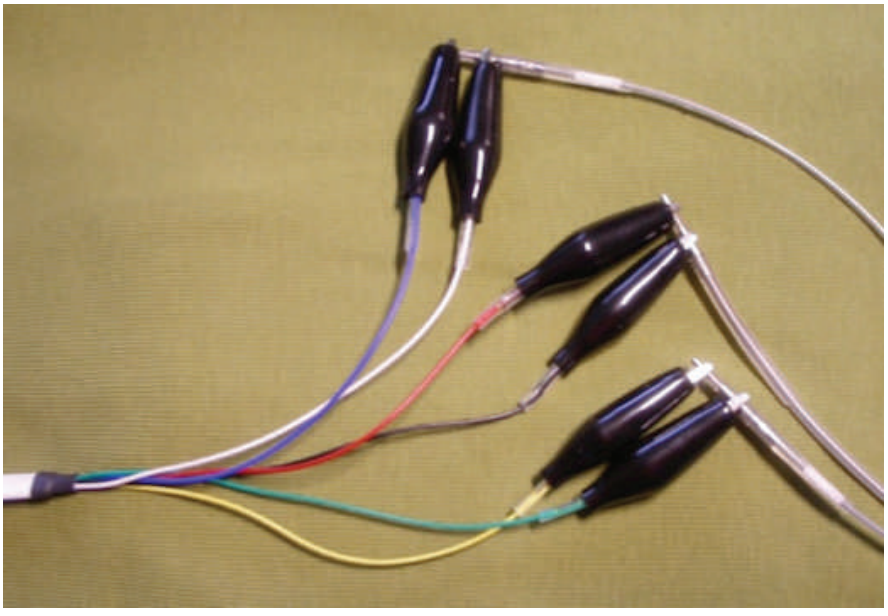


Figure 12. OMNI II programmer for OPTIMIZER™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY) implantable pulse generators and charger with portable Bluetooth® (Kirkland, WA) printer.

force, including noninvasive cardiac output monitors (eg, by bioimpedance monitors), continuous beat-to-beat cardiovascular monitors, echocardiography, and others. The implanting physician may choose any suitable method, if it is sensitive enough to detect small cardiac function changes and is practical for use during the implant procedure. There are more accurate but invasive approaches to assess LV function, which are less often used.

In some studies, online assessment of changes in LV dP/dt$_{max}$ was performed using an LV Millar catheter (Millar Instruments, Houston, TX) with an analysis system that can be obtained through Millar, or using the Monita hemodynamic measurement system (Impulse Dynamics; Figure 13). If initial electrode placement does not result in a specified increase in dP/dt$_{max}$ (eg, approx. 5% from baseline value), the electrodes may be repositioned until such an effect is achieved.

End of Procedure. Before completing the procedure, all three leads have to be affixed properly. The leads should be oriented somewhat horizontally in a plane roughly parallel to the clavicle. This orientation avoids excessive bending stress on the leads at the point at which they exit the vein. The suture sleeves are advanced down the shafts of the lead bodies to the vicinity of venous entry. Three ligatures (nonabsorbable suture material such as silk) are applied around each suture sleeve and lead, incorporating a generous amount of pectoral muscle (Figure 14A). Then, the wires are removed and each lead is connected to the Optimizer device. The gauze in the pocket is removed and the pocket is reinspected for hemostasis.

When the device is placed into the pocket (Figure 14B), care must be taken to avoid bends or kinks in the leads. Because the Optimizer has more than one lead, it is important to ensure that the leads are placed in parallel so as not to cross each other (in order to minimize lead-to-lead friction, and that the leads surrounding the Optimizer IPGs avoid placement under the Optimizer's header, to minimize lead-to-can pressure. The IPG should also be affixed with a nonabsorbable thread.

Closure of the pocket consists of approximation of the muscular and subcutaneous tissues in three layers with an absorbable suture material.

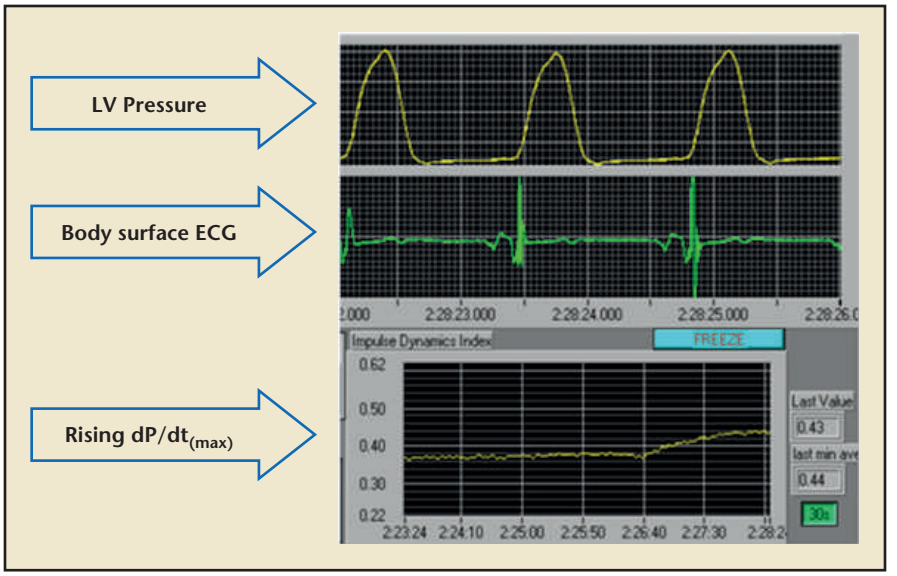


Figure 13. dP/dt$_{max}$ display evaluation during OPTIMIZER™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY) implant by the Monita system (Impulse Dynamics Inc.), indicating increase in contractility when CCM is active. CCM, cardiac contractility modulation; dP/dt$_{max}$, rate of left ventricle pressure rise in early systole; L, left ventricular.

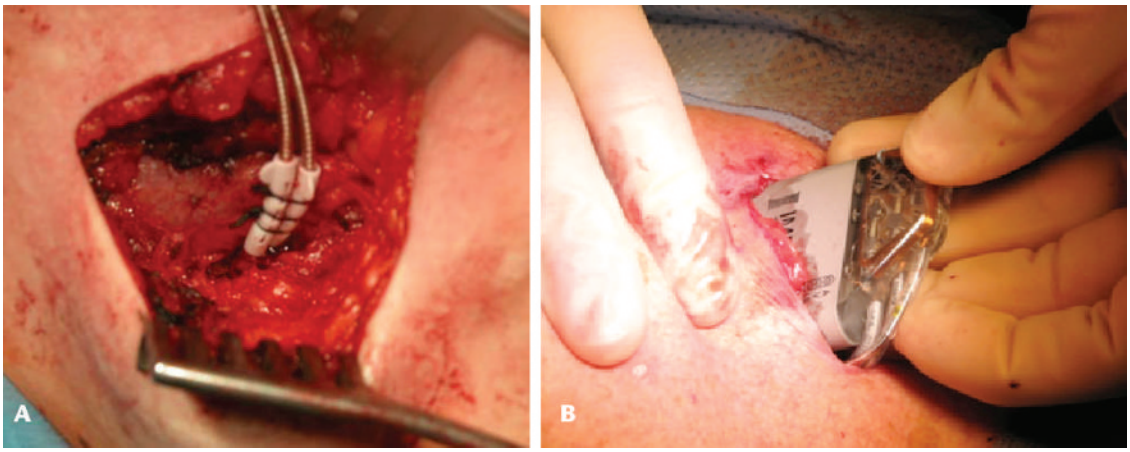


Figure 14. **(A)** Fixation of the suture sleeves. **(B)** Pocket with OPTIMIZER™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY).

The skin is closed with 4-0 semi-synthetic absorbable suture material, which does not require removal. After closure of the skin, the wound is coated with an antiseptic ointment, and the suture is additionally secured with butterfly closures.

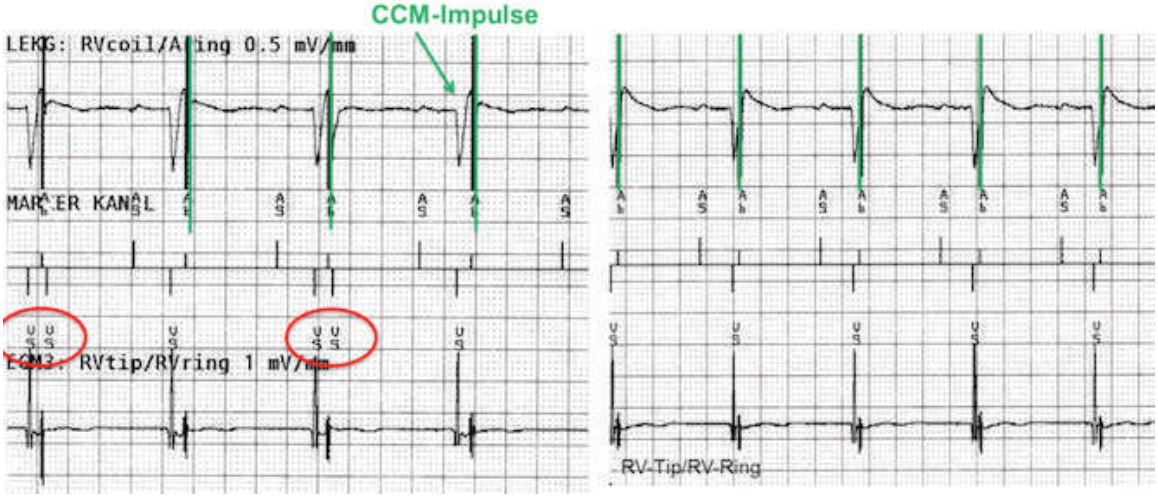
Before reactivation of the implanted ICD, a crosstalk test between the two devices is mandatory to ensure there is no double-counting and inadequate ICD shocks (Figure 15). During the crosstalk test the delay in which the CCM pulse train is applied after local sensing is increased substantially, to a maximum of approximately 60 ms longer than the typical programming, and the ICD is interrogated to observe if any double-counting occurs by the ICD. The final programming of the CCM signal delay should be to a value at which no double-counting is observed by the ICD, preferably well below the maximum tested delay.

CCM Programming

The programming of the current Optimizer system requires setting a sensitivity level through the atrial lead and the two ventricular leads, and setting the programmable time windows to a minimum and maximum expected timing of the sensed events relative to the RV sensed event. As an example only, a window for acceptable timing of right atrial to RV events could be programmed to a minimum of 100 ms and a maximum of 200 ms, and a window for acceptable timing of RV to second RV events could be programmed to a minimum of −5 ms and a maximum of 20 ms. The algorithm also includes a maximal heart rate (minimum RR interval) up to which the therapy will be delivered. CCM delivery is inhibited in heart beats with timing that does not meet these criteria, or in case of a missing expected electrical activity.

In the presence of an active pacemaker (or even CRT pacing), the setting of the sensitivity

Figure 15. Intracardiac ECG of an implanted ICD. With CCM activated and CCM train delay programmed to the maximum value, the ICD reports double counting (*left*). With CCM activated and a properly adjusted CCM train delay programmed, there is no reported double counting (*right*). CCM, cardiac contractility modulation; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator.



level can be set to detect the tissue electrical activity or the pacing artifact, according to the physician's decision, for obtaining stable event detection by the Optimizer to ensure efficient CCM signal delivery.

Postoperative Care

Minimizing postoperative pain through wound cooling and compression is necessary. Some patients may need additional pain medication (eg, novaminsulfon or piritramide). Acute postprocedural complications should be excluded in these patients. A chest radiograph should be performed 6 hours after the operation to exclude pneumothorax or hemothorax and to confirm correct electrode positions (Figure 16). A pericardial effusion must be excluded through transthoracic echocardiography.

It is important that the patient receive detailed training in device operation. Before hospital discharge, the patient must know how to handle the Optimizer mini charger and where to obtain assistance in case of technical problems. A confiding relationship between the HF patient and HF specialist is essential to guarantee an optimal therapy result.

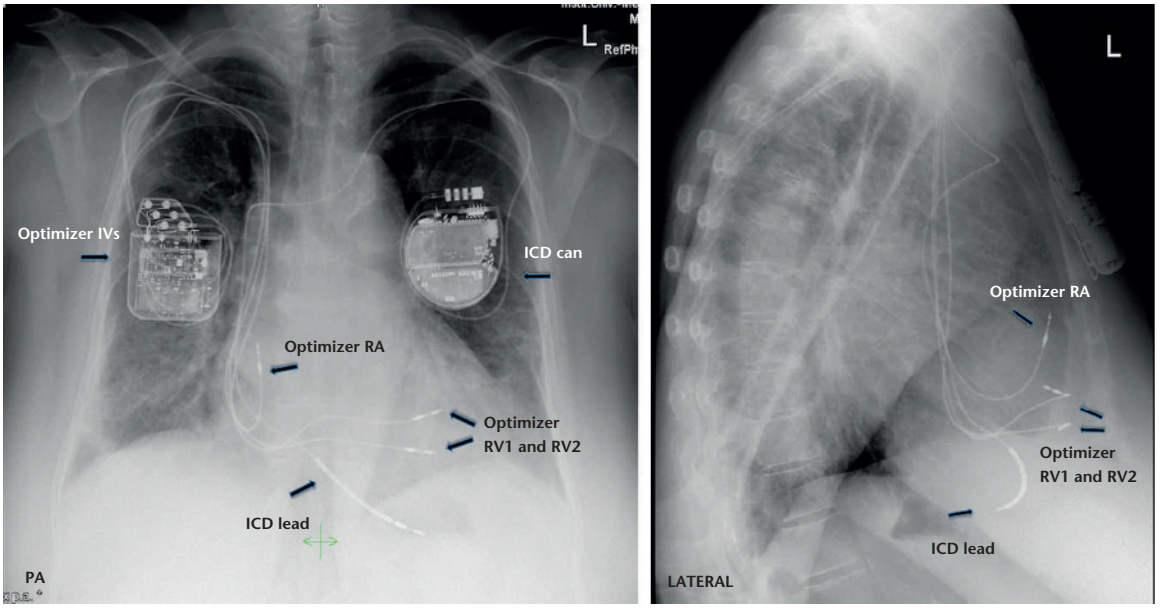
Cardiac Contractility Modulation in Special Cases

CCM and Subcutaneous ICDs

The majority of patients eligible for CCM who have reduced ejection fraction will also need an ICD. To date, three pacing electrodes are mandatory for CCM signal delivery. As there is no device that currently combines CCM with ICD functions, most CCM patients will need multiple intracardiac electrodes, which potentially increases the cumulative risk for complications. The long-term complications associated with transvenous ICD leads have led to the development of a totally subcutaneous ICD (SICD).[19] The SICD system (Boston Scientific) senses, detects, and treats malignant ventricular arrhythmias (ventricular tachycardia/fibrillation) without intracardiac leads. The subcutaneous pulse generator and electrode are placed extrathoracically. Based on initial experience, the two technologies (SICD and CCM) can successfully work together.[20] A careful intraoperative crosstalk test and postoperative ergometer testing while both devices are activated is essential to exclude interactions between the two devices.

Major requirements for a successful combination of both techniques include relatively stable sinus rhythm and the absence of significant bradycardia, a high number of premature ventricular beats, or recurrent slow ventricular tachycardia that requires antitachycardia pacing. The combination of the two techniques (SICD and CCM) is more likely to be considered in younger patients with advanced HF, or in patients who have had lead complications in the past. Because CCM signals are delivered during the absolute refractory period when pacemakers, CRT, or ICD devices are prevented from discharging, programming for the coexistence of CCM with these other therapies is possible. Ultimately, a device combining ICD, pacemaker, and CCM functions is desirable.

Figure 16. Chest radiograph (PA and lateral) of a successfully implanted CCM. CCM, cardiac contractility modulation; ICD, implantable cardioverter-defibrillator; PA, posterior-anterior; RA, right atrium; RV, right ventricle. OPTIMIZER ™ IV$_s$ (Impulse Dynamics Inc., Orangeburg, NY).



Conclusions

The use of CCM therapy for treating HF patients is growing, and the need to share information regarding implant procedure and the potential to standardize it is desired. This article describes the various steps that are commonly used by implanters that have substantial successful experience with CCM, starting from the identification of relevant cases, through the preparation, implantation, testing, and postoperative actions. ■

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MAIN POINTS

- Cardiac contractility modulation (CCM) is a device-based heart failure (HF) therapy that enhances contractile strength of the myocardium independent of the synchrony of myocardial contraction. CCM signals are nonexcitatory high-voltage electric impulses that are applied during the absolute refractory period. These signals do not initiate a new contraction, but modify calcium homeostasis in the cardiomyocyte and enhance its contractility without increasing the myocardial oxygen consumption.
- Indications for CCM include patients with reduced or moderately reduced left ventricular ejection fraction (LVEF) and normal or slightly prolonged QRS duration, thus filling a therapeutic gap among the two-thirds of patients with HF who do not meet criteria for cardiac resynchronization therapy.
- Two prospective randomized multicenter studies have demonstrated significant improvements of New York Heart Association functional class, quality-of-life, and peak oxygen uptake during cardiopulmonary exercise testing in patients with symptomatic HF with reduced LVEF.
- Recently, in the European Society of Cardiology's Guidelines on Acute and Chronic Heart Failure (2016), it was stated that CCM may be considered in select patients with HF.