Modulation of Heart Contractility

Modulação da Contratilidade Cardíaca

Tiago Luiz Silvestrini[1*], Rafael de March Ronsoni[1], Celso Salgado[2]

ORCID IDs

Silvestrini TL https://orcid.org/0000-0002-5714-7308
Ronsoni RM https://orcid.org/0000-0001-7135-9844
Salgado C https://orcid.org/0000-0002-2715-2448

ABSTRACT

Patients with heart failure (HF) are being benefited by electric therapy through conventional pacemakers when associated to bradycardia and cardiac resynchronization therapy or with low ejection fraction and presence of QRS longer than 150 ms, mainly in the presence of left branch block. Other groups of patients with HF present limitations regarding electrotherapy. However, an old concept has gained space in the treatment of patients who are outside the national and international guidelines for electrotherapy in HF: the modulation of heart contractility. This article has the purpose of presenting a review of already produced scientific evidence regarding this new modality for HF treatment.

KEYWORDS: Heart failure; Artificial pacemaker; Electric stimulation therapy.

RESUMO

Pacientes com insuficiência cardíaca (IC) vêm se beneficiando da terapia elétrica por meio de marcapassos convencionais quando associada à bradicardia e à terapia de ressincronização cardíaca ou com fração de ejeção rebaixada e presença de QRS maior que 150 ms, principalmente na presença de bloqueio de ramo esquerdo. Outros grupos de pacientes com IC apresentam limitações ao tratamento com eletroterapia. No entanto, um conceito antigo tem tomado espaço no tratamento de um grupo de pacientes que fica fora das diretrizes nacionais e internacionais para eletroterapia na IC: a modulação da contração cardíaca. Este artigo tem como objetivo apresentar a revisão das evidências científicas já produzidas e publicadas acerca dessa nova modalidade de tratamento da IC.

PALAVRAS-CHAVE: Insuficiência cardíaca; Marcapasso artificial; Terapia por estimulação elétrica.

INTRODUCTION

Electrotherapy has been helping patients with heart failure (HF) since 1990 and has solidified as an option in the therapeutic arsenal for these patients. In the last decade, important studies showed the benefits in life quality, morbidity, and mortality rate of cardiac resynchronization therapy (CRT) and in the reduction of mortality by using an implantable cardiac defibrillator (ICDs)[1,2].

Regarding the improvement in the quality of life and clinical, laboratory and hemodynamic parameters, CRT remains as the only therapeutic option to be used in most patients, when there is an indication to implant an artificial device of cardiac stimulation.

However, lately only a minimal group of patients are being benefited from this therapy: those with dilated myocardiopathy with severe dysfunction of the left ventricle (LV), QRS with duration longer than 130 ms (mainly longer than 150 ms) and symptoms associated to HF[2].

Modulation of heart contractility (MHC) through an implant of artificial heart stimulation has been presenting benefits in life quality, six-minutes walking test and hemodynamic parameters in group of patients for which CRT does not have conventional indication, such as those with disabling symptoms, with QRS with duration less than 130 ms and ejection fraction (EF) between 25 to 45%[3].

DEVICE DESIGNED FOR THE MODULATION OF CONTRACTILITY

It is a device with a similar structure of conventional cardiac pacemakers. There are three connections, one for the atrial electrode lead and two for the ventricular electrode leads to be implanted in the interventricular septum of the right ventricle (RV). The electrode leads have the same conventional heart stimulation. The device has an external battery charger used to recharge the battery at least once every three or four weeks and a specific programmer (Fig. 1)[3].

The device implantation is very similar to a conventional pacemaker, with atrial electrode leads being implanted on the atrial appendix or lateral wall, and ventricular electrode leads in the medium-septum region of the interventricular septum, with a minimum distance of 2 cm between the ends of these leads. The

performed tests are the same as the ones performed for the evaluation of conventional electrode leads, in which it is searched as the best parameter, a functional sensitivity of ventricular signal[3] (Figs. 2 and 3).
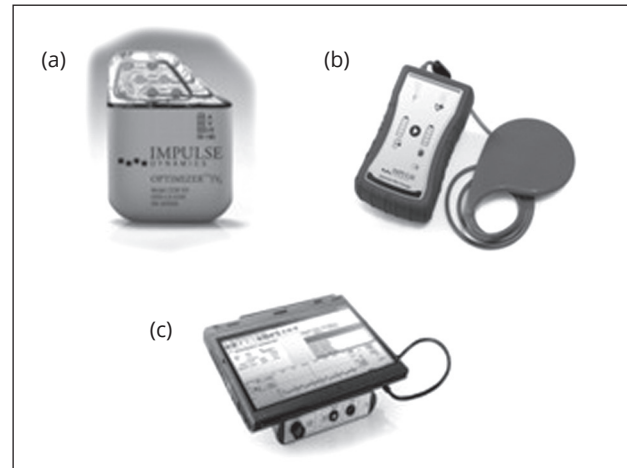

Figure 1. (a) pulse generator Optimizer IVs; (b) External charger used for recharging the battery and (c) device programmer.
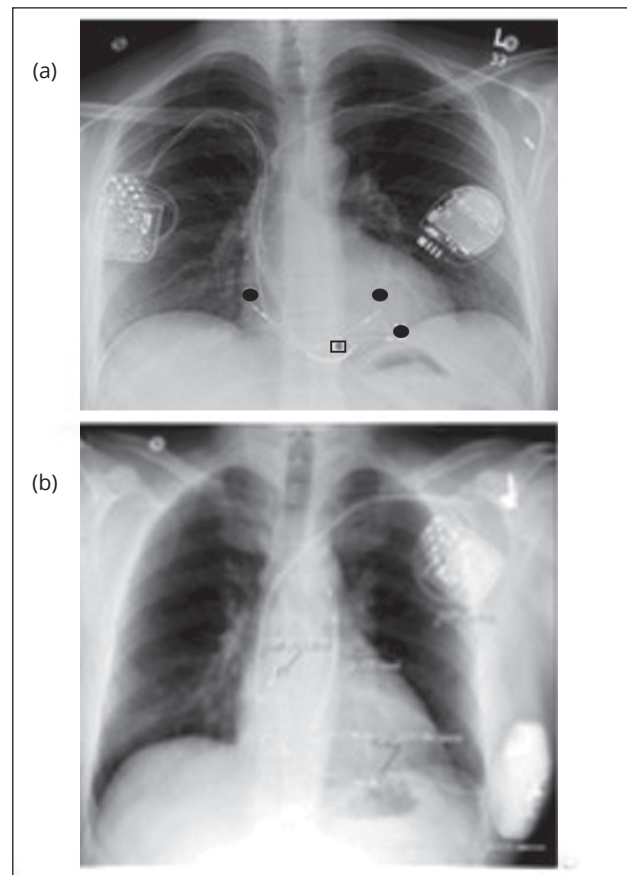

Figure 2. (a) Post-implant radiography of a patient with unicameral ICD implanted on the left and MHC implanted on the right (black circles showing the leads of the MHC lead wires and black square showing the lead of the ICD lead). (b) radiography after implantation of subcutaneous ICD and MHC, both in left hemithorax.
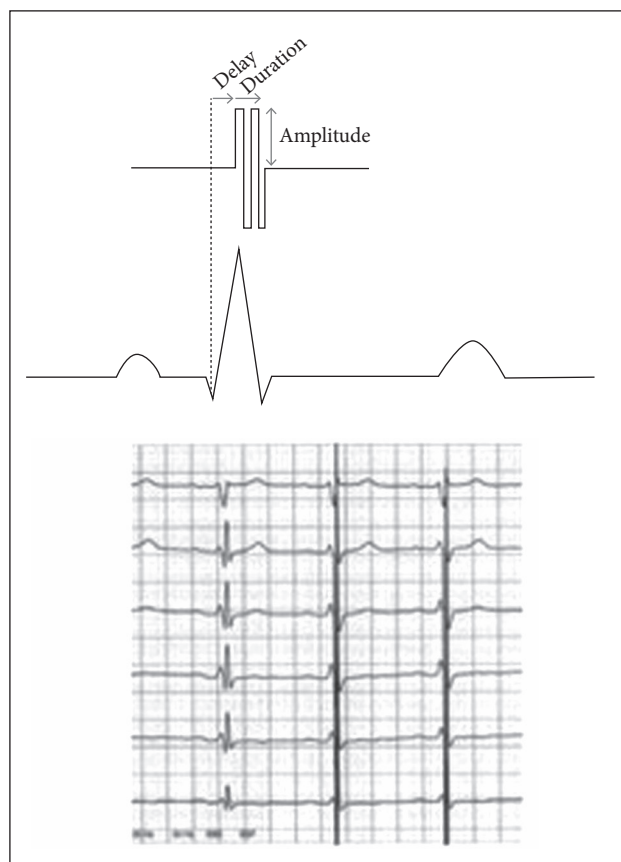
Figure 3. (a) Drawing showing the biphasic signals released by the MHC after a pre-set delay to trigger during the ventricular refractory period and thus do not cause ventricular excitation. (b) Surface ECG showing one beat before the onset of MHC and then 2 beats after application.

MHC is performed through the liberation of a dual-phase high voltage signal of 7.5 v with 22 ms of duration during the absolute refractory period[3].

CALCIUM PHYSIOLOGY IN THE HEART CONTRACTILITY- RELAXATION CYCLE

To comprehend the mechanism of action of this new device, it is essential to remember the role of the calcium cycle in the excitation-contraction coupling of the heart muscle. This is very important in the acute and sub-acute phase of MHC.

Calcium has a leading role in the regulation of contraction and relaxation phases of the heart muscle. The association between calcium flow and the connection of the contractility with the excitation wave (excitation-contraction on coupling) is relatively well understood. The central hypothesis is related to the liberation of calcium from the sarcoplasmic reticulum (SR)[4,5].

Small amounts of calcium come and go from the cardiomyocyte each cardiac cycle through the sarcoplasmic membrane, and a higher quantity of calcium arrives at the cell cytoplasm coming from the SR (Fig. 4).
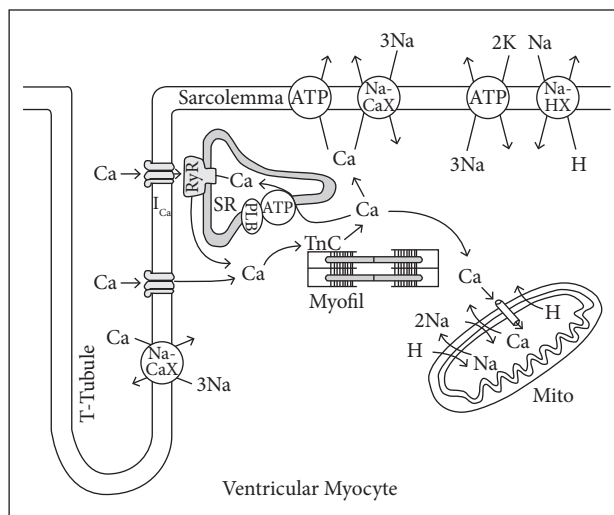

Figure 4. Schematic diagram of calcium flows within the myocyte during the cardiac cycle.

Each wave of cardiac depolarization that goes through the myocytes by the T tubules opens the L-type calcium channels from the cytoplasmic membrane, near the SR, activating, this way, the channels of calcium release, called ryanodine receptors. Therefore, the myocyte depolarization releases a great amount of calcium in the cytosol as a response to the small entrance in the cardiomyocyte from depolarization. This process elevates in up to 10 times the concentration of calcium ion in the cytosol. The result in the enhance of calcium ion interaction with troponin C to initiate the process of contractility.[4,5]

CHANNELS OF CALCIUM LIBERATION FROM SR
Ryanodine Receptors

Each L-type calcium channel from the sarcolemma controls a group of six to 20 channels of liberation from SR to anatomic proximity from T tubules calcium channels with channels located in the SR[4].

Ryanodine receptors have two functions: 1) to control calcium release channels from the SR; and 2) to act together with the support that has a series of key regulating proteins for the junctional complex. These proteins include the ones that respond to the phosphorylation of the A-kinase protein (KAP) and its anchorage protein AKAP[4].

The inactivation of calcium release by the SR after its increase in the cytosol is not well understood, and there are several hypotheses for this phenomenon: 1) increase in the calcium concentration in the cytosol inhibits the process of more calcium release; 2) the increase of calcium concentration in the cytosol may activate a calcium uptake pump by the SR; 3) the SR has less calcium; and 4) ryanodine receptor becomes inactivated, making it resistant to calcium concentration. Regardless of the way it happens, the decreased calcium concentration in cytosol provokes the beginning of the diastole[4].

CALCIUM UPTAKE BY THE SR THROUGH CALCIUM ATPase

Calcium ions are uptaken to the interior of the SR through a calcium pump called SERCA, that has many isomorphic shapes, being predominant in the heart the SERCA2a[4,5]. For each hydrolyzed ATP by this enzyme, two calcium ions are uptaken to the interior of the SR. The source of energy comes from the generation of ATP from cytosol through glycolysis. Meaningful connections between SERCA and heart contractility are found. For instance, in HF, the activity of SERCA is diminished[4,5].

Phospholamban is the name given for "phosphate receptors," and their activity is guided by a state of phosphorylation, a process that alters the molecular configuration of SERCA to promote their activity. Two more significant kinase proteins are involved in this process: one is activated through PKA in response to beta-adrenergic stimulation and cyclic AMP, and the other is activated through calcium and calmodulin, which acts in two different phosphorylation sites. When phospholamban responds to the beta-adrenergic stimulation of the cardiomyocyte by gaining calcium uptake through SERCA within SR, improving the relaxation rate, the higher activation is the phosphorylation of the PKA site. Additionally, the higher calcium content within SR corresponds to the more significant calcium release by ryanodine receptor; the answer, subsequently to the depolarization wave, generates higher frequency and force of contraction[4].

Calcium, uptaken within SR by the calcium re-uptake pump, stays stored there until the next release. Calcequestrin, a protein that stores calcium in the SR, stays in the region of SR next to T tubules. Calcium storage by calsequestrin makes it available for the releasing process as soon as it loads calcium inside the entrance of its releasing channel. This process exchanges calcium ions released from the external entrance to the cytosol interior. Calreticulin is another protein that stores calcium with structure and similar functions to calsequestrin[4-6].

SARCOLEMA CONTROL OF CALCIUM AND SODIUM IONS
Calcium Channels

The beginning of the excitation-contraction process occurs by the opening of the L-type calcium channels in the sarcoplasmic membrane. This channel is highly calcium-selective and allows its transfer to the cytosol interior in its open state when the depolarization of the membrane occurs[4].

Once it is activated (open) by membrane depolarization, the calcium channel is inactivated (closed) by: 1) increase of voltage during depolarization due to a more positive potential than negative during activation; and 2) increasing of internal calcium concentration, especially calcium flux from ryanodine receptor that pushes its concentration, present in the subsarcolemmal internal space, to near the entrance of L channels of the T tubules to help terminate the current flow[4,5].

Ion Pumps and Ion Switchers

To counterbalance the calcium entrance within the cardiac cell in each cycle, the same quantity must leave in any of these two processes: 1) calcium may be switched by sodium through the calcium-sodium exchange; e 2) through the calcium pump by ATP use that transfers it to the outside of the cell against a concentration gradient[4].

In HF, the changes in the calcium cycle are fundamental to the worsening of the heart muscle contractility. Calcium storage in the SR is severally affected due to the combination of adverse effects: 1) less SERCA activity; and 2) calcium escape in the diastolic phase associated to the hyperphosphorylation and abnormal function of the ryanodine receptor. These alterations provoke decrease of calcium in the SR, decrease of liberation in the SR, diastolic escape of calcium and increase of its concentration in the cytosol. Besides that, the action of the L-type channels is down-regulated[4].

ACTION MECHANISM OF THE MHC

The action mechanism of the MHC is related to the management of the calcium cycle in the acute phase. Chronically, the improvement of the heart contractility occurs due to the increase of phosphorylation of the regulatory paths of calcium keys, which enhances contractility and restores usual standards, which is the profile of the fetal gene of HF[3].

Acute Increase of Contractility

Studies in eye muscle tissues in rabbits and dogs with HF produced by coronary embolization and trabecular muscle in patients with HF have shown an increase in contractility and EF with the beginning of the stimulation with a modulator of heart contractilit[7,8].

Among the benefits of the calcium cycle provoked by MHC are the up-regulation of L-type calcium channels and improvement of calcium uptake within SR, provoking improvement of the extracellular influx during contractility after the begging of the modulation and calcium release from this reticulum[3] (Fig. 5).

CHRONIC EFFECTS IN HF

Modulation has shown improvement of EF, in the systolic volume, dP/dT from LF VE and delay of enhancing the diastolic volume and final systolic from LV and RV[9].

HF produces changes in the cardiomyocyte phenotype to a more juvenile pattern via reversion to a program of a fetal gene. This way, there is an increase in the expression of BNP (*brain natriuretic peptide*) and the calcium-sodium exchanger, with decreasing the expression of SERCA2A, alpha-MHC (*major histocompatibility complex*) and phospholamban. Chronic use of MHC in animals with HF causes reverse remodeling of the fetal gene in direction, again, to the regular adult program[10,11]. This way, the calcium cycle within the cardiomyocyte is improved.

The up-regulation of SERCA and the higher phosphorylation of phospholamban increase calcium uptake by SR, resulting in higher release in beating subsequently and, therefore, increasing cardiac contractility.

Studies have shown that these actions in changing the expression of genes in calcium regulation in cardiomyocytes are seen two hours after the beginning of the stimulation, locally, in cardiomyocytes near the tip of the electrode leads [14]. However, after three months of MHC, distant sites have also shown the same benefits. This represents a general reversion of the physiopathology in the expression of the fetal gene in HF[11,12].

Clinical Studies

Over 3.000 patients all around the world have received the implant of the MHC devices. Several clinical
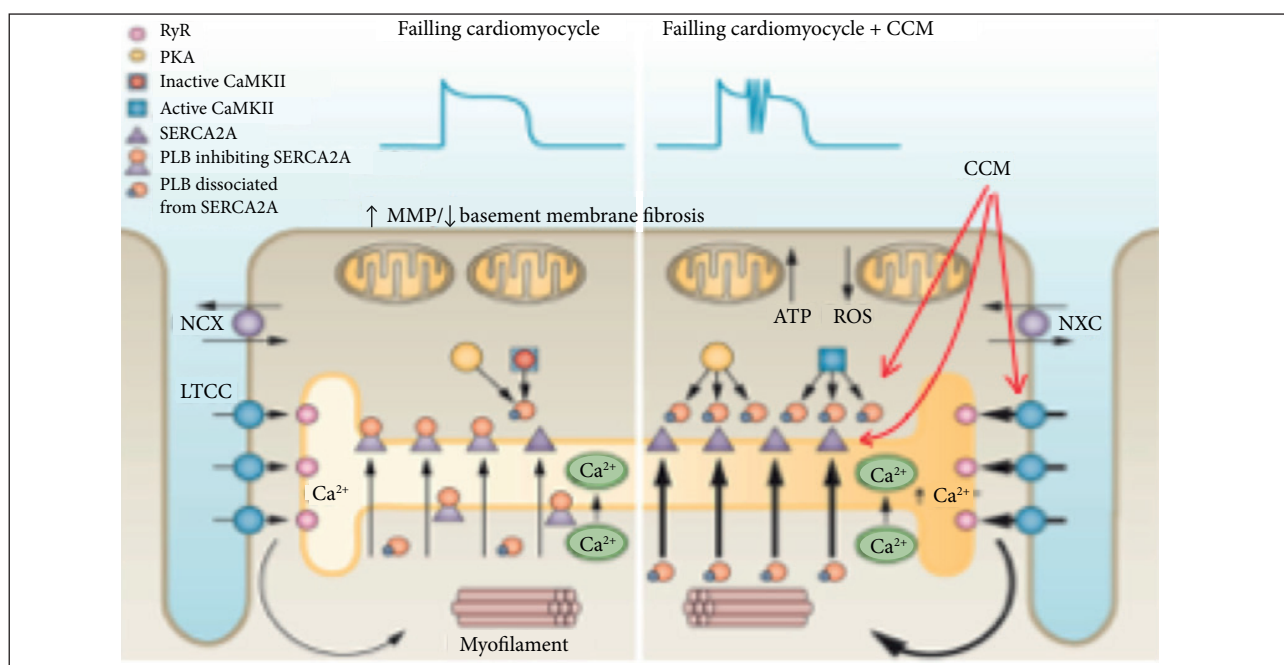

Figure 5. Schematic diagram of calcium flow in the diseased myocardium (right) and mechanism of action of MHC (left).

studies have confirmed good results in pre-clinical studies, pointing in the direction that MHC can bring benefits beyond medical therapy optimized for HF[3].

In the first major clinical study in humans, the FIX-HF-3, published in 2004, 25 patients, with mean age of 62 years, submitted themselves to the implant of the modulator of heart contractility, with HF from functional class from *New York Heart Association* (CF NYHA) III, refractory to the optimized medicament therapy. Still, regarding inclusion criteria, patients with EF under 35% and QRS lower or equal to 130 ms were selected. Twelve patients had idiopathic myocardiopathy disease as base disease and 13 coronary illness. The dP/dT gave the acute evaluation. After the implant, the generator was activated for three hours a day for eight weeks[13].

In 23 of 25 patients, the device was implanted successfully. There was a significant improvement of CF NYHA from III to II in 15 patients and for I in 4 patients. EF rose from 22 to 28%, and the score in quality of life for patients with HF in the *Minnesota* Living with Heart Failure Questionnaire (*MLHFQ*) improved from 43 points to 25 points. The 6-minute walking test rose from 411 m to 465 m[13].

Regarding adverse effects, nine patients have presented some discomfort intermittent with the stimulation. There were two deaths not related to the device. Schmidinger et al.[16], with these results, have concluded that MHC is a promising technique to improve the systolic function and symptoms in patients with refractory HF regarding optimized medicament treatment[13].

These results have stimulated the conduction of a more significant clinical study, the FIX-HF-4, published in 2008. Patients with symptomatic HF (CF NYHA higher or equal to II), of idiopathic or ischemic origin, EF < 35% and oxygen peak uptake (VO_{2max}) between 10 and 20 mL 0_2/min/Kg were included in the study. Patients were using maximum tolerated medication for HF. Patients with an indication of conventional CRT, atrial fibrillation, acute myocardium attack in three months prior randomization, other modalities of coronary disease, excessive HF, and frequent ventricular arrhythmia were excluded from the study[14].

A total of 164 patients were randomized in two groups (1 and 2) during two periods (phase 1 and 2) for 12 weeks each phase[14].

At the end of each phase, the following protocol was performed: cardiopulmonary stress test (with VO_{2max}), MLHFQ, six-minute walking test, and evaluation of CF NYHA[17].

The primary endpoints were the measures of VO_{2max} and the MLHFQ at the end of every phase in every group. Secondary endpoints were the changes in CF and six-minute walking test[14].

Group 1 was composed of 80 patients who initially received the device turned on, while in group 2, 84 patients received the device turned off. In phase 2, the groups received the opposite treatment regarding the initial situation[14].

During the first phase, VO_{2max} enhanced similarly in both groups; however, in the second phase, VO_{2max} continued enhancing in the group with the active treatment and diminished in the group where the device was turned off initially[14].

MLHFQ improved in both groups in the first phase, being better in the group with active treatment, and continued improving after cross-over in the group where the device was turned on, while it got worse in the group where the device was turned off[14].

The walking test had similar behavior to the VO_{2max} result, and the evaluation of CF improved in both groups during the two phases[14] (Fig. 6).

The authors concluded that there was consistent improvement regarding tolerant to exercise and quality of life with MHC.

The FIX-HF-5 study was the most important study performed to evaluate the security and effectiveness of MHC. It was performed in 50 centers in the USA and included 428 patients with CF NYHA III/IV, with narrow QRS and EF ≤ to 35%, which were randomized to receive optimized medical treatment (OMT) (213 patients) versus OMT+MHC (215 patients). The primary endpoint regarding effectiveness was the anaerobic ventilation limit, and the secondary was VO_{2max} and MLHFQ after six months. The primary safety endpoint was the test of non-inferiority between the groups in 12 months for all causes of deaths and hospitalization[15].

Regarding the security endpoint, the OMT group presented 103 events in 213 patients (48.4%) and the OMT+MHC group 112 events in 215 patients (52.1%). This difference was within the preestablished limited, presenting, therefore, security endpoint for the treatment with MHC[15].

Regarding effectiveness results, anaerobic ventilation limit (primary endpoint of effectiveness) diminished in both groups in 0.14 mL/kg.min after 24 weeks. VO_{2max}

increased in the group OMT + MHC and diminished in the group OMT, with a significant statistical difference. MLHFQ and NYHA improved significantly more in the OMT+ MHC group than in the OMT group. There was also non-significant improvement in the 6-minute walking test in the group OMT + MHC[15].

This study has managed to find the primary security endpoint, however, did not reach primary effectiveness endpoint, which was the improvement of the anaerobic ventilation limit. However, there was an improvement in VO_{2max} and in MLHFQ, as well as in CF of NYHA. The two last findings were similar to the ones
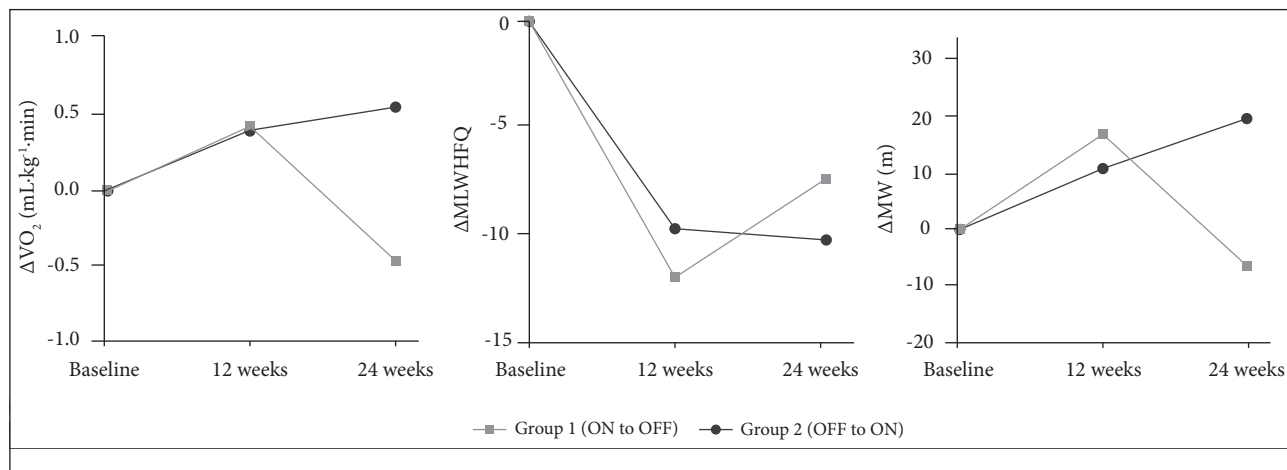
Figure 6. (a) VO_{2max} changes in each group compared to their respective baseline values. Results presented for cases with complete data; These results substantially agree with those based on multiple assignments. (b) Minnesota Living with Heart Failure Questionnaire changes in each group compared to their respective baseline values. Results presented for full data cases; these results substantially agree with those based on multiple assignments. (c) Changes in the 6-minute walk test in each group compared to their respective baseline values[17].
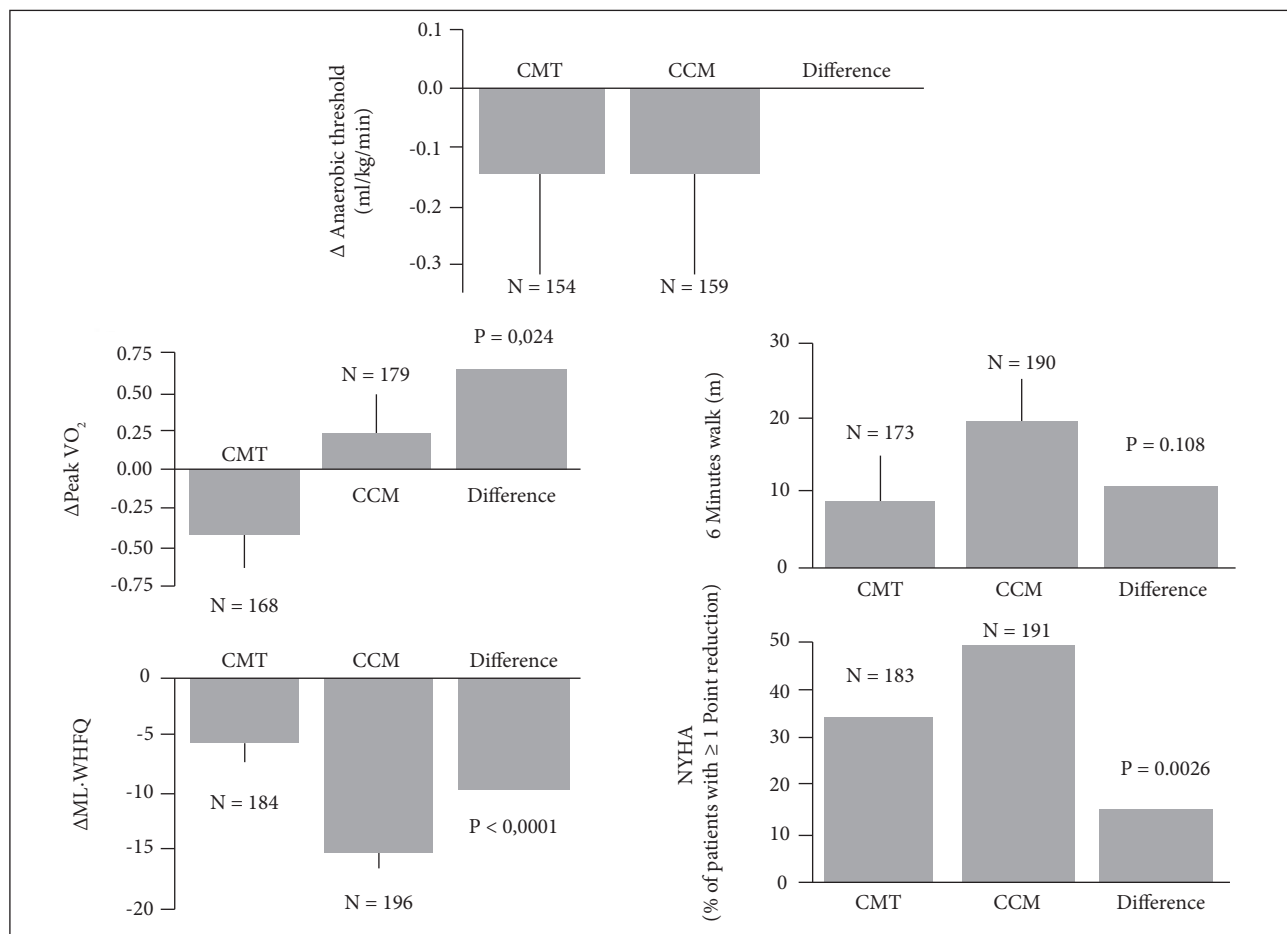

Figure 7. Graphs with summary results of the FUX-HF-5 study.

found in a study that validated the use of the devices in CRT[15].

In the subgroup analysis, it was noticed that NYHA III and EF above 25% obtained the best results [18] (Fig. 7).

The use of this primary *endpoint* (anaerobic ventilation limit) for this study was required by the Food and Drug Administration (FDA), since it was about a not blind study and measures such as quality of life and exercise tolerance is subjective parameters, susceptible to the placebo effect[15].

The authors criticized, among other aspects, this fact and affirmed that, although the anaerobic ventilation limit is an objective parameter of evaluation, it has not been validated as an *endpoint* in HF studies[15].

Two meta-analyses about the theme have been published. In 2012, Cheuk-Man et al[19]. published a meta-analysis regarding the controlled studies registered in Cochrane, MEDLINE, and EMBASE, comparing MHC and OMT or *sham* treatment. The results of interest were all the causes of mortality, all the causes of hospitalization and adverse effects. Three studies randomized 641 patients and the analysis of this population has shown that compared to the control, MHC has not significant

statistically diminished mortality, hospitalization. However, it did not enhance the risks of adverse effects[16].

Another meta-analysis, published in 2014 by Giallauria et al[17], having as a database the same population of the previous publication, used primary VO_{2max}, *endpoints*, six-minute walking test and quality of life in the MLHFQ questionnaire. This analysis concluded that compared to standard treatment for HF, MHC has significant improved VO_{2max}, the walked distance in the six-minute test and the quality of life in the MLHFQ questionnaire (Fig. 8).

Long Term Results

Four publications presented long term results in the mortality of patients treated with MHC. Schau et al.[18] evaluated retrospectively 54 patients submitted to MHC implant between 2003 to 2010. Patients presented moderate to severe ventricular dysfunction, NYHA III/IV, and mean EF of 23%. Following three years, 24 patients died (18.4% by year). The mortality was equivalent to the expected prevision by the prediction model of mortality for HF from the Seattle Heart Failure Model (*SHFM*).
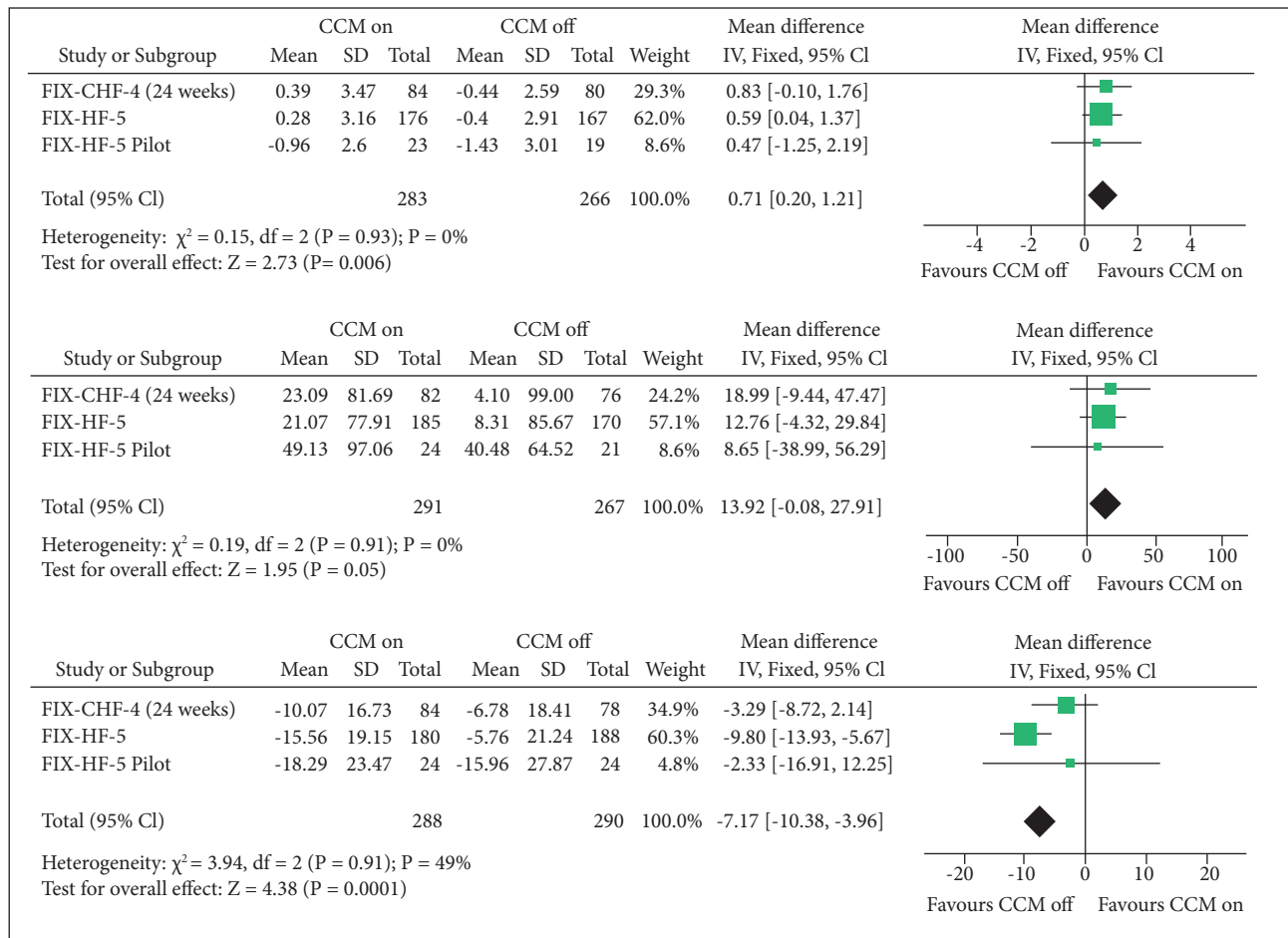

Study or Subgroup	CCM on			CCM off			Weight	Mean difference IV, Fixed, 95% Cl	Mean difference IV, Fixed, 95% Cl
	Mean	SD	Total	Mean	SD	Total			
FIX-CHF-4 (24 weeks)	0.39	3.47	84	-0.44	2.59	80	29.3%	0.83 [-0.10, 1.76]	
FIX-HF-5	0.28	3.16	176	-0.4	2.91	167	62.0%	0.59 [0.04, 1.37]	
FIX-HF-5 Pilot	-0.96	2.6	23	-1.43	3.01	19	8.6%	0.47 [-1.25, 2.19]	
Total (95% Cl)			283			266	100.0%	0.71 [0.20, 1.21]	

Heterogeneity: $\chi^2 = 0.15$, df = 2 (P = 0.93); P = 0%
Test for overall effect: Z = 2.73 (P= 0.006)

Study or Subgroup	CCM on			CCM off			Weight	Mean difference IV, Fixed, 95% Cl	Mean difference IV, Fixed, 95% Cl
	Mean	SD	Total	Mean	SD	Total			
FIX-CHF-4 (24 weeks)	23.09	81.69	82	4.10	99.00	76	24.2%	18.99 [-9.44, 47.47]	
FIX-HF-5	21.07	77.91	185	8.31	85.67	170	57.1%	12.76 [-4.32, 29.84]	
FIX-HF-5 Pilot	49.13	97.06	24	40.48	64.52	21	8.6%	8.65 [-38.99, 56.29]	
Total (95% Cl)			291			267	100.0%	13.92 [-0.08, 27.91]	

Heterogeneity: $\chi^2 = 0.19$, df = 2 (P = 0.91); P = 0%
Test for overall effect: Z = 1.95 (P = 0.05)

Study or Subgroup	CCM on			CCM off			Weight	Mean difference IV, Fixed, 95% Cl	Mean difference IV, Fixed, 95% Cl
	Mean	SD	Total	Mean	SD	Total			
FIX-CHF-4 (24 weeks)	-10.07	16.73	84	-6.78	18.41	78	34.9%	-3.29 [-8.72, 2.14]	
FIX-HF-5	-15.56	19.15	180	-5.76	21.24	188	60.3%	-9.80 [-13.93, -5.67]	
FIX-HF-5 Pilot	-18.29	23.47	24	-15.96	27.87	24	4.8%	-2.33 [-16.91, 12.25]	
Total (95% Cl)			288			290	100.0%	-7.17 [-10.38, -3.96]	

Heterogeneity: $\chi^2 = 3.94$, df = 2 (P = 0.91); P = 49%
Test for overall effect: Z = 4.38 (P = 0.0001)

Figure 8. VO_{2max} change results tables (top table).

In another study, published by Kuschyk et al.[19] conducted by only once center, 81 patients were followed up for three years, between 2004 and 2012. This population had a mean EF of 23%, and the majority presented NYHA III/IV. The authors found long term improvement in the quality of life, NYHA, EF, and pro-BNP measures in the follow-up of these patients. The survival curve presented significant diminishing in the mortality when compared to the prediction model of mortality of HF from *Meta-analysis Global Group in Chronic Heart Failure* (MAGGIC) – 13.1% *versus* 18.4% in the first year and 32.1% *versus* 40% in the third year.

A recent study, conducted by Liu et al.[20], evaluated the effects of this therapy in 41 patients with EF < 40%. The follow up was of six years, and the cases were compared 1:1 with control, with similar age, EF, medication, and cause of HF. The primary *endpoints* were all causes of mortality, and the secondary *endpoints* included hospitalization for HF and death by cardiovascular disease. EF was of 28%, and all the causes of mortality were inferior in the MHC group. When stratified by EF, patients with below 25% did not show significant improvement in mortality. However, in population with EF between 25 to 40%, the diminishing in mortality was expressive in MHC. Similar improvement was found in secondary endpoints.

Kloppe et al.[21] have followed up for 4.5 years 68 patients submitted to MHC implant and with mean EF of 26% in two centers in Germany. This study showed a diminishing in the mortality in year 1, 2, and 5 in group MHC comparing to the prediction model of mortality from *SHFM*.

Future Perspectives

Nonetheless, the great potential regarding this new therapy, a series of challenges still must be overcome so it can be included in the therapeutic arsenal for HF.

A significant part of the patients with an indication for MHC is based on current European guidelines[22] and clinical studies, and it is already with cardiac devices such as CRT and ICD. This means that these people already have one, two, three, or more electrode leads within the heart. With this therapy, in the current state of the art, demands the implant of at least three electrode leads, which means that many of the problems regarding the excess of leads, such as thrombosis, higher risk for infections, may appear. There are studies regarding the upgrade of this therapy, for example, with the coupling of a cardio defibrillator to the same device of MHC.

Another current limitation is the need for detection of the P wave for the liberation of impulse by the MHC, which prevents patients with atrial fibrillation and frequent ectopies to be candidates to use this device. Improvements in the algorithm, avoiding the need for synchronization with a P wave, would allow these patients also to make use of this therapy, as well as would avoid the use of an electrode lead in the atrium.

Although the improvement in the quality of life parameter and functional capacity is essential, there remains to show, with large randomized, double-blind and multicenter studies, the impact on survival and improvement in mortality of these patients, in order to change paradigms regarding this new therapy.

Currently, the European guidelines for the treatment of HF patients consider those with ventricular dysfunction, CF II-III and QRS <120 ms possible candidates to the use of this new technology[22].

AUTHORS' CONTRIBUTION

Conceptualization, Salgado C; Investigation, Silvestrini TL; Writing, Silvestrini TL; Revision, Ronsoni; Supervision, Salgado C.

REFERENCES

1. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmic Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51(21):e1-62. https://doi.org/10.1016/j.jacc.2008.02.032

2. Wilcox JE, Fonarow GC, Zhang Y, Albert NM, Curtis AB, Yancy CW et al. Clinical effectiveness of cardiac resynchronization and implantable cardioverter-defibrillator therapy in men and women with heart failure: findings from IMPROVE HF. Circ Heart Fail. 2014;7(1):146-53. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000789

3. Abi-Samar F, Gutterman D. Cardiac contractility modulation: a novel approach for the treatment of heart failure. Heart Fail Rev. 2016;21(6):645-60. https://doi.org/10.1007%2Fs10741-016-9571-6

4. Braunwald E, Zipes DP, Libby P, Bonow RO. Braunwald's hearth disease: a text book of cardiovascular medicine. 7a ed. 2015.

5. Dibb KM, Graham HK, Venetucci LA, Eisner DA, Trafford AW. Analysis of cellular calcium fluxes in cardiac muscle to understand calcium homeostasis in the heart. Cell Calcium. 2007;42(4-5):503-512. https://doi.org/10.1016/j.ceca.2007.04.002

6. Bears DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198-205. https://doi.org/10.1038/415198a

7. Burkhoff D, Shemer I, Felzen B, Shimizu J, Mika Y, Dickstein M, et al. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. Heart Fail Rev. 2001;6(1):27-34.

8. Morita H, Suzuki G, Haddad W, Mika Y, Tanhehco EJ, Sharov VG, et al. Cardiac contractility modulation with nonexcitatory electric signals improves left ventricular function in dogs with chronic heart failure. J Card Fail. 2003;9(1):69-75. https://doi.org/10.1054/jcaf.2003.8

9. Morita H, Suzuki G, Haddad W, Mika Y, Tanhehco EJ, Goldstein S, et al. Long-term effects of non-excitatory cardiac contractility modulation electric signals on the progression of heart failure in dogs. Eur J Heart Fail. 2004;6(2):145-150 https://doi.org/10.1016/j.ejheart.2003.11.001

10. Butter C, Rastogi S, Minden HH, Meyhofer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol. 2008;51(18):1784-9. https://doi.org/10.1016/j.jacc.2008.01.036

11. Imai M, Rastogi S, Gupta RC, Mishra S, Sharov VG, Stanley WC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. J Am Coll Cardiol. 2007;49(21):2120-8. https://doi.org/10.1016/j.jacc.2006.10.082

12. Lyon AR, Samara MA, Feldman DS. Cardiac contractility modulation therapy in advanced systolic heart failure. Nat Rev Cardiol. 2013;10(10):584-98. https://doi.org/10.1038/nrcardio.2013.114

13. Stix G, Borggrefe M, Wolpert C, Hindricks G, Kottkamp H, Bocker D, et al. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. Eur Heart J. 2004;25(8):650-5. https://doi.org/10.1016/j.ehj.2004.02.027

14. Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J. 2008;29(8):1019-28. https://doi.org/10.1093/eurheartj/ehn020

15. Kadish A, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011;161(2):329-37. https://doi.org/10.1016/j.ahj.2010.10.025

16. Kwong JS, Sanderson JE, Yu CM. Cardiac contractility modulation for heart failure: a meta-analysis of randomized controlled trials. Pacing Clin electrophysio. l. 2012;35(9):1111-8. https://doi.org/10.1111/j.1540-8159.2012.03449.x

17. Giallauria F, Vigorito C, Piepoli MF, Stewart Coats AJ. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. Int J Cardiol. 2014;175(2):352-7. https://doi.org/10.1016/j.ijcard.2014.06.005

18. Schau T, Seifert M, Meyhofer J, Neuss M, Butter C. Long-term outcome of cardiac contractility modulation in patients with severe congestive heart failure. Europace. 2011;13(10):1436-44. https://doi.org/10.1093/europace/eur153

19. Kuschyk J, Roeger S, Schneider R, Streitner F, Stach K, Rudic B, et al. Efficacy and survival in patients with cardiac contractility modulation: long-term single center experience in 81 patients. Int J Cardiol. 2015;183(15):76-81. https://doi.org/10.1016/j.ijcard.2014.12.178

20. Liu M, Fang F, Luo XX, Shlomo BH, Burkhoff D, Chan JY, et al. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: a case-control study. Int J Cardiol. 2016;206(1):122-6. https://doi.org/10.1016/j.ijcard.2016.01.071

21. Kloppe A, Lawo T, Mijic D, Schiedat F, Muegge A, Lemke B. Long-term survival with cardiac contractility modulation in patients with NYHA II or III. Int J Cardiol. 2016; 209 (15):291-295 https://doi.org/10.1016/j.ijcard.2016.02.001

22. Ponikowiski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129-2200. https://doi.org/10.1093/eurheartj/ehw128