CorSalud 2020 Apr-Jun;12(2):198-208

CorSalud

Cuban Society of Cardiology

Review Article

Cardiocentro ERNESTO CHE GUEVARA SANTA CLARA CUBA

Non-pharmacological approaches in heart failure

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Este artículo también está disponible en español

ARTICLE INFORMATION

Received: March 1st, 2019
Accepted: May 9, 2019

Competing interests
The author declares no competing interests

Abbreviations
CRT: cardiac resynchronization therapy
ICD: implantable cardioverter-defibrillator
LVEF: left ventricle ejection fraction
NYHA: new York Heart Association
OMT: optimal medical treatment

ABSTRACT
Therapeutic options are limited for patients with advanced heart failure who become refractory to conventional drug therapies. Knowing the non-pharmacological alternatives in the management of these patients is essential in their comprehensive evaluation, and it is the second therapeutic option in this group of increasingly prevalent patients.
Keywords: Advanced heart failure, Treatment, Non-pharmacological interventions

Alternativas no farmacológicas en la insuficiencia o falla cardíaca

RESUMEN
Las opciones terapéuticas son limitadas para los pacientes con insuficiencia cardíaca avanzada que se vuelven refractarios a las terapias farmacológicas convencionales. Conocer las alternativas no farmacológicas en el tratamiento de estos enfermos resulta imprescindible en su evaluación integral, y es la segunda opción terapéutica en este grupo de enfermos cada vez más prevalentes.
Palabras clave: Insuficiencia cardíaca avanzada, Tratamiento, alternativas no farmacológicas

INTRODUCTION

The therapeutic approach of patients suffering from heart failure becomes more and more complex every day, because the world's population ageing, as well as the high life expectancy and survival to previously fatal conditions –thanks to the therapeutic approaches that support it– have considerably increased the prevalence of the disease. According to the American Heart Association, between 2012 and 2030, its prevalence will increase by 50%, what means that, more than eight million people over the age of 18 years old will suffer from heart failure[1]; but, in addition, its incidence is not negligible either, especially in young people suffering from diseases such as cardiomyopathies, whose clinical expression, in addition to sudden death, is mainly heart failure. Then, it is not uncommon to find patients whose functional class, according to the New York Heart Association (NYHA), is III or IV practically from the beginning of the disease, in whom the pharmacological treatment is insufficient in its comprehensive therapeutic approach.

Such is the case that, different scientific societies of reference in the USA

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and Europe set out, in their respective action guidelines[2,3], specific criteria in this sense, based on the scientific evidence that the large multicenter studies offer in their results. At the same time, experts from the different societies, dedicated to this subspecialty, open a little bit the diapason of non-pharmacological options and address the topic involving other pathophysiological elements of the disease, what generates alternatives not previously considered in the guidelines, but with scientific basis and experimental studies, some with results already and others still in the execution phase, nevertheless, with a more comprehensive vision facing a growing disease, where the therapeutic management we follow with the patients must be in line with the multifactoriality and the very high associated comorbidity, beyond the limit of the heart transplantation as the last option[4].

STAGES OF THE DISEASE AND PATIENTS

In the bibliography on the subject, the approach to this disease is very general; however, there are clinically two moments or forms of presentation in which the therapeutic management has particularities. That is why we affirm that, not only in chronic heart failure these therapeutic approaches are implemented, but also in its acute phase; and some of these measures are applied and complemented in both clinical states, according to the stage of the disease.

Generally speaking, non-pharmacological therapeutic approaches for heart failure include:

- Cardiac resynchronization therapy (CRT) / Implantable cardioverter-defibrillator (ICD)
- Surgery for heart valve disease and ventricular dysfunction
- Mechanical circulatory support
- Experimental treatments
- Heart transplantation

Among patients with heart failure, who would benefit the most from these therapeutic options would be those with the characteristics outlined in the **box**[5].

ACUTE HEART FAILURE

A. Optimizing oxygenation (PO_2 > 90%)

Non-Invasive ventilation

Non-invasive mechanical ventilation can be used to relieve dyspnea and to improve oxygen saturation in patients with acute pulmonary edema[6]. Evidence shows that it does not change mortality in these patients, and the effects on reducing the need for invasive mechanical ventilation are discordant (Level of evidence B); but this ventilatory modality has important effects on patients with heart failure[2,6,7].

Effects on the respiratory system [6]:

- Alveolar recruitment (prevents its collapse), with improved gas exchange and oxygenation

Box. Patients who would benefit from non-pharmacological therapeutic options[5].

- Advanced heart failure, stages C and D
- Frequent admissions or repeated attendance to emergency services
- Significant deterioration of the kidney function
- Weight loss without any other cause (cardiac cachexia)
- ACE/ARB intolerance due to hypotension or kidney dysfunction
- Intolerance to beta-blockers due to low blood pressure or clinical worsening
- Blood pressure frequently < 90 mmHg
- III-IV NYHA Functional Class: Dyspnea at minimum exertion (e.g., dressing, bathing)
- Need to progressively increase doses of diuretics to maintain optimal blood volume
- Progressive hyponatremia < 133 mEq/L
- Frequent shocks of the implantable cardioverter-defibrillator

ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin-II receptor blockers

- Induction of the displacement of liquids returning from the alveoli and interstitial space to the pulmonary circulation
- Reduction of the load on the respiratory muscles and the breathing effort

Hemodynamic effects[7]:
- Reduced systemic venous return and decreased right ventricular load due to the increase of the intrathoracic pressure
- Changes in total pulmonary vascular resistance, which is the main determinant factor of the right ventricular afterload.

B. Circulation: ensuring cardiac output >2.2 L/minute

Mechanical circulatory support[8,9]

The indication for mechanical circulatory support should be considered in patients with refractory heart failure, requiring continuous intravenous inotropes and with parameters of severe hemodynamic impairment: a) pulmonary capillary pressure > 20 mmHg, b) cardiac index < 2 L/min/m^2 and c) systolic blood pressure < 80 mmHg.

Mechanical circulatory support may be of short or prolonged duration. Among the devices of short duration, the intra-aortic balloon pump is the most widely used. A complex mechanical circulatory support can be used as a bridge to the transplantation, to the recovery or, in the long term, in patients not susceptible to transplantation[8].

Indications for the intra-aortic balloon pump

Class I
- Cardiogenic shock from acute myocardial infarction associated with reperfusion strategy (Level of evidence B).
- Interventricular communication or severe mitral regurgitation due to acute myocardial infarction (Level of evidence B).
- Cardiogenic shock without response to supportive therapy with vasoactive drugs and feasibility of heart transplantation (Level of evidence C).

Class IIa
- Refractory heart failure with potentially reversible cause (bridge to the recovery) in absence of complex devices (Level of evidence C).

Class IIb
- As a bridge to surgical alternative or other form of complex and prolonged mechanical circulatory support (Level of evidence C).

Class III
- Patients with refractory cardiogenic shock without recognizing any potentially reversible cause (Level of evidence C).
- Patients with aortic regurgitation, aortic dissection, or severe aorto-iliac disease (Level of evidence B).

C. Tissue Perfusion

Ultrafiltration

A new therapy in acute heart failure is ultrafiltration, particularly for those patients with hydrosaline retention, refractory to conventional medical therapy, and impaired renal function. However, at present, there is no a clearly established role for this procedure in patients who adequately respond to diuretic therapy (Level of evidence B)[10].

Peritoneal dialysis[11,12]

Indications
1. Optimal medical treatment (OMT).
2. Advanced heart failure refractory to treatment.
3. Renal dysfunction (glomerular filtration rate < 45 ml/min/1.73 m^2 of body surface.
4. Volume overload: dyspnea, NYHA III-IV, edema, ascites, refractoriness to OMT.
5. More than two admissions due to heart failure in less than six months.

Contraindications
1. Renal failure in dialysis treatment.
2. Unstable patient.
3. Extra-cardiac comorbidities with life expectancy of less than one year.
4. Abdominal wall integrity alteration due to recent abdominal surgery or recent intra-abdominal vascular prosthesis (less than four months).

D. Contractility

Heart valve disease and ventricular dysfunction: surgical alternatives

Heart failure, as a consequence of coronary disease, is a result of ventricular dysfunction associated with acute or chronic ischemia, acute reversible systolic or diastolic ventricular dysfunction, mechanical complications of acute myocardial infarction, mitral regurgitation, ventricular rupture, interventricular

communication, ventricular aneurysm or a combination of these processes[13].

Surgical treatment, with Class IIa indication and level of evidence C, is considered in patients with severe and symptomatic primary (organic) mitral regurgitation in functional Class II-IV (NYHA), who present severe deterioration of the left ventricular ejection fraction (LVEF < 0.30 or telesystolic diameter > 55 mm, or both) in whom plasty success is highly probable[13].

HEART FAILURE IN CHRONIC PHASE

The 2016[2] Guidelines of the European Society of Cardiology listed the therapeutic indications with a synthetic summary of the non-pharmacological interventions; in this case, the CRT when the width of the QRS complex is greater than 130 msec. On the other hand, those of the American Heart Association[3], in their therapeutic summary, make more comprehensive considerations in stages C and D, where these options have a clear indication. However, other considerations should be made in this regard, advocating the need to offer other options to these patients and considering the etiology of the disease and associated comorbidities, among other aspects.

Renal denervation

Catheter-guided renal denervation is a minimally invasive procedure that is based on the physiological premise that disruption of the afferent and efferent renal nerves will result in a decrease in renal sympathetic signal, which reduces renin release and sodium retention, and increases renal blood flow; which, consequently, lowers blood pressure (**Figure 1**)[14,15]. The results of the studies carried out up to date indicate that, in refractory high blood pressure, it is an effective and safe treatment, complementary to pharmacological treatment; therefore, it is useful in patients in whom resistant high blood pressure is the cause of heart failure[14].

Ultrafiltration and hemodialysis are also useful at this clinical stage.

Cardiac resynchronization therapy[2,5,16-18]

The CRT is contraindicated in patients with QRS < 130 ms. Its indications according to the Guidelines[2] of the European Society of Cardiology are the following:

- Recommendation Class I and level of evidence A
  - Recommended for symptomatic patients with heart failure, in sinus rhythm with QRS ≥ 150 ms and left bundle branch block QRS morphology, with LVEF ≤ 35% despite receiving OMT, in order to improve symptoms and reduce morbidity and mortality.
  - CRT, instead of right ventricular pacemakers, is recommended for patients with heart failure and reduced LVEF, regardless of the NYHA functional class, who have an indication for ventricular pacemakers and high-grade atrioventricular block, in order to reduce mortality. This includes patients with atrial fibrillation.
- Recommendation Class I and level of evidence B
  - CRT is recommended for symptomatic patients with heart failure, in sinus rhythm with QRS of 130-149 ms and left bundle branch block QRS morphology, with LVEF ≤ 35% de-

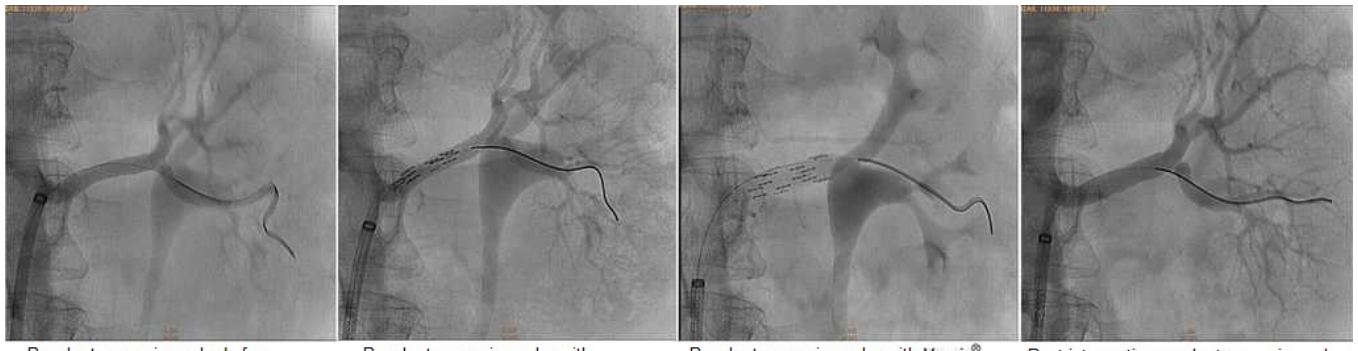

Figure 1. Sequence of arteriographic images during the renal denervation procedure. Taken from Marín-Orozco *et al.* Rev Colomb Cardiol. 2015;22:305-11[15] (License CC BY-NC-ND 4.0).

spite receiving OMT, in order to improve symptoms and reduce morbidity and mortality.

- Recommendation Class IIa and level of evidence B
  - CRT must be considered for symptomatic patients with heart failure, in sinus rhythm with QRS ≥ 150 ms and left bundle branch block QRS morphology, with LVEF ≤ 35% despite receiving OMT, in order to improve symptoms and reduce morbidity and mortality.
  - CRT must be considered for patients with LVEF ≤ 35% and NYHA III-IV, on spite of the OMT, in order to improve symptoms and reduce the morbidity and mortality if the patient is in atrial fibrillation and has a QRS duration ≥ 130 ms, provided that biventricular capture is available or the patient is expected to return to sinus rhythm. Regarding the functional class, medical judgment should be used for patients in conservatively treatable end-stage heart failure, rather than using treatments to improve the symptoms or the prognosis.
- Recommendation Class IIb and level of evidence B
  - CRT may be considered for symptomatic patients with heart failure, in sinus rhythm with QRS 130 -149 ms and left bundle branch block QRS morphology, with LVEF ≤ 35% despite receiving OMT, in order to improve symptoms and reduce morbidity and mortality.
  - CRT may be considered for patients with heart failure and reduced LVEF who have a conventional pacemaker or an ICD, and then experiencing a worsening in the heart failure despite the OMT, having a high percentage of right ventricular stimulation. This does not apply for patients with stable heart failure.

Implantable cardioverter-defibrillator

Recommendations for the use of this device are shown in **table**[2,3,19-21].

Tabla. Recommendations for the use of an implantable cardioverter defibrillator in patients with heart failure. Modified from Ponikowski *et al*. Eur Heart J. 2016; 37:2129-200[2].

Recommendations	RC	LE
Secondary prevention To implant an ICD is recommended for reducing the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability and having a life expectancy > 1 year with a good functional status.	I	A
Primary prevention To implant an ICD is recommended for reducing the risk of sudden death and all-cause mortality in patients with symptomatic heart failure (NYHA II-III) and LVEF ≤ 35%, despite the optimal medical treatment during three or more months provided that their life expectancy is significantly > 1 year with a good functional status, and having also the following conditions:		
- Ischemic heart disease (except if they have suffered a myocardial infarction in the last 40 days).	I	A
- Dilated cardiomyopathy.	I	B
Patients should be carefully assessed by an experienced cardiologist prior to the generator's replacement because the treatment goals and the patient needs may have changed.	IIa	B
The use of a portable ICD for a short time or as a bridge to the implantation of a device may be considered for patients with heart failure who are at risk of sudden cardiac death.	IIb	C
The implantation of an ICD is not recommended under the following conditions:		
- Within the first 40 days after an acute myocardial infarction, because its implantation in that period does not improve the prognosis.	III	A
- In NYHA functional Class IV patients with severe and refractory symptoms to pharmacological treatment, except if they are candidates for CRT, ventricular assist device or heart transplantation.	III	C

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LE, level of evidence; LVEF, left ventricular ejection fraction; RC, recommendation class.

Surgical treatment for heart valve disease and ventricular dysfunction

It is indicated in patients with: a) previous extensive anterior myocardial infarction (with great aneurysmal eschar), b) severe systolic dysfunction of the left ventricle, c) severe heart failure and c) akinesia area ≥ 35% of the ventricle perimeter.

The endoventricular circular patch plasty or Dor procedure (**Figure 2**)[22], is a surgical technique consisting of reducing the left ventricular volume and recovering its normal ellipsoid shape, through the exclusion of the necrotic and akinetic myocardial segment; although there are situations considered to be not favorable to carry out a ventricular restoration surgery (which includes mitral valve surgery, if concomitant mitral regurgitation and aortocoronary revascularization, if the anatomy is favorable):

- Severe right ventricular dysfunction with associated inferior necrosis.
- Pulmonary hypertension not associated to heart failure.
- Marked akinesia without ventricular dilatation.
- Restrictive pattern of left ventricular filling with poor functional class and mitral regurgitation.

Left mechanical circulatory support[9]

One of the main achievements of this technique has been the recognition that the support with left ventricular-assist devices is sufficient for the great majority of patients with advanced heart failure, even with biventricular failure. The most frequent indication for this complex type of assistance, which represents 80% of the implantations, is the bridge to heart transplantation in patients with severe cardiocirculatory failure[9,23].

Among the precise indications are the presence of severe symptoms lasting more than two months, despite the OMT with drugs and devices, absence of severe right ventricular dysfunction and severe tricuspid failure, and more than one of the following factors[2,9,23]:

- LVEF < 25% and peak VO_2 < 12 mL/kg/min (if measured).
- At least three hospitalizations due to heart failure in the last 12 months without an obvious precipitating cause.
- Dependence on intravenous inotropic treatment.
- Progressive dysfunction of vital organs (deterioration of kidney or liver function) due to reduced perfusion rather than inadequate ventricular filling pressures (pulmonary capillary wedge pressure ≥ 20 mmHg and systolic blood pressure ≤ 80-90 mmHg or cardiac index ≤ 2 L/min/m^2).

Indications such as target therapy or bridge to recovery are less frequent[23]. The current high cost of

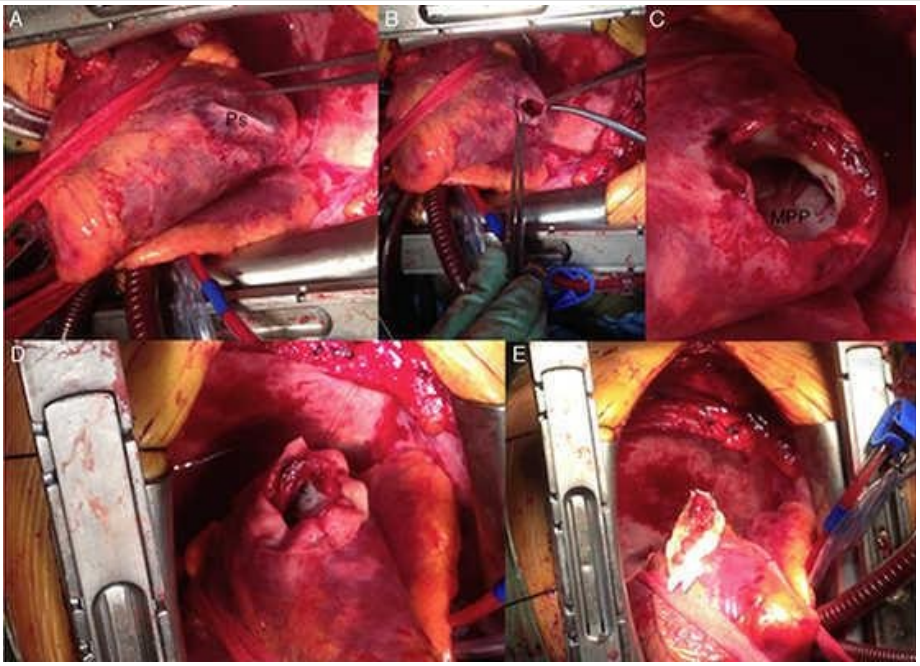

Figure 2. Surgical anatomy and modified Dor technique for left ventricular pseudoaneurysm repair. A, B, and C: let´s observe the correspondence with the imaging tests*, leaving the transmural rupture defect of the ventricular wall with "fresh" muscle (C) only contained by a layer of epicardium that invaginates with the negative interventricular pressure already in cardiopulmonary bypass (A). D and E: modified Dor technique with a first circular ventriculography supported by a patch of bovine pericardium and later hemostatic closure with a second layer of continuous suture also supported by bovine pericardium. Taken from Martín Gutiérrez *et al*. Cir Cardiov. 2016;23(4):212[22] (License CC BY-NC-ND 4.0).
MPP: posterior papillary muscle. Ps: left ventricular pseudoaneurysm (Acronyms in Spanish).
* The caption figure text of the original publication[22] is maintained, which is why it does not correspond to the imaging tests.

these devices limits their use in our field, which is why the recommendations for their indication only refer to their application in highly complex centers that have this equipment and trained personnel for its use[24].

EXPERIMENTAL TREATMENTS

There are three studies, one of which began around 2001.

Stem cell therapy or cellular cardiomyoplasty

A technique that consists in implanting stem cells (**Figure 3**), in order to induce the growth of new muscle fibers (myogenesis) and the development of angiogenesis in the damaged myocardium, which could contribute to improve the ventricular function and to reverse the process of postischemic remodeling of the ventricular chambers[26,27]. Therefore, the ultimate goal of this technology is that the transplanted cells differentiate into myocytes, regenerate the heart tissue and ultimately contribute to improve the patient's cardiac function[28].

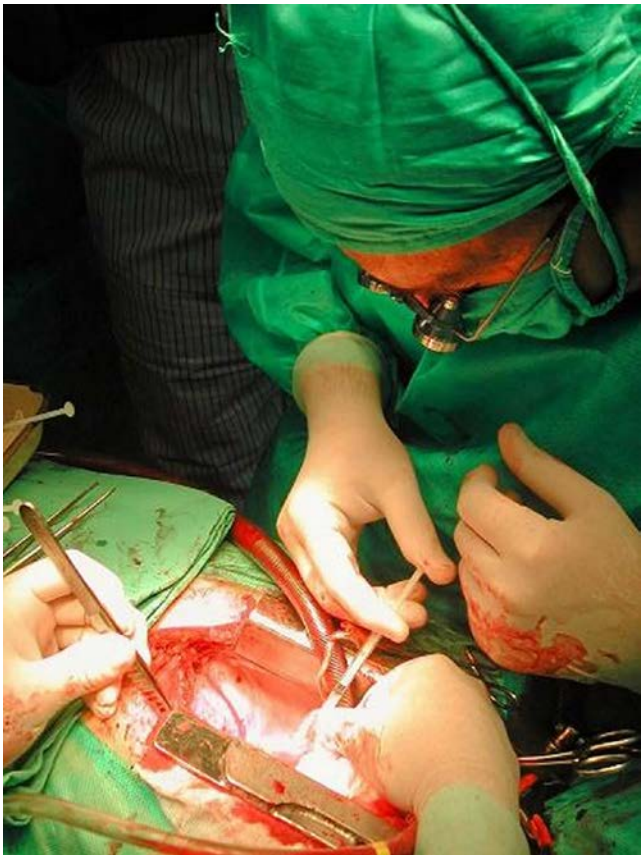

Figure 3. Dr. José R. Hidalgo Díaz (*Instituto de Cardiología y Cirugía Cardiovascular*, Havana, Cuba) implants stem cells directly (surgically) into the heart of a patient who had suffered a myocardial infarction. Taken, with the consent of CorSalud, from Hidalgo Díaz *et al*. CorSalud. 2018;10:47-51[25].

The action mechanisms of the cellular cardiomyoplasty, according to Chachques *et al*[29], are shown in **figure 4**; however, the efficacy of this alternative has been partially questioned by studies that found no changes in LVEF, a variable dependent on changes in preload, post-load, myocardial contractility and neuro-humoral activation, among others.

The cell therapy represents a promising advance for Cardiology, although there are still many doubts to be clarified, including: the selection criteria of patients prone to this treatment modality, the cell sources to be used, their implantation route, the amount of cells to be implanted and the time of application, among others.

Pacemakers in the vagus nerve

The increased stimulation of the sympathetic system in heart failure responds to the imbalance of a complex system of afferent inhibitory and stimulating signals (especially due to a depression of the sympathetic inhibitors reflexes) coming from the arterial and cardiopulmonary baroreceptors, arterial chemoreceptors, and muscular and pulmonary metabolic receptors[30,31]. The net result is an increase in the efferent sympathetic tone (with the attenuation of the parasympathetic tone) which consequence is the increase in circulating noradrenaline levels, which at the same time is a result of both, the increase on its secretion and the reduction on its reuptake[32]. Contrary to the initial hypotheses that considered the central nervous system (CNS) as a simple integrator of afferent information and a passive transmitter of the efferent signals, current models establish that vegetative reflex mechanisms can be modulated in the CNS by the action of other molecules, such as angiotensin II[30].

The new therapy, which began to be assessed several years ago with the European multicenter clinical trial NECTAR-HF[31], consists in the stimulation of the vagus nerve (partly responsible for the cardiac innervation); since previous studies had shown that the stimulation of this nerve is capable of improving the systolic function and, therefore, of improving symptoms. For the implantation of the neurostimulator, the neurosurgeon will make two

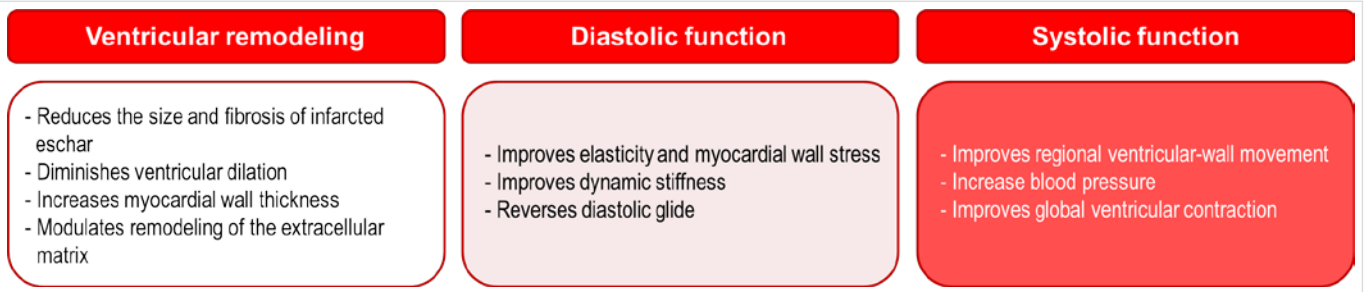

Figure 4. Action mechanisms of the cellular cardiomyoplasty [29].

incisions of about 5 cm: one on the right side of the neck, above the clavicle, where the vagus nerve is located, and another below, to house −at a subcutaneous level− a device of a size similar to a pacemaker, which is connected to a helical electrode that is wound around the vagus nerve, after being exposed for about 4 cm in length, between the carotid artery and the internal jugular vein. However, according to Zannad *et al*[31], the aforementioned NECTAR-HF clinical trial could not demonstrate that vagal stimulation had a significant effect on cardiac remodeling and functional capacity in patients with symptomatic heart failure, but it did have a significant effect on the life quality.

Reduction on the left ventricular wall stress and improvement of function: use of Algisyl

Ventricular wall stress reduction is considered a cornerstone in heart failure treatment, in its simplest form −based on Laplace's law−, the ventricular wall stress is directly proportional to ventricular diameter and pressure, and inversely proportional to wall thickness. The general opinion is that the increase in ventricular wall stress is responsible for the adverse remodeling process in which the ventricles become progressively more dilated and, eventually, lead to heart failure. Clinical and experimental studies in animals have shown that increased wall stress induces changes in proteins, contractile element synthesis and gene expression that support the remodeling process[33]. According to Hung *et al*[34], increased wall stress has shown to be an independent predictor of subsequent left ventricular remodeling.

Recently, the Algisyl (alginate hydrogel, absorbable and biocompatible) injection into the left ventricle, as a treatment for dilated cardiomyopathy, has gained attention in the medical community[35]. This treatment has been shown to be effective in preventing or even reversing the progression of heart failure in studies with animals and, most recently, in a clinical trial in humans[35,36]. Unlike other devices, this treatment aims to reduce the ventricular wall stress by increasing its thickness, by injecting the previously mentioned substance in the free wall of the left ventricle, which thickens and continues to reduce the size of the left ventricle over time[35-37]. Lee *et al*[36] demonstrated, using cardiac magnetic resonance, the thickening of the LV wall, and the significant reduction in its size, in a patient six months after receiving Algisyl-LVR (LoneStar Heart Inc., Laguna Hills, CA, USA).

The injection of biomaterials into the sick myocardium has proven to reduce both, myofibrillary and wall stress, to restore the left ventricular geometry, and to improve its function; therefore, this treatment represents a promise in preclinical and clinical studies[35]. Anker *et al*[37] and Mann *et al*[38] found, in the AUGMENT-HF study, that the use of Algisyl, together with standard medical treatment, provided sustained benefits at six months and one year in exercise capacity, symptoms and clinical status, in patients with advanced heart failure; although it did not provide significant results in terms of mortality.

HEART TRANSPLANTATION

Heart transplantation is an accepted treatment for end-stage heart failure[39,40]. Although randomized studies have never been carried out, there is consensus that transplantation, provided adequate selection criteria are applied, significantly improves: survival, exercise capacity, quality of life and the possibility of returning to work.

Apart from the shortage of heart donors, the main problems of transplantation are a consequence of

the low efficacy and complications of immunosuppressive treatment in the long term: antibody-mediated rejection, infection, high blood pressure, renal failure, malignant disease and coronary vasculopathy. Patients to be considered for heart transplantation are those with end-stage heart failure, severe symptoms and unfavorable prognosis, with no other treatment alternatives; who are motivated, well informed and emotionally stable, and able to comply with the intensive treatment required during the postoperative period[4,39,40].

Contraindications[2,4,39,40]

- Active infection.
- Severe peripheral arterial or cerebrovascular disease.
- Irreversible pulmonary hypertension with pharmacological treatment (implanting a left ventricular assist device and re-evaluating the patient will be assessed).
- Cancer (in collaboration with oncologists, each patient will be evaluated according to the risk of the tumor's recurrence).
- Irreversible chronic kidney disease (creatinine clearance < 30 ml/min).
- Multiorgan systemic disease.
- Other comorbidities with poor prognosis.
- Body mass index before transplantation > 35 kg/m^2 (it can be re-evaluated after the body weight loss).
- Current alcohol or drug abuse.
- Any patient whose social support is considered insufficient to meet the requirements for the treatment in outpatient care.

FINAL CONSIDERATIONS

Finally, beyond all therapeutic alternatives, pharmacological and non-pharmacological, the most effective treatment in heart failure and all chronic non-communicable diseases comply with a general principle, more sustainable than any other, based on the scientific evidence of its positive effect on health, and it is the intervention protocol for modifying lifestyles.

From primary health care, intervention programs to modify lifestyles, based on modifiable risk factors, as well as the clinical and humoral stability of diseases that degenerate into heart failure or insufficiency, not only prevent the harmful consequences for health, but also reduce the unsustainable health costs of the absence of a health system with levels of care that scale up medical assistance.

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