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HEART FAILURE - CURRENT PATHOPHYSIOLOGY AND THERAPEUTIC IMPLICATIONS

INSUFICIÊNCIA CARDÍACA - FISIOPATOLOGIA ATUAL E IMPLICAÇÕES TERAPÊUTICAS

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ABSTRACT

Understanding of the pathophysiology of heart failure has led to a therapeutic evolution in its management that has resulted in improved clinical outcomes, including a reduction in mortality. The concept of ventricular remodeling associated with neurohumoral activation, initially described via activation of the renin-angiotensin-aldosterone system and later, via sympathetic activation, led to the use of ACE inhibitors and beta blockers, respectively, altering the course of history of heart failure. In addition to the pharmacological category, more recently the modulation of the neprilysin route, through the use of the compound sacubitril/valsartan, brought additional impacts in reducing mortality in patients with heart failure. Finally, devices that also interfere in the process of ventricular remodeling, such as biventricular resynchronization pacemakers, have demonstrated significant clinical benefits. New molecular targets, microRNAs, or intracellular signaling molecules should increase as potential areas of research on disease progression, and could potentially become therapeutic targets.

Keywords: Heart failure; Pathophysiology; Treatment.

RESUMO

Conhecer a fisiopatologia da insuficiência cardíaca propiciou uma evolução terapêutica em seu manejo, que se traduziu em melhora de desfechos clínicos relevantes, incluindo redução da mortalidade. O conceito do remodelamento ventricular, associado à ativação neuro-humoral descrita inicialmente, via ativação do sistema renina-angiotensina-aldosterona, e posteriormente via ativação simpática, levou ao uso de inibidores da ECA e de betabloqueadores, respectivamente, que mudaram o curso da história da insuficiência cardíaca. Ainda na categoria farmacológica, mais recentemente a modulação da rota da neprilisina, através do uso do composto sacubitril/valsartan, trouxe impacto adicional de redução de mortalidade em pacientes com insuficiência cardíaca. Por fim, dispositivos que também interfiram no processo de remodelamento ventricular, como marcapassos de ressincronização biventricular, demonstraram benefícios clínicos significativos. Novos alvos moleculares, microRNAs ou moléculas de sinalização intracelular, devem crescer como potenciais áreas de investigação na progressão da doença e, potencialmente, se transformarem em alvos terapêuticos.

Descritores: *Insuficiência cardíaca; Fisiopatologia; Tratamento.*

INTRODUCTION

Within the concept of translational medicine applied to cardiology, the knowledge of the physiopathology of heart failure is perhaps the most emblematic and of substantial clinical relevance. The understanding of the pathophysiology of heart failure, in particular the mechanisms that lead to ventricular remodeling, is didactic and helps the comprehension of treatment evolution of this syndrome. In addition, the knowledge of the pathophysiology is critical for better understanding of the effect of various medicinal and therapeutic strategies, and facilitates the analysis of data produced by various clinical trials addressing the management of heart failure.

In this review, we will discuss only heart failure with reduced ejection fraction, since it is in this phenotype that most of the explored and robust associations between the axes of pathophysiological activation and pharmacological and non-pharmacological modulations are found, and which, once characterized experimentally, have led to successful therapeutic strategies that have modified the clinical course of heart failure. Our review is also limited to therapeutic options which, by modulating well-known pathophysiological

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axes, have established changes in clinical practice Due to the undeniable benefits brought to patients.

IMPROVED SURVIVAL BASED ON CLASSIC PATHOPHYSIOLOGICAL BASES

Classically, the development of heart failure is triggered by an injury to the heart either by a chronic (e.g. hypertension) or acute (e.g. acute myocardial infarction) nature. Once damage to the myocardium is established - either by exaggerated parietal stress, change in filling pressures and/or loss of heart muscle - a cascade of events are activated by neurohumoral mechanisms in order to compensate the reduction on cardiac output. However, this can evolve into a maladaptation, causing an overload to the cardiovascular system in various functional aspects.

The most emblematic and perhaps pioneering mechanism elucidated in the development of heat failure was the acivation of the renin-angiotensin-aldosterone system (RAAS). Pfeffer et al. demonstrated the activation of this axis had deleterious consequences to the myocardium, describing its importance in ventricular remodeling and on the vascular system in an experimental model of acute myocardial infarction in rats.[1] In a second study, these authors elegantly demonstrated that the use of captopril, an angiotensin-converting enzyme (ACE) inhibitor, promoted an improvement in the ejection fraction, a reduction of ventricular dilation (reverse remodeling) and an increase in the survival of these animals.[2]

From these findings, numerous randomized clinical trials using ACE inhibitors have demonstrated increased survival in patients with heart failure and improvement across all functions. Thus, the concept of preventing and/or reversing adverse ventricular remodeling was recognized as being the most effective means to improve clinical outcomes, such as the reduction of total mortality in heart failure.[3-5]

The other class of drugs, which constitutes one of the pillars in the treatment of congestive heart failure today, is the beta-blockers. For a long time, they were forbidden from the therapeutic armamentarium of heart failure, as they are traditionally considered negatively inotropic agents.[6] However, adrenergic activation, which occurs during the development of heart failure, promotes direct damage to cardiomyocytes by overloading them with an influx of calcium, leading to apoptosis. Secondarily, a desensitization of beta 1 receptors occurs in the myocardium, presumably in a process of "self-protection" upon increased and continued adrenergic stimulation.[7,8] Based on these precepts, Swedberg et al. postulated that the modulation (attenuation) of this axis would produce beneficial anti-remodeling effects which could result in clinical benefits.[9]

Recently, the therapeutic armamentarium for the treatment of heart failure was boosted with the launch of a drug that combines valsartan (inhibitor of the angiotensin II receptor) and a new drug, sacubitril (available as a pro-drug). The great novelty of this new drug is in the modulation of an important neurohumoral axis activated in heart failure, the natriuretic peptide (NP) axis. Sacubitril is an inhibitor of the enzyme neprilysin, which degrades NPs.[10] As a result, there is an increase in circulating NPs, as well as the concomitant blockade of the RAAS by valsartan, resulting in powerful vasodilation. This effect is potentially the major cause of positive outcomes in clinical studies, the most representative of these being the PARADIGM-HF study which showed a relative reduction of cardiovascular mortality or hospitalization due to heart failure of around 20% with sacubitril/valsartan compared to with enalapril.[11]

Today, beta-blockers, along with ACE inhibitors and more recently sacubitril/valsartan, are drugs that influence important pathophysiological axes and can revert, partially or completely, the adverse remodeling of the left ventricle. Thus, we can state that these drugs are the most powerful tools to improve outcomes in patients with heart failure, potentially through a universal mechanism: the anti-remodeling effect.

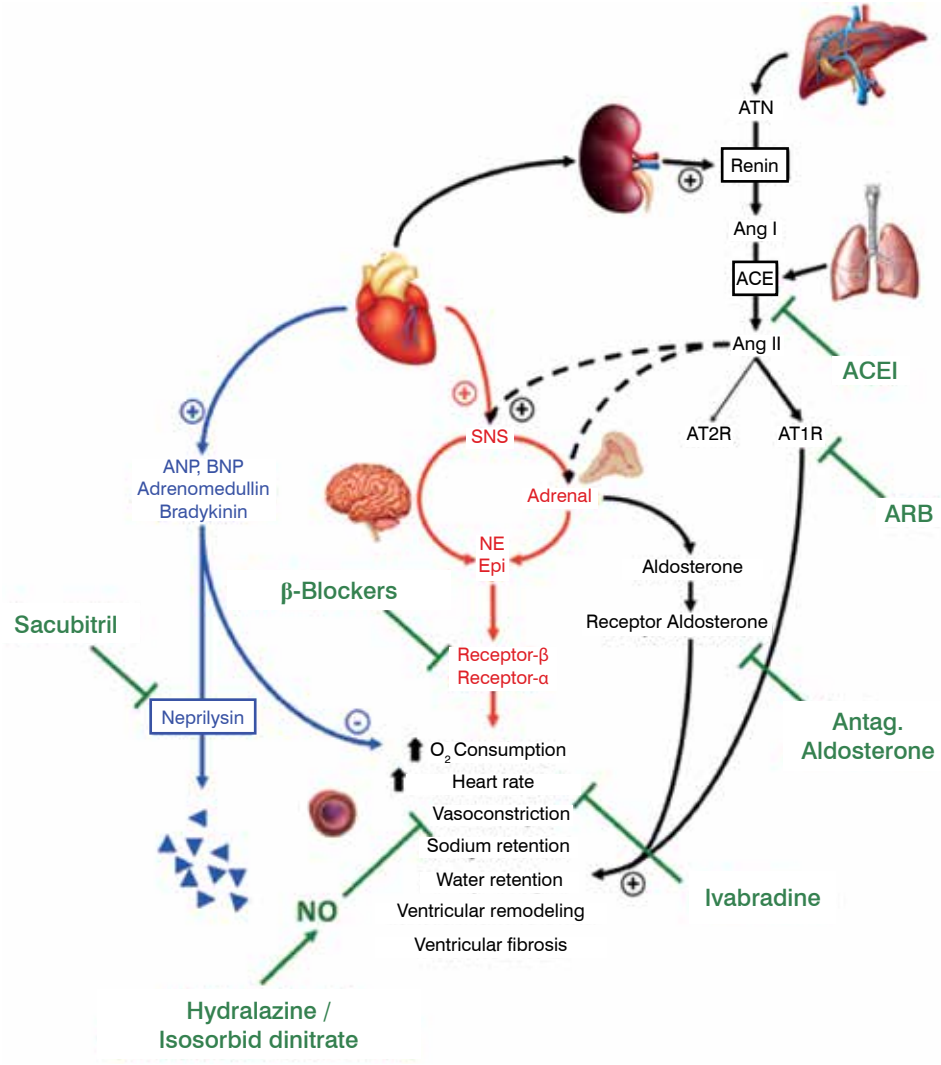
Finally, in addition to these drugs, another effective tool against the adverse remodeling of the left ventricle may be cardiac resynchronization through the use of a biventricular pacemaker. Through the activation of a different electrical axis to the left bundle branch block (LBBB) and mitochondrial alteration with a regional increase in oxidative phosphorylation, cardiac resynchronization therapy may be able to contribute to reverse remodeling. As observed with pharmacological interventions, clinical studies have demonstrated that cardiac resynchronization therapy is associated with improved outcomes, such as increased survival, improved quality of life and reduced hospitalizations.[12,13] Figure 1 represents the pathophysiological axes activated in heart failure and Table 1 summarizes these axes and the therapeutic implications involved in specific modulations.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

The RAAS is well-established as a therapeutic target in heart failure with reduced ejection fraction. In the last decades, significant advances have been achieved in terms of reducing mortality and hospitalization and improving symptoms through the development of ACE inhibitors, Ang II receptor blockers (ARBs) and mineralocorticoid receptor antagonists.[4-6,15-19]

During the occurrence of low cardiac output, with consequent low renal output, the RAAS is activated through the release of renin, which hydrolyses angiotensinogen into Ang I, which in turn is transformed into the vasoactive peptide Ang II through the action of ACE. Ang II has a central role in this system through the activation of its main receptors: AT1R, which promotes vasoconstriction, proliferation of smooth muscle, cell growth, secretion and synthesis of aldosterone secretion of vasopressin, and release of catecholamines; and AT2R, which leads to vasodilation, natriuresis, the release of bradykinins, and inhibition of cell growth and differentiation. In addition to its vasoactive function, Ang II also promotes positive inotropic and negative lusitropic effects in cardiac tissue, myocyte hypertrophy, apoptosis, and myocardial fibrosis through the activation of TGF-β.[26] Ang II subsequently undergoes cleavage into Ang III, Ang IV and Ang 1-7. Ang III has a lower pressor effect, but equally induces the production of aldosterone, unlike Ang IV which has an action similar to that of Ang II.[26,27]

Recently, particular interest has been given to the effects of Ang 1-7, a heptapeptide cleavage product of both Ang I



SNS=Sympathetic nervous system; NE=norepinephrine; Epi=Epinephrine; AGT=Angiotensinogen; Ang I=Angiotensin I; Ang II=Angiotensin II; ACE= angiotensin-converting enzyme; AT1R= Angiotensin II receptor type I; AT2R= Angiotensin II receptor type II; ACEI= angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; ANP=Atrial Natriuretic Peptide; BNP= Brain Natriuretic Peptide; NO= Nitric Oxide; Figure adapted from ref.14.

Figure 1. Pathophysiological axes of heart failure and the mechanisms of action of the main drugs used in therapy.

and Ang II through ACE2. Ang 1-7 binds to the MAS receptor, promoting vasodilation through the release of nitric oxide, and reverses the inflammatory process and fibrotic tissue, besides reducing insulin resistance and dyslipidemia.[26,28]

In clinical studies, chronic treatment with ACE inhibitors increased levels of Ang 1-7 and the Ang 1-7/Ang II ratio, compared to patients with congestive heart failure.[29] On the other hand, patients with more severe heart failure had an increased ACE/ACE2 ratio, showing the important role of the vasopressor and antiproliferative ACE, which opposes the Ang II axis.[30]

Activation of mineralocorticoid release receptors through Ang II is well-established in the pathophysiology of heart failure. Besides promoting the retention of sodium and water, the release of the mineralocorticoid hormone aldosterone also contributes to hypokalemia and hypomagnesemia, which can induce electrical instability and myocyte death. In addition, this hormone is related to vasoconstriction, impairment of endothelial function, reduction of baroreceptor sensitivity, as well as ventricular hypertrophy and fibrosis, thus promoting ventricular remodeling. [18,19]

Although the use of ACE inhibitors, ARBs and aldosterone receptor blockers is well-established, it is accepted that these have limited effectiveness.[27] This is why the ACE inhibitors can promote an increase in plasma renin activity and levels of Ang I, and restore the levels of Ang II[31]. Furthermore, there are alternative ways to produce Ang II independently of ACE, such as through the enzyme

Table 1. Table of medications used in the treatment of heart failure and covered in this review.

Medication	Mechanism of action	Benefits demonstrated	Study
Drugs indicated for all patients			
Beta-blockers (bisoprolol, carvedilol, metoprolol succinate)	Inhibition of beta 1 and beta 2 and alpha 2 receptors (carvedilol)	*Versus* placebo -Reduction of total and cardiovascular mortality, reduction of sudden death, reduction of hospitalization due to heart failure, and improvement of symptoms.	MDC[6]; MERIT-HF[15]; CIBIS I e II[16], COPERNICUS[17]
ACE inhibitors	Inhibition of ACE Reduction of Ang II production	*Versus* placebo: - Reduction of total and cardiovascular mortality, reduction of sudden death, reduction of hospitalization due to heart failure, and improvement of symptoms.	CONSENSUS[4] SAVE[5]
Mineralocorticoid/aldosterone receptor antagonist (spironolactone, eplerenone)	Aldosterone blockage	*Versus* placebo: - Reduction of total and cardiovascular mortality, hospitalization.	RALES[18] EMPHASIS-HF[19]
Drugs indicated in selected symptomatic patients			
Angiotensin receptor blockers (candesartan, valsartan, losartan)	Blocking of AT1R receptors	*Versus* placebo: - Reduction of hospitalization due to heart failure, but increased risk of hospitalization due to other causes. There is no benefit in mortality, rate of stroke or AMI. *Versus* ACE: - Lower rate of adverse events. No difference in relation to mortality, hospitalization, rate of AMI or stroke.	ARCH-J; CHARM-Alternative SPICE; STRETCH ELITE ELITE II; HEAVEN; REPLACE[20]
Sacubitril/valsartan	Inhibition of neprilysin and Ang-II receptor.	*Versus* Enalapril: - Reduction of mortality from all causes, due to cardiovascular causes as well as decrease in hospitalization for decompensated heart failure.	PARADIGM-HF[11]
Hydralazine nitrate +	Exogenous source of the venous arterial vasodilator +	*Versus* Enalapril in African-American patients: - Reduced total mortality, cardiovascular mortality, hospitalization, with improvement in quality of life and increase in exercise tolerance.	V-HeFT I e II[21, 22] A-HeFT[23]
Adjunct therapies			
Cardiac resynchronization therapy	- Mechanical synchrony and reverse remodeling. - Increased pulse pressure. - Increase in mitochondrial oxidative phosphorylation	- Improvement in quality of life. - Improvement in the walking test. - Improvement of ventricular function. - Improvement of functional capacity. - Decrease in mortality.	MUSTIC[24] MIRACLE-ICD[12] COMPANION[25] CARE-HF[13]

chymase, which is not inhibited by ACE inhibitors[32]. For example, the intracellular dodecapeptide Ang 1-12 can be metabolized into Ang I or II by chymase[33]. This intracrine pathway is responsible for the largest source of Ang II in the maladaptive process related to heart failure and explains the limited benefit from the use of ACE inhibitors and ARBs in the reduction of positive outcomes.[27]

ACE inhibitors are first-line drugs in the treatment of heart failure with reduced ejection fraction[34] based on the results of large clinical trials, with benefits in mortality, and reduction in reinfarction rates and hospitalization for heart failure.[34] ARBs are recommended only for patients who are intolerant to ACE inhibitors, since the trials demonstrated less robust evidence, confirmed in a systematic review.[20] We do not recommend the combined use of ACE inhibitors and ARBs due to the higher risk of adverse events.[20]

The RALES and EMPHASIS-HF studies have demonstrated that the use of the mineralocorticoid blockers spironolactone and eplerenone, respectively, in patients with reduced ejection fraction, New York Heart Association functional class II-IV and optimized therapy, when compared to placebos, produces benefits in reducing total mortality and cardiovascular

diseases, in addition to the reduction of the rates of hospitalization due to heart failure.[18,19]

In order to better suppress the RAAS, direct renin inhibitors have been developed, but have showed little clinical efficacy in the treatment of heart failure.[35]

SYMPATHETIC NERVOUS SYSTEM

The activation of the sympathetic nervous system (SNS) is one of the first adaptive processes in heart failure. The generalized sympathetic activation followed by the reduction of the parasympathetic system results in injury to heart rate variability, elevation of blood pressure and peripheral vascular resistance, positive inotropic and chronotropic effects, redistribution of peripheral blood volume for maintenance of perfusion and activation of the RAAS, among other physiological responses.[26]

The activation of the SNS occurs through two major groups of receptors: alpha and beta. The beta 1 and beta 2 receptors, in cardiac tissue, play a fundamental role in response to heart failure and present positive inotropic, chronotropic and lusitropic effects, and promote epicardial vasodilation, myocyte damage, apoptosis, and pro-arrhythmic effects, in addition to fibroblast hyperplasia. Beta 3 receptors are not yet fully known, but tend to present negative inotropic responses. Chronic exposure of the cardiac tissue to catecholamines promotes deterioration of cardiac function with ventricular dysfunction and increased mortality. Physiologically, this phenomenon can be explained by chronic overload of Ca^{2+}, which causes the death of myocytes.[36,37]

Initially, beta-blockers were banned in heart failure treatments due to their negative inotropic effect. However, this paradigm has been broken through clinical trials, such as the MDC in 1993.[6] Subsequently, several studies with bisoprolol (beta 1 selective blocker), metoprolol succinate (beta 1 selective blocker) and carvedilol (alpha 1, beta 1 and beta 2 blocker), were evaluated in patients with reduced ejection fraction, the majority of whom were using ACE inhibitors, and demonstrated benefit in control of symptoms, in reduction of hospitalizations due to heart failure and in mortality.[13]

A recent meta-analysis, using data from 11 large clinical trials, sought to investigate the role of beta-blockers on prognosis in heart failure stratified by ejection fraction and the presence of a sinus rhythm. When compared to a placebo, the benefit of this class of medication was consistent in all ranges of ejection fraction. Similar results were identified for cardiovascular death, and cardiovascular hospitalization, and there was also an increase in the ejection fraction in relation to the measure at the beginning of follow-up. Consistent evidence was not found in patients with atrial fibrillation rhythm.[38]

As the beta receptors are highly polymorphic, beta-blockers were the drugs most studied in the context of the pharmacogenomics of heart failure. The main polymorphisms identified were in the genes ADRB1 (Arg389Gly and Ser49Gly), ADRB2, ADRA1D and ADRA2D. These changes are responsible for the different responses to therapy as evidenced in the BEST and GENETIC-AF studies.[39]

NITRIC OXIDE (NO) PATHWAY

Organic nitrates, such as isosorbide dinitrate (ISBD), undergo an enzymatic bioconversion process that promotes the release of nitric oxide (NO), which in turn stimulates signaling pathways controlled by cGMP, promoting a relaxation of the venous and arterial vasculature. Consequently, this leads to the improvement of hemodynamic parameters, decrease of preload, improvement of ventricular perfusion, reduction of dilation and improvement of ventricular function.[40]

On the other hand, hydralazine (HID) is a drug that has a vasodilator action. Thus, the combination of HID and ISBD (HID-ISBD) would lead to a decrease in the filling pressure of the right and left ventricles and an increase in cardiac output. Based on this precept, two randomized controlled trials, the V-HeFT I and II studies, were conducted to evaluate the effects of the HID-ISBD combination in patients with heart failure with placebo and enalapril as controls respectively, but only the former demonstrated a benefit in mortality.[41]

At the beginning of the 1990s, clinical studies (SOLVD and V-HeFT I and II) demonstrated that African-American patients present a higher incidence and worse prognosis of heart failure, with higher all-cause mortality, and higher mortality and hospitalizations due to heart failure. [42]

Data suggested that this population responded less to the use of enalapril compared to Caucasians, which led to the development of the A-HeFT study. The completion of this clinical study was anticipated, given the benefit of a 43% relative reduction in mortality. The Food and Drug Administration (FDA) approved the use of HID-ISBD as the first drug for exclusive treatment for African-Americans,[42] which generated strong bioethical discussions.[42-44]

Several studies have demonstrated that African Americans have a greater resistance to NO, a higher production of the superoxide radical ($O^{\bullet}_2$), higher activity of NADPH oxidase and an increased production of peroxynitrite (ONOO-). Moreover, a sub-study of A-HeFT, the GRAHF study, analyzed the genetic heterogeneity of endothelial nitric oxide synthase (eNOS), and showed that there were variants of eNOS in African-Americans which were associated with better response to treatment with HID-ISBD.[45] Therefore, a treatment that increases the supply of NO, with HID-ISBD, would benefit patients.

The function of ISBD is to be an exogenous NO source, however, the role of HID is still not elucidated. It is known that HID in supra-pharmacological doses has an antioxidant effect, either by direct action on the superoxide radical, such as reacting with it or scavenging it, or through its ability to inhibit the activity of NADPH oxidase, thereby decreasing the production of superoxide radicals.[40]

The decrease in superoxide has an important role in maintaining the levels of NO, due to the great reaction velocity between $O^{\bullet}_2$ and NO in forming peroxynitrite (ONOO-). Thus, HID acts as an NO potentializing agent, increasing its biological half-life.[40]

NATRIURETIC PEPTIDES (NPS)

Several peptides, such as NPs, bradykinin and adrenomedullin, counteract the above-mentioned deleterious effects of RAAS stimulation and SNS activation, both of which are important for the development of congestive heart failure.

These peptides attenuate vasoconstriction and sodium retention, and delay cardiac and vascular remodeling.[26]

The synthesis and release of atrial and brain NPs (ANPs and BNPs) are stimulated by stress, such as volume or pressure overload assessed by echocardiography, allowing the correlation of NPs levels with disease severity and with parameters of ventricular dysfunction. They cause vasodilation and increased glomerular filtration, promoting natriuresis and diuresis, in addition to having an anti-hypertrophic and antifibrotic effect.[26] Considering their biological actions, substantial interest has been given to the potential therapeutic effects of NPs.

In summary, three NP receptors were described in mammals: RPN-A, RPN-B, and RPN-C. The NPs operate by binding RPN-A and RPN-B which activate guanylate cyclase, producing cyclic guanosine monophosphate (cGMP), responsible for all known biological effects due to the antagonism of the RAAS. RPN-C is associated with the clearance of NPs by allowing the binding of ANP and BNP and promoting the internalization of the receptor and later lysosomal degradation. The NPs can still be metabolized by the enzymatic action of neprilysin.[10]

Neprilysin catalyzes the degradation of a heterogeneous group of peptide vasodilators, including NPs, bradykinin, adrenomedullin, vasoactive intestinal peptide, as well as Ang II. As a result, its inhibition leads to an increase in the synthesis of cGMP. However, this is counteracted by vasoconstriction, sodium retention and the stimulation of cardiac fibrosis by the increase of circulating levels of Ang II.[46]

After unsatisfactory clinical results for the inhibition of neprilysin and ACE with candoxatril and omapatrilat in the treatment of heart failure in the 90s and 2000s, the inhibition of neprilysin and Ang II receptor with sacubitril and valsartan was proposed. Sacubitril/valsartan, at a molar ratio of 1: 1[47], was superior to the current treatment. When compared to enalapril in patients with heart failure class ≥ II and ejection fraction ≤ 35% who were already taking ACE inhibitors or ARBs, there was a significant decrease in the primary outcomes of death due to cardiovascular causes and hospitalization due to decompensation of heart failure as well as all-cause mortality.[11] Therefore, combined inhibition of Ang II receptor and neprilysin is superior to isolated inhibition of the RAAS.

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Heart failure is known to be associated with various conduction abnormalities.

The delays in conduction, described in dogs in 1925[48] and understood after the quantification of segmental function in the 80s, favor suboptimal ventricular filling, the reduction of ventricular contractility, an increase in the duration of mitral valve regurgitation, and the anomalous paradoxical movement of the interventricular septum.[49]

Biventricular pacing and the consequent cardiac resynchronization therapy (CRT) improves cardiac synchrony with the induction of a different activation pattern of the LBBB, with the right ventricular activation starting from the apex toward the base, delaying the stimulation of the interventricular septum and the base of the right ventricle in relation to the left ventricular free wall.[50]

In addition to the mechanical synchrony and the improvement of pulse pressure, an improvement in the function of myocytes is observed due to a positive adjustment of the beta receptors;[51] there is a regional increase in the heterogeneity of gene expression in patients with response to CRT,[52] with an increase in the carboxylation of pyruvate and branched-chain amino acid oxidation, increasing oxidative phosphorylation in the mitochondria.[53] Finally, an association between circulating microRNAs and response to CRT is being investigated.[54]

Although biventricular stimulation was described in 1979, it was only in 1987 that the concept of CRT for heart failure was formed and, years later, demonstrated to improve left ventricular function and functional capacity.[55] In 2001, the MUSTIC and PATH-HF studies were the first to test the safety and efficacy of CRT, showing improvement in the 6 minute walk test, the quality of life and the peak oxygen consumption (VO_2). Several studies have demonstrated reverse ventricular remodeling through CRT.[12,13]

Patients with congestive heart failure and ventricular dysfunction have a higher risk of sudden death - 6-9 fold when compared to the normal population - and is the main cause of death in patients with heart failure.[56] At the beginning of the 21st century, several studies showed benefits for primary and secondary prevention of sudden death in patients with decreased ejection fraction, with the MADIT II, DEFINITE, and SCD-HeFT studies having a large clinical impact.[57] From these studies, the American Heart Association/ American College of Cardiology Foundation recommended the prophylactic implantation of these devices in ischemic patients with ejection fraction ≤35%, functional class II or III, >40 days after acute myocardial infarction with life expectancy of >1 year and optimized medical therapy (OMT) (level of evidence A), as well as in patients with ejection fraction <30% functional class I, 40 days after acute myocardial infarction, life expectancy of >1 year and OMT (level of evidence B).

The addition of CRT to the implantable defibrillator (CRT-D) was first studied by the MIRACLE-ICD trial, in which patients using OMT were randomized to either receive CRT or not. After six months, there was an improvement in the quality of life and functional class in the CRT group. Comparing CRT and CRT-D with OMT and OMT with CRT, the COMPANION and CARE-HF[13] studies showed a significant difference in hard outcomes and established CRT as a treatment of patients with functional class III and IV heart failure, decreased ejection fraction, and enlarged QRS.[58] In addition to these studies, the MADIT-CRT, REVERSE and RAFT studies built evidence for the use of CRT in even earlier stages of heart failure,[59] and constitute the bases of the current guidelines for the indication of CRT.

INNOVATIVE TARGETS

The comprehensive knowledge of the pathophysiological pathways, such as the RAAS, remains one focus of translational research in heart failure. Several studies have been published in order to establish new therapeutic targets, such as the conversion pathways of Ang II independent of ACE.[32]

The application of pharmacogenetics in the context of heart failure has promising prospects, although the results published so far are inconsistent.[60] The main genes studied involve the beta 1, beta 2, and alpha 2 receptors, and the RAAS.[60] The rationale is to establish genetic patterns that assist in a more efficient and safe therapeutic choice and to optimize dose.[60]

MicroRNAs act in the post-transcriptional regulation of gene expression through binding with various sites of messenger RNAs and, thus, modulating various processes of cellular metabolism.[61] The role of microRNAs in pathophysiological processes is being studied in diagnosis, prognosis and therapy,[62] by pharmacological manipulation of their expression.[63]

Mitochondrial dysfunction is closely involved in ventricular hypertrophy and dysfunction. The maintenance of the biogenesis of this organelle, as well as the reduction of reactive oxygen species are two promising therapeutic targets. The development of mitochondrial antioxidants, such as MitoQ, has proven to be beneficial in the protection against ischemic injury and arterial blood pressure in animal models; a phase II study is in progress.[64]

CONCLUSIONS

Our knowledge of heart failure is a good example of success with regard to the progressive understanding of its pathophysiology and changes in therapeutic targets and management over the years, which has resulted in a significant decrease in mortality and other relevant clinical outcomes. The dominion of knowledge of the RAAS and SNS and their implications in the progression of ventricular remodeling (a significant factor in the pathogenesis of this disease) led to the universal use of ACE inhibitors and beta-blockers. With this combination, mortality reduction of around 50% was observed in patients with congestive heart failure. Thereafter, the advent of cardiac resynchronization therapy also greatly influenced the management of patients who met specific criteria for its use. Finally, the arrival of sacubitril/valsartan brings yet more success as data indicate that this compound can replace with advantage the ACE inhibitors to block effectively and safely the degradation of NPs, without interfering with RAAS blockage. Although much progress has been made in the knowledge of the pathophysiology of congestive heart failure and consequent improvements in their treatment, future targets remain an object of experimental research involving molecular targets, microRNAs and routes of cellular signaling seeking to increase the therapeutic armamentarium still necessary for the control of this prevalent clinical condition.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in conducting this study.

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